Study Medication: All doses of study medications were administered intravenously by the attending physician or designate every 3 months. Subjects were instructed to take their calcium supplement with the evening meal.

Efficacy Measures

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

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: The safety parameters were: adverse events; renal function (creatinine); liver function (ALT, GGT, AP); Vitamin D (25-OH vitamin D); and bone biopsy and histomorphometric assessment (in a subgroup of patients).

Withdrawal criteria: Subjects were withdrawn from the study if they experienced excessive bone loss defined as a decrease in BMD of 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 Withdrawn patients were not replaced.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 morphometric 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 90% power. The 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 PP population was used in all analyses of all non-fracture (bone mineral density and bone turnover marker) endpoints. The ordering of hypotheses was defined as follows:

H01: There is no difference in the time to the event 'first new vertebral fracture' between placebo and 1 mg ibandronate.
H02: There is no difference in the time to the event 'first new vertebral fracture' between placebo and 0.5 mg ibandronate.

H03: In the time to the event 'first new vertebral fracture', there is either an advantage for the 0.5 mg ibandronate group or no difference between 0.5 mg ibandronate and 1.0 mg ibandronate.

Protocol Amendments

The study protocol was amended 4 times. Amendment 1(1996) provided for evaluations of quality of life and pharmacoeconomic impact of treatment at selected study centers, done by questionnaire at Visits 5, 9 and 13. Amendment 2 (February 1998) prolonged study MF 4380 for another two years provided the 3-year results showed at least a trend in fracture reduction in favor of one ibandronate group, no deterioration in fracture rates in the third year, no abnormalities in bone biopsies taken from a subset of patients, and a statistically significant enhancement of BMD. A change in sponsorship occurred May 14, 1998. Amendment 3 (October 1998) described the changes in the primary contact person for the study and the named sponsor (previously Boehringer Mannheim GmbH). This amendment also removed the 2-year extension design modifications made by Amendment 2 (provided for in a separate protocol for study MF 4380F), and added a partial crossover study (MF 4492) for resolution of effect after 3 years of treatment. The amendment also modified the rules for stopping treatment and withdrawal from study; the processing of AEs by the new sponsor (F. Hoffman-La Roche Ltd), and new contacts for reporting SAEs; updated the reporting of serious adverse events (SAEs) in accordance with ICH guidelines and the new Sponsor's standard operating procedures; described procedures to assure blinding of BMD data, and modifications of data handling. Amendment 4 (January 2000) replaced "Assessment of Incident Vertebral Fractures" and "Statistical Plan and Evaluation" with a detailed Data Analysis Plan.

Results

Patient Disposition: A total of 2862 patients were randomized into 3 treatment groups: 950 to placebo, 951 to 0.5 mg and 961 to 1.0 mg ibandronate. Of the 2860 patients who received at least one dose of study medication, 2657 (92.9%) completed the first year of the study, 2461 (86.0%) completed 2 years, and 2359 (82.5%) completed the full 3 years of the study (Table below).

MF4380: Patient Disposition			
	Placebo	Iban 0.5 iv	Iban 1.0 iv
Enrolled	950	951	961
No treatment	1	1	0
At least one dose	949	950	961
Withdrew - AE	71	77	105
Withdrew - Other	91	75	82
Deaths	13	8	15
Completed 3 Years	787	798	774

Protocol Violations: A total of 371 subjects had protocol violation and were excluded from the PP analyses. The most common reason was lack of compliance relating to the number of injections of study medication received (< 9 injections), which involved 356 subjects across all treatment groups.

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

Demographics: As shown in the table below, the baseline demographics for the study population were balanced across the 3 groups. The average age of the population was 67 years. Study participants were, on average, 19 years past menopause and the majority were Caucasian (99%). The baseline LS BMD spinal T-score was –2.81.

MF 4380: Patient Demographics			
	Placebo	Iban 0.5 mg iv q3mo	Iban 1.0 mg iv q3mo.
N	949	950	961
Age (yrs.)	67.2 ± 5.0	66.8 ± 5.1	66.9 ± 5.1
Body Weight (kg)	64.4 ± 9.1	64.5 ± 9.1	64.9 ± 9.2
Body Height (cm)	160 ± 6	160 ± 6	161 ± 6
Race			
Caucasian	938 (99%)	935 (98%)	947 (99%)
Asian	6 (1%)	7 (1%)	4 (0%)
Black	1 (0%)	1 (0%)	1 (0%)
Other	4 (0%)	7 (1%)	9 (1%)
Time since Menopause (yrs)			
Mean ± SD	20.8 ± 7.8	20.9 ± 8.0	20.8 ± 8.0
Subjects having received HRT			
Yes	214 (22.6%)	247 (26.9%)	244 (25.4%)
LS T-score	-2.84	-2.84	-2.76
% Prevalent Vert Fx	98.6%	98.2%	98.3%

Primary Efficacy Outcomes

Incidence of New Vertebral Fractures: Over the 36 months of the study, 251 subjects experienced at least one new morphometric vertebral fracture. Fracture rates were lower for both ibandronate groups compared with placebo at the end of each study year, but, by life-table analysis, these differences were not statistically significant in the ITT population. In the PP analysis, a significant difference in the proportion of patients with new vertebral fractures was observed between the placebo (11.0%) and the 1.0 mg (8.2%) group (p=0.05).

MF4380: Lifetable Analysis for the First New Incident Vertebral Fracture			
	Placebo	Iban 0.5	Iban 1.0 mg
		iv q3mo	iv q3mo
	(N=949)	(N=950)	(N=960)
Primary:			
First new fracture	95	76	80
Estimate for incidence	10.7%	8.7%	9 2%
Relative Risk reduction		18 9%	14.4%
p-Value		0.14	0.24

Secondary Efficacy Outcomes

Rate of New Incident Vertebral Fractures at Three Years: For the ITT population, the mean annual rate of new vertebral fractures was 6.1%, 3.7% and 4.1% for the placebo, 0.5 mg, and 1.0 mg groups, respectively, with no statistically significant differences between groups. For the PP population, the mean annual rates were 6.9%, 4.4% and 3.5% for the placebo, 0.5 mg, and 1.0 mg groups, respectively. As in the life-table analysis discussed above, the difference between placebo and 1.0 mg was of nominal statistical significant ($p = 0.05$).

Rate of New Vertebral Fractures at Three Years (including clinical fractures): To evaluate a possible dose-response relationship in the time to the first clinically evident vertebral fracture, confirmatory testing was performed using the ordered set of pre-defined hypotheses. In the ITT analysis, the first test showed no difference in time to event between placebo and 1.0 mg ibandronate, therefore the company conducted no further testing.

Multiple New Vertebral Fractures: Within the ITT population, the number of placebo subjects who experienced two or more new vertebral fractures was approximately double that for each of the ibandronate groups. The risk reduction observed for both active-drug groups was statistically significant when compared to placebo: 54.4% reduction for 1.0 mg ($p = 0.01$) and 47.3% reduction for 0.5 mg ($p = 0.03$).

New or Worsening Osteoporotic Vertebral Fractures: In this analysis, results for new vertebral fractures were combined with those for worsening vertebral fractures. Subjects who experienced a worsening of a pre-existing fracture totaled 46 (1.6% of ITT population). Subjects who had a new and a worsening fracture were counted in the new fracture group only. A total of 274 subjects [102 (10.8%) in the placebo group, 84 (8.8%) in the 0.5mg group and 88 (9.2%) in the 20mg group] experienced new or worsening vertebral fractures. Combining the totals of patients with new and with worsening vertebral fractures did not substantially alter the results of the primary analysis.

Other Clinical Fractures (Table): Clinical osteoporotic fractures included symptomatic vertebral fractures plus all non-vertebral fractures, except those considered non-osteoporotic. The number of osteoporotic non-vertebral fractures after 36 months was 78 (8.9%) in the placebo group, 69 (7.9%) in 0.5 mg, and 68 (8.0%) in 1.0 mg ibandronate group. The differences in fracture rates between active treatment and placebo were not statistically significant.

MF4380: Summary of Clinical Fractures Over 36 Months (ITT)			
	Placebo	Ibandronate I.V.	
Fracture Type		0.5 mg	1.0 mg
	N=949	N=950	N=961
	n (%)[A]	n (%)[A]	n (%)[A]
Clinical Vertebral Fractures[B]	38 (4.3%)	23 (2.8%)	29 (3.3%)
Osteoporotic Non-vertebral Fractures	78 (8.9%)	69 (7.9%)	68 (8.0%)
Clinical Osteoporotic Fractures[C]	111 (12.6%)	88 (10.2%)	92 (10.8%)
All Clinical Fractures	118 (13.3%)	98 (11.4%)	110 (13.1%)
Hip Fractures			

MF4380: Summary of Clinical Fractures Over 36 Months (ITT)			
	Placebo	Ibandronate I.V.	
Fracture Type		0.5 mg	1.0 mg
	N=949	N=950	N=961
	n (%)[A]	n (%)[A]	n (%)[A]
proximal femur	11 (1.3%)	7 (0.8%)	6 (0.7%)
total hip fractures[D]	17 (2.0%)	11 (1.3%)	13 (1.5%)
Wrist/Forearm Fractures	30 (3.4%)	39 (4.5%)	31 (3.6%)
Rib Fractures			
ascertained rib fracture	8 (0.9%)	7 (0.8%)	8 (0.9%)
rib fracture	32 (3.6%)	29 (3.3%)	16 (1.7%)
Total Fractures	173 (19.3%)	150 (17.0%)	157 (17.8%)

[A] n = the total number of patients with fracture. Fracture rates are based on Life-table or Kaplan-Meier analyses adjusted for effective sample size. Includes fractures reported up to 36 months (study day 1098).
[B] Includes only new fractures.
[C] Includes new and worsening fractures.
[D] Total hip = hip, pelvis, and femur.

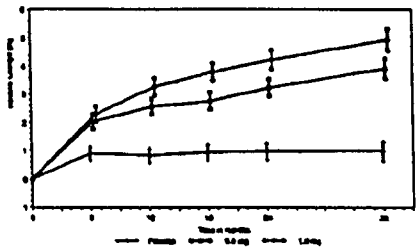
Height: Height data showed high variance and no significant changes between active- and placebo-treatment were found.

Bone Mineral Density of Lumbar Spine: Both ibandronate-treated groups showed dose-dependent increases in lumbar spine BMD (L2-L4) as compared with placebo. These changes in BMD were significantly different compared with the placebo group as early as Month 6. The maximal increase occurred during the first year, but further increases were seen throughout the study. For the 1.0 mg group, the change in lumbar spine BMD over 36 months was 4.0% greater than placebo.

MF4380: Mean Relative Change (%) in Lumbar Spine BMD (L2-L4) at Month 36			
Parameters	**Placebo**	**Ibandronate I.V.**	
		0.5 mg	1.0 mg
	N=788*	N=773	N=765
Mean relative change (%) (± SD)	0.98% (± 4.90%)	3.92% (± 4.95%)	4.94% (±5.20%)
Difference in means, versus placebo		2.94%	3.96%
Difference in means btw. iban. groups		1.02%	
p-value (t-test vs. placebo)		0.0001	0.0001
p-value (t-test btw. active treatments)		0.0001	
Least square mean % change (SE)	0.91% (± 0.21%)	3.82% (± 0.21%)	4.73% ± 0.22%)
Difference in LS means, versus placebo		2.92%	3.82%
p-value		< 0.0001	< 0 0001
Difference in LS means btw. iban. groups		0.91%	
p-value		< 0.0001	

* N for each group is based on effective sample size at Month 36, i.e. the number of patients in each treatment group that have a relative change from baseline value for lumbar spine (L2-L4).

Figure: Study MF4380
Change in Lumbar Spine BMD

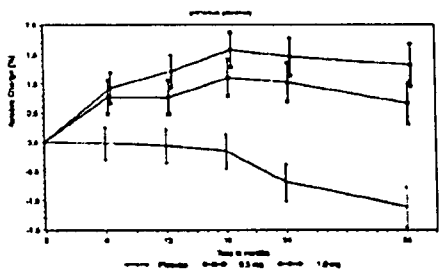


Bone Mineral Density of Proximal Femur: Relative to placebo, statistically significant, dose-dependent increases in BMD were demonstrated for both ibandronate groups at all sites measured at the hip: trochanter, femoral neck, intertrochanter, and Ward's triangle, (Table below). The relative increases in BMD were significant at Month 6.

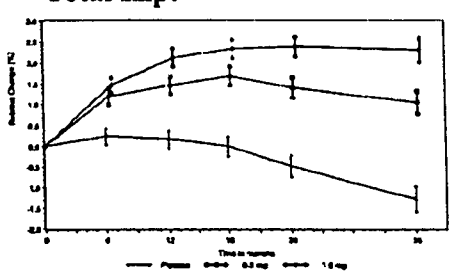
MF4380: Mean Relative Change (%) in Hip BMD at Month 36			
Site Measured	**Placebo**	**Ibandronate I.V.**	
		0.5 mg	1.0 mg
Femoral Neck	N=785	N=759	N=760
Mean relative change (SD)	-1.11% (4.89)	0.66% (5.06)	1.32% (5.01)
p-value (relative to placebo)		< 0.0001	< 0.0001
p-value (relative to active treatment)		0.01	
Trochanter	N=785	N=759	N=760
Mean relative change (SD)	-0.56% (6.47)	3.01% (5.67)	4.07% (5.07)
p-value (relative to placebo)		< 0.0001	< 0.0001
p-value (relative to active treatment)		0.0003	
Total Hip	N=720	N=701	N=707
Mean relative change (SD)	-1.28% (4.18)	1.05% (3.71)	2.31% (3.81)
p-value (relative to placebo)		< 0.0001	< 0.0001
p-value (relative to active treatment)		< 0.0001	
Least square mean % change (SE)	-0.87% (± 0.22%)	1.29% (± 0.22%)	2.55% (± 0.22%)
Difference in LS means, vs placebo		2.16%	3.42%
p-value		0.0001	0.0001
Difference in LS means btw. iban. groups		1.26%	
p-value		0.0001	

Figures: MF 4380: Change in Proximal Femur BMD

Femoral Neck:



Total Hip:



Bone Mineral Density of Forearm: BMD measurements for all locations of the forearm varied greatly over time. At the distal radius + ulna (measured by ——— , mean BMD increased in the ibandronate groups, and was significantly different compared with placebo at 36 months. At the 1/3 radius (measured by Hologic or Lunar), the percentage BMD change from baseline was statistically different compared with placebo at 36 months in the 1.0 mg ibandronate group. For all the other distal forearm sites, BMD decreased in all groups.

Bone Turnover Markers: In this study, markers of bone turnover were measured prior to each quarterly injection. Measurements at these time points therefore represent only the residual anti-resorptive effect of ibandronate. Sampling for markers at intermediate time points was not done.

Values for markers of bone resorption are listed in the table below. Urinary CTX decreased in all 3 groups and appeared to reach a plateau at approximately 6 months. There was a statistically significant difference in the median changes from baseline between the placebo and the 0.5 mg ibandronate groups at 24 and 36 months. There was also a statistically significant difference between the placebo and 1.0 group in CTX change from baseline at all times points.

MF380: Resorption Markers - Relative Change (%) from Baseline over 3 Years (PP)

		Baseline	Relative Change to Baseline (%)					
			Month 3	Month 6	Month 12	Month 18	Month 24	Month 36
Urinary CTX/Creatinine (µg/µmol)								
Placebo	N	204	167	162	163	157	159	146
	Median	0.313	-28.61	-39.25	-36.70	-36.90	-27.53	-34.18
0.5 mg	N	206	167	163	159	153	153	137
	Median	0.307	-35.94	-41.48	-44.50	-40.81	-36.87*	-41.43*
1.0 mg	N	204	162	156	157	153	152	145
	Median	0.305	-37.41*	-48.50*	-49.75*	-50.00*	-48.29*	-44.97*
Urinary NTX/Creatinine (nmol/mmol)								
Placebo	N	203	165	153	162	156	158	145
	Median	70.000	-30.16	-37.50	-27.71	-32.34	-20.96	-18.98
0.5 mg	N	206	165	156	159	153	153	137
	Median	70.000	-32.26	-38.71	-28.07	-35.48*	-32.09*	-36.67*
1.0 mg	N	204	159	149	157	153	152	144
	Median	65.000	-35.59*	-46.94*	-42.55*	-42.86*	-46.23*	-42.59*

* The p-value (Wilcoxon/Kruskal-Wallis rank sum, Z-test) for the difference between active group and placebo was <0.05.

Values for markers of bone formation are listed in the table below. All groups displayed reduced levels of serum osteocalcin from baseline values. Values decreased gradually over time for all groups, but the relative change for the ibandronate groups showed a statistically significant reduction. A statistically significant, dose-dependent reduction in serum BSAP from baseline levels was observed for both ibandronate groups, compared to placebo. The difference in BSAP values between the 1.0 mg and placebo groups was statistically significant as early as Month 3, and remained so throughout the 36 months.

MF380: Formation Markers - Relative Change (%) from Baseline over 3 Years (PP)								
		Baseline	Relative Change to Baseline (%)					
			Month 3	Month 6	Month 12	Month 18	Month 24	Month 36
Osteocalcin (ng/nmol)								
Placebo	N	205	168	165.	166	161	159	153
	Median	10.10	-7.23	-12.28	-13.24	-15.31	-15.79	-27.95
0.5 mg	N	206	168	168	163	159	158	152
	Median	27.65*	-13.16*	-20.26*	-24.92*	-24.37*	-30.37*	-37.89*
1.0 mg	N	204	162	160	161	158	156	152
	Median	29.50	-16.73*	-26.17*	-29.15*	-33.05*	-38.41*	-43.58*
Bone Specific Alkaline Phosphatase (nmol/mmol)								
Placebo	N	205	168	165	165	161	159	152
	Median	50.00	-16.06	-19.12	-12.96	-13.73	-9.52	-25.29
0.5 mg	N	206	168	168	163	159	158	152
	Median	52.00	-22.88	-26.10*	-27.87*	-18.75*	-21.85*	-32.61*
1.0 mg	N	204	162	160	162	158	156	150
	Median	53.00	-26.99*	-37.42*	-32.35*	-29.84*	-32.67*	-44.92*
* The p-value (Wilcoxon/Kruskal-Wallis rank sum, Z-test) for the difference between active group and placebo was <0 05.								

Serum intact PTH concentrations were measured in a subset of patients. No group- or time-specific changes were observed

Bone Histology: A total of 192 subjects were enrolled for bone biopsy. Biopsies were also performed at baseline in 47 of these subjects, allowing an analysis of paired biopsies. Biopsy cores were obtained in 55, 58 and 79 subjects in the placebo, 0.5 mg and 1.0 mg groups, respectively. Of these, 157 biopsy cores were available for quantitative analysis, 71 from Month 22 and 86 from Month 34.

The primary efficacy parameter for bone remodeling was mineralizing surface (MS) (Table below). The median percent MS for the placebo group at Month 34 was lower than the median value at Month 22. This suggests a progressive inhibitory effect on bone turnover, possibly due to calcium and vitamin D supplementation. The median values for MS in the 0.5 mg and 1.0 mg groups showed a dose-dependent decrease at Month 22 relative to placebo (49.6% in the 0.5 mg and 75.4% in the1.0 mg group). At Month 34, median MS values for both ibandronate groups were higher than at Month 22, but were still below that of placebo (approximately 19.3% and 41.5% below placebo, respectively), suggesting a diminished treatment effect in reducing bone turnover.

Supportive evidence for suppression of bone remodeling includes data for osteoid surface (OS), activation frequency (AcF), and bone formation rate (BFR). The median values for OS suggested an inhibition of bone turnover in the 1.0 mg group at Month 22, but no difference in the 0.5 mg group as compared with placebo. This effect was less pronounced at Month 34 in 1.0 mg group. Median AcF showed a dose-dependent inhibition of bone turnover for the ibandronate groups at Month 22, and to a lesser extent at Month 34, relative to placebo. Similarly, BFR was reduced at 22 months, but not at 34 months in both ibandronate groups. The decrease in activation frequency, together with the tendency to positive bone balance, suggest that the remodeling

space was decreased by ibandronate at some early point in the treatment period, but that this reduction was not excessive.

MF4380: Bone Biopsy Efficacy Results						
	Placebo	0.5 mg	1.0 mg	Placebo	0.5 mg	1.0 mg
	22 months			34 months		
Mineralizing Surface						
N	20	23	25	23	25	38
Median	6.955	3.510	9.690	4.870	3.930	2.845
Osteoid Surface						
N	20	23	21	23	25	38
Median	8.750	8.700	4.800	8.400	6.400	7.000
Activation Frequency						
N	19	23	23	23	25	36
Median	0.606	0.319	0.168	0.488	0.408	0.293
Bone Formation Rate						
N	20	23	24	23	25	37
Median	0.042	0.024	0.012	0.033	0.025	0.035

Forty-seven patients had a bone biopsy procedure at baseline, along with a repeat procedure at Month 22 or 34 for paired biopsy analysis. The placebo subjects showed a small increase in median MS at Month 22, while a marked decrease from baseline was observed in both active-drug groups. An attenuation of the effect was seen in the 1.0 mg group at 34 months, while the values for both placebo and 0.5 mg patients were reduced from the 22 month level.

MF4380: Paired Biopsies Mineralizing Surface Change				
Treatment Group	Absolute Change (%)		Relative Change (%)	
	22 mo.	34 mo.	22 mo.	34 mo.
Placebo				
N	7	7	7	7
Median	0 83	-2.70	11.64	-48 22
0.5 mg				
N	9	4	9	4
Median	-3.29	-5.69	-48.38	-52.55
1.0 mg				
N	11	8	11	8
Median	-2.86	-1.81	-71.11	-46.18

Osteoid thickness (OTh) was the primary safety parameter. In the 47 patients with paired biopsies, median OTh decreased from the baseline value after 22 and 34 months in both active-treatment groups. The difference in mean osteoid thickness between active treatment and placebo was < 2.5 μm for both ibandronate dose groups.

Medical Officer's Conclusion: This study failed to demonstrate that q 3 month intravenous doses of 0.5 mg and 1.0 mg ibandronate significantly reduce the 3-year incidence of new morphometric vertebral fractures compared with placebo in a population of postmenopausal osteoporotic women. The PP analysis did show a significant reduction in the incidence of vertebral fractures between the 1.0 mg ibandronate and placebo groups (p=0.05), however. In an analysis of a secondary efficacy parameter, compared with placebo, a statistically significant risk reduction in multiple incident vertebral fractures was seen in both ibandronate-treated groups (relative risk reduction 54.4% in the 1.0 mg group, p=0.01 and 47.3% in the 0.5 mg group, p=0.03).

Treatment with i.v. ibandronate over 3 years resulted in significant increases in BMD, compared with placebo, regardless of whether the skeletal site contained predominantly trabecular or cortical bone. Urinary NTX and CTX decreased in both active-treatment groups and reached nadirs at 6 months. Serum bone-specific alkaline phosphatase and osteocalcin were consistently reduced relative to placebo in both ibandronate doses by Month 3. Histomorphometric data obtained at 22 or 34 months confirmed that ibandronate had no adverse effects on either bone mineralization or microstructure. Ibandronate treatment reduced the rate of bone turnover as assessed by a decrease in the mineralizing surface, however, the extent was less than expected.

The results of this study indicate that 0.5 mg and 1.0 mg ibandronate i.v. every 3 months is a suboptimal regimen for the treatment of postmenopausal osteoporosis. The sponsor concludes that a different i.v. dosing regimen with a higher dose or more frequent dosing interval, or both, may prove effective.

COMMENT: The fracture efficacy of oral and i.v. dosing regimens of ibandronate have been studied in two 3-year trials. Oral ibandronate at doses of 2.5 mg daily and 20 mg intermittently was effective, relative to placebo, in reducing the risk for morphometric vertebral fractures. Intravenous ibandronate at doses of 0.5 mg q3 months and 1.0 mg q3 months, however, failed to meet the standard fracture efficacy criterion.

It's safe to conclude that the difference in fracture results between the oral and i.v. dosing regimens was not related to differences in study populations or methods for assessing incident vertebral fractures. The demographic profiles of the patients in the oral and i.v. trials were nearly identical, as were the methods of fracture assessment. The similar rates of new vertebral fractures in the placebo groups from both studies provides additional support for the similarities of the patient populations and the technique of fracture assessment in the oral and i.v. studies.

It is likely that the dissimilar fractures results are due to differential effects of the dosing regimens on bone density and bone turnover.

As shown in the following table, while BMD of the LS increased by statistically significant amounts relative to placebo in the i.v. and oral ibandronate treatment arms, the placebo-subtracted increases were greater with 2.5 mg oral ibandronate compared with 1.0 mg q3 month i.v. ibandronate.

MF4411 & MF4380: Bone Mineral Density							
		po (4411)			iv (4380)		
N		2946			2861		
		975	977	977	949	950	961
		Placebo	2.5mg qd	20mg int	Placebo	0.5mg q3m	1.0mg q3m
LS T-score baseline		-2.76	-2.75	-2.71	-2.84	-2.84	-2.76
Δ LS BMD (%)		1.26	6.54	5.67	0.98	3.92	4.94
	0-1 fx	0.998	6.80	5.77	1.02	4.00	4.97
	≥ 2 fx	1.58	6.22	5.51	0.94	3.83	4.93

The inhibition of markers of bone resorption and formation was also less with the i.v. compared to the oral dosing regimen. For example, relative to placebo, levels of urinary CTX/creatinine decreased by approximately 55% in the 2.5 mg oral treatment group and by approximately 11% in the group that received 1.0 mg q3 month i.v. ibandronate. Similarly for markers of bone formation, relative to placebo, levels of osteocalcin decreased by approximately 35% in the 2.5 mg oral ibandronate group and by roughly 15% in the 1.0 mg q 3 month i.v. ibandronate group. See Appendix XI.B.3

To summarize, in contrast to daily oral doses of 2.5 mg ibandronate, q3 month i.v. doses of 0.5 mg and 1.0 mg ibandronate failed to reduce the incidence of morphometric vertebral fractures by a statistically significant amount in an intent-to-treat population of postmenopausal women with osteoporosis. The most likely explanation for the different fracture results relates to the smaller gains in BMD and the reduced suppression of bone turnover observed with the i.v. vs. the oral regimens.

VI.C.2 Prevention of Postmenopausal Osteoporosis Trials

VI.C.2.a MF4499: This was a randomized, double-blind, placebo-controlled dose-finding study of the efficacy and safety of ibandronate for prevention of bone loss in postmenopausal women during 2-year treatment, using a continuous oral dosing regimen (0.5, 1.0, or 2.5 mg daily).

Objectives: The objectives of this study were to investigate the dose-response, efficacy, and safety of ibandronate in a continuous oral administration for the prevention of bone loss in postmenopausal women.

Study Design: This was a randomized, double-blind, placebo-controlled, dose-finding study of continuous oral ibandronate in postmenopausal, non-osteoporotic women. Patients were allocated into 1 of 4 strata according to the length of time since menopause (TSM) and the baseline BMD T-score of the LS (Table below). Patients were then randomized within each stratum to receive either placebo or ibandronate (0.5, 1.0 or 2.5 mg) daily for two years. In addition to study drug, all patients received supplemental doses of calcium (500 mg/day orally). A full schedule of assessments can be found in Appendix XI.B.4.a

Time Since Menopause	Baseline Lumbar Spine [L1-L4] BMD T-score	
	> –1 SD	≤ –1 SD and ≥ –2.5
1–3 years	Stratum A	Stratum B
> 3 years	Stratum C	Stratum D

Patient Population: The study population comprised healthy, early postmenopausal women.

Inclusion Criteria:

At least one year post-menopause
Provided written informed consent

Exclusion Criteria:

Mean BMD T-score of the lumbar spine (L1-L4) below –2.5
One or more osteoporotic fractures in her medical history
Bilateral oophorectomy
Abnormality of the esophagus delaying esophageal emptying
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 abnormality

Study Medication: All medications were administered orally. Subjects received either ibandronate (0.5, 1.0 or 2.5 mg) or placebo daily. 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 30 minutes after taking the medication was required. Subjects were instructed to take their calcium supplement with the evening meal.

COMMENTS: This study utilized a 30-minute post-dose fast. In study MF4491, the 30-min fast group showed a smaller increase in lumbar spine BMD than the 60-minute group and did not meet the predefined criterion for non-inferiority. The overall incidence of adverse events was higher in the 30-min group as well. Thus, these Reviewers believes that the labeling should recommend a 60-minute post-dose fast for both the treatment and prevention indications.

Efficacy Measures

Primary: Relative change in BMD of the LS at 2 years

Secondary: Change in BMD of proximal femur
Change in BMD of distal forearm
Change in BMD of total body
Serum C-telopeptide (CTX)
Urinary excretion of C-telopeptide (ratio of C-telopeptide/creatinine)
Serum osteocalcin concentration
Serum parathyroid hormone concentration

Safety Measures: Discussed in detail in the Safety Section.

Withdrawal Criteria: Patients with symptomatic vertebral fractures, which were confirmed radiologically, were excluded from further participation in the study. Subjects with excessive bone loss (defined as a decrease in BMD of >8% at the total hip or lumbar spine during the first year) confirmed by repeated measurement after three months, were informed by the investigator and could choose to withdraw have the option to receive active treatment for osteoporosis and continue in the study.

Statistical Analyses: For the primary efficacy variable, a closed test procedure was adopted. The primary model was an ANOVA, which took treatment and allocated stratum into account as independent factors. The primary analysis was performed on the ITT population. All patient data were included in the ITT analysis of BMD, even if study medication was interrupted or stopped, or an alternative treatment was administered.

Protocol Amendments: The study protocol was amended twice. The first amendment (June 26, 1998) modified the named sponsor and primary contact person for the study, and revisions were made to the serious adverse event (SAE) reporting form. In addition, minor changes were made in data handling. The second amendment (November 30, 1998) deleted the category "AEs of special interest" (esophagitis, heartburn, stomach pain), as well as the "Stopping Rules" requirement of a BMD T-score lower than –2.5 to define excessive bone loss, and added information to the exclusion criteria regarding the use of hormonal therapy, other

bisphosphonates, or sodium fluoride during the study. This amendment also updated the investigator list and sponsor personnel, and provided further information regarding patient withdrawal from study, concomitant medications, screening of laboratory values for critical levels, processing of efficacy laboratory collection, and blinding of investigators to laboratory measurements for efficacy and BMD parameters.

Results

Patient Disposition: A total of 653 subjects were enrolled at 11 study centers. Subjects were assigned to one of four strata (Table below), then randomized into four treatment groups: 162 in the placebo group, 162 in 0.5 mg group, 166 in 1.0 mg group, and 163 in the 2.5 mg group. Five subjects did not receive study medication (three in placebo and one each in the 0.5 mg and 1.0 mg groups).

MF4499: Distribution of Randomized Subjects					
			Oral Daily Ibandronate		
Stratum	T-score, TSM	Placebo	0.5mg	1.0 mg	2.5 mg
		N	N	N	N
A	>-1 SD, 1-3 yrs	29	27	28	28
B	(-1 to –2.5 SD, 1-3 yrs)	48*	50	53*	48
C	(>-1 SD, > 3 yrs)	29*	29	29	29
D	(-1 to –2.5 SD, > 3 yrs)	56*	56*	56	58
	Total	162	162	166	163
* one subject did not receive study medication					

Of the 648 subjects who received at least one dose of study medication, 547 (82 % - 87%) completed the full two years of treatment (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%)
Completed	132 (83.0)	138 (85.7)	144 (87.3)	133 (81.6)

Withdrawal Due to Excessive Loss of BMD: None

Protocol Violations: From the randomized population of 653 subjects, five (0.8%) were excluded from the safety analysis (no study drug taken), 33 (5.1%) from the ITT analysis, and 138 (21.1%) from the PP analysis. The percentage of subjects excluded from each analysis population, overall and by reason, was balanced across the four treatment groups. The large majority of subject exclusions from the ITT analysis (27/33, 82%) were due to lack of a follow-up BMD assessment, while the majority of exclusions from the PP analysis (84/138, 61%) were due to lack of compliance with the dosing regimen.

Demographics: The baseline demographics were balanced across the four treatment groups. (Table below). The average age was 58 years and the average baseline LS T-score was –1.0.

Across the four strata, baseline demographics for the treatment groups were also balanced. Subjects who experienced at least one fracture of any kind prior to entering the study numbered 55 (35%), 58 (36%), 63 (38%), and 48 (29%) in the placebo, 0.5 mg, 1.0 mg, and 2.5 mg groups, respectively.

MF4499: Patient Demographics				
	Placebo (N=159)	0.5 mg (N=161)	1.0 mg (N=165)	2.5 mg (N=163)
Age (yrs)				
N	159	161	165	163
Mean (SD)	57.9 (8.6)	58.8 (8.9)	57.6 (8.0)	58.2 (8.6)
Time Since Menopause (yrs)				
N	159	161	165	163
Mean (SD)	8.2 (8.2)	8.9 (9.0)	8.1 (8.4)	9.0 (9.9)
Weight (kg)				
N	155	160	164	161
Mean (SD)	75.1 (17.3)	73.6 (16.2)	70.9 (14.6)	73.0 (14.4)
BMD Spine (L1-L4) T-Score				
N	158	161	165	163
Mean (SD)	-1.0 (1.2)	-1.0 (1.1)	-1.0 (1.0)	-1.1 (0.9)
25(OH)Vitamin D (ng/mL)				
N	158	161	165	162
Mean (SD)	39.7 (15.6)	39.2 (13.8)	40.2 (15.8)	39.1 (14.3)
Race				
Caucasian	137 (86%)	141 (88%)	143 (87%)	142 (87%)
Asian	18 (11%)	15 (9%)	16 (10%)	14 (9%)
Black	1 (1%)	0	0	0
Other	3 (2%)	5 (3%)	6 (4%)	7 (4%)

COMMENT: Roughly one-third of the women who entered this trial reported a history of having had a fracture, raising the possibility that some had osteoporosis at baseline. But since it is unknown if these fractures occurred at skeletal sites traditionally associated with osteoporosis and resulted from minimal trauma, this issue will remain unanswered. Nevertheless, this lack of information should have little, if any, affect on interpretation of the study results.

Primary Efficacy Outcomes

Bone Mineral Density of Lumbar Spine: Over the course of the 2-year study, LS BMD decreased by approximately 1% in the placebo group and by 0.5% in the ibandronate 0.5 mg dose group (Table below). In contrast, BMD increased by 0.4% and 2.0% in the ibandronate 1.0 mg and 2.5 mg groups, respectively ($p<0.001$ vs. placebo). The difference in the mean change in LS BMD between the ibandronate 2.5 mg group and the placebo group was 3.13%.

MF 4499: Lumbar Spine BMD Relative Change (%)						
Treatment Group	**Baseline**	**Month 6**	**Month 12**	**Month 18**	**Month 24**	**Endpoint**
Placebo						
N	150	148	141	140	141	150
Mean	1.0070	-0.1584	-0.6828	-0.7282	-1.1907	-1.1878
SD	0.1429	2.3024	2.9499	3.1444	3.5497	3.4961
Ibandronate 0.5 mg						
N	157	157	150	142	143	157
Mean	1.0022	0.0883	-0.1538	-0.3076	-0.5417	-0.5474
SD	0.1283	2.0761	2.6999	3.3287	3.7134	3.6067
p-Value (a)	0.52939	0.36283	0.11045	0.34581	0.15662	0.12373
Ibandronate 1.0 mg						
N	160	153	155	149	148	160
Mean	1.0017	0.4469	0.0973	0.4201	0.3838	0.3011
SD	0.1239	2.3763	3.0691	3.4093	3.7878	3.7238
p-Value (a)	0.70419	0.02365*	0.02006*	0.00371*	0.00035*	0.00027*
Ibandronate 2.5 mg						
N	153	150	140	141	137	153
Mean	0.9967	1.1334	1.9872	1.7545	2.0109	1.9391
SD	0.1152	2.5789	2.9461	3.5978	4.1697	4.0564
p-Value (a)	0.20209	0.00000*	0.00000*	0.00000*	0.00000*	0.00000*
(a) F-test: current treatment group versus placebo adjusted for stratum.						
* Difference between active group and placebo was statistically significant ($p < 0.05$).						

Subgroup analyses were conducted by stratum as shown in the table below. Across the various strata, changes from baseline in LS BMD reflected the results of the overall study population, with one exception – stratum B, the 0.5 mg group. Compared to the results of the overall ITT population, slightly larger increases in LS BMD were seen in all ibandronate groups of Strata C and D (subjects greater than 3 years post-menopause).

MF4499: Lumbar Spine BMD Change, by Stratum						
			Oral Ibandronate			
	BMD Subgroup	**Placebo**	**0.5 mg**	**1.0 mg**	**2.5 mg**	**** 2.5 mg-Placebo**
		% change (n)	% change (n)	% change (n)	% change (n)	% change
Stratum	(T-score, TSM)					
A	(>-1 SD, 1-3 yrs)	-2.0713 (28)	-1.3545 (27)	-0.2699 (27)*	0.5114 (27)*	2.5827
B	(-1– -2.5 SD, 1-3 yrs)	-1.7710 (45)	-2.3859 (49)	-1.5386 (50)	1 0429 (42)*	2.8139
C	(>-1 SD, > 3 yrs)	0.3824 (25)	1.5743 (29)	1.8695 (28)	3.3889 (28)*	3.0065
D	(-1– -2.5 SD, > 3 yrs)	-0.9623 (52)	0.4210 (52)*	1.4554 (55)*	2.5748 (56)*	3.5371
* Difference between active group and placebo was significant ($p < 0.05$).						
** Difference in the mean relative change between Ibandronate 2 5 mg Endpoint and Placebo Endpoint						

Subgroup analyses were also conducted for the following variables: baseline body weight (tertiles), calcium compliance (yes/no), and baseline vitamin D status (tertiles)(Table below). For the 2.5 mg dose, versus placebo, there was a significant increase in BMD from baseline to endpoint in all vitamin D tertiles. Compared to the analysis of the overall population, the mean changes in BMD in the 2.5 mg groups with higher vitamin D levels (tertiles 2 and 3) were larger. Subjects in the lowest vitamin D tertile (0–33 ng/ml) showed a smaller treatment effect across all active treatment groups. The number of subjects who were not compliant with calcium

supplementation was very low (N ≤ 27) in all groups. Subjects in all groups who complied with the calcium supplement regimen had improved spine BMD changes when compared to non-compliant subjects. When analyzed by weight, subjects with the lowest weight (tertile1: 0-65.3kg) had the smallest increase in LS BMD compared to those in the upper tertiles. The change from baseline, compared to placebo, in all 3 tertiles showed dose-dependent increases similar to those seen in the primary analysis of the entire population.

MF4499: Subgroup Analyses for Spine (L1-L4) BMD: Mean Relative Change				
	Placebo	Oral Ibandronate		
BMD Subgroup		0.5 mg	1.0 mg	2.5 mg
	% change (n)	% change (n)	% change (n)	% change (n)
Vitamin D (ng/ml)				
1st tertile (0–33)	-0.9371 (56)	-0.6145 (54)	0.1685 (56)	1.3372 (63) *
2nd tertile (> 33–45)	-1.1218 (45)	-0.3163 (55)	0.2586 (51)	2.4276 (43) *
3rd tertile (> 45)	-1.5689 (48)	-0.7366 (48)	0.4821 (53) *	2.3321 (46) *
Calcium Compliance				
Compliant	-0.9845 (128)	-0.5827 (130)	0.5398 (138) *	2.2486 (128) *
Non-compliant	-2.3709 (22)	-0.3773 (27)	-1.1962 (22)	0.3545 (25) *
Weight (kg)				
1st tertile (0–65.3)	-0.8904 (49)	-1.1194 (51)	-0.2041 (60)	1.2891 (49) *
2nd tertile (65.3–76.8)	-2.3632 (41)	-0.8980 (50)	0.3047 (54) *	2.4543 (52) *
3rd tertile (> 76.8)	-0.4964 (58)	0.2911 (55)	0.8760 (45)	2.1602 (50) *
* Difference between active group and placebo was significant (p < 0.05)				

COMMENT: The subgroup analyses consist of relatively small sample sizes per stratum, making interpretation of the data difficult.

Secondary Efficacy Outcomes

Bone Mineral Density of Proximal Femur: In general, the ibandronate groups showed dose-dependent increases in mean change from baseline BMD at the proximal femur (total hip, femoral neck, trochanter and Ward's triangle) versus that for placebo (Table below). The largest increases in proximal femur BMD relative to placebo were observed with the 2.5 mg dose of ibandronate (p<0.05 at all skeletal sites).

MF4499: Summary of Hip BMD: Mean Relative Change from Baseline to Endpoint (ITT)					
	Placebo	Oral Ibandronate			
		0.5 mg	1.0 mg	2.5 mg	** 2.5 mg-Placebo
Hip Region	% change	% change	% change	% change	% change
	(n=150)	(n=156))	(n=159))	(n=153))	
Total Hip	-0.5840	-0 4871	-0.0160	1.2199*	1.8039
Femoral Neck	-1.6250	-0.9041	-0.3213*	0.3377*	1.9627
Trochanter	-0.1753	-0.3328	0.1892	1.8915*	2.0668
Ward's Triangle	-2.3209	-0 9835	-0.0267*	0.9751*	3.2960
* Difference between active group and placebo was significant (p < 0 05).					
** Difference in the mean relative change between Ibandronate 2 5 mg Endpoint and Placebo Endpoint					

Overall, women who were more than 3 years post-menopause at baseline (strata C and D) had larger gains in hip BMD than woman who were less than 3 year post-menopause at baseline (strata A and B)(Table below).

MF4499: Total Hip BMD by Stratum: Mean Relative Change				
	Placebo	Oral Ibandronate		
Stratum (T-Score, TSM)		0.5 mg	1.0 mg	2.5 mg
	% change (n)	% change (n)	% change (n)	% change (n)
A (>-1 SD,1-3 yrs)	-1.2204 (28)	-1.6585 (27)	-0.3670 (27)	0.3047 (27)
B (-1 to -2.5 SD, 1-3 yrs)	-0.6782 (45)	-0.4455 (49)	-1.0254 (50)	0.7271 (42) *
C (>-1 SD,> 3 yrs)	0.3515 (25)	0.3225 (28)	0.0428 (27)	2.5093 (28) *
D(-1 to -2.5 SD, > 3 yrs)	-0.6096 (52)	-0.3540 (52)	1.0451 (55) *	1.3860 (56) *
* Difference between active group and placebo was significant ($p < 0.05$).				

Bone Mineral Density of Forearm: BMD at the radius 1/3 and the ultra distal radius decreased from baseline for all groups (Table below).

MF4499: Forearm BMD: Mean Relative Change				
	Placebo	Oral Ibandronate		
Distal Forearm Region		0.5 mg	1.0 mg	2.5 mg
	% change (n)	% change (n)	% change (n)	% change (n)
Radius 1/3	-1.5062 (147)	-1.5635 (153)	-1.8064 (157)	-0.9378 (146)
Ultra Distal Radius	-1.6456 (147)	-1.7735 (153)	-1 9242 (157)	-1.6220 (146)

Bone Mineral Density of Total Body: Total body BMD decreased from baseline for all treatment groups in the primary analysis (Table below). The greatest reduction occurred in women who were less than 3 year post-menopause at baseline (strata A and B). Women who were greater than 3 years post-menopause (strata C and D) showed small increases in total body BMD with the 2.5 mg dose of ibandronate. The difference between the placebo and 2.5 mg groups in osteopenic patients (strata D and B) was significant at Month 24 ($p<0.05$).

MF4499: Total Body BMD by Stratum: Mean Relative Change				
	Placebo	Oral Ibandronate		
		0.5 mg	1.0 mg	2.5 mg
	% change (n)	% change (n)	% change (n)	% change (n)
Total Body	-1.4335 (147)	-1.4583 (154)	-1.1345 (156)	-0.3092 (144)*
Stratum (T-Score, TSM)				
A (>-1 SD, 1-3 yrs)	-1.6123 (27)	-1.8041 (27)	-1.3362 (26)	-1.1916 (26)
B (-1 to -2.5 SD, 1-3 yrs)	-2.4915 (45)	-2.4321 (49)	-2.5278 (50)	-0.9599 (38)*
C (>-1 SD, > 3 yrs)	-0.3023(25)	-0.6631 (28)	-0.5383 (27)	0.1867 (27)
D (-1 to -2.5 SD, > 3 yrs)	-0.9503 (50)	-0.7625 (50)	-0.0711 (54)	0.3376 (53)*
* Difference between active group and placebo was significant ($p < 0.05$)				

Bone Turnover Markers: A summary of bone turnover markers at study end are presented in the table below. Serum CTX concentrations were decreased from baseline in a dose-dependent fashion with 0.5 mg, 1.0 mg, and 2.5 mg ibandronate treatment. A consistent suppression of serum CTX, with a median of approximately 35% from baseline, was observed in the 2.5 mg dose group beginning at Month 1, while median serum CTX

concentrations in the placebo group increased by 12% from baseline to Month 24. At all time points, the decrease in serum CTX in the 2.5 mg group was significantly different from placebo. Urinary CTX excretion showed a consistent dose-dependent reduction throughout the study. At all time points, the decrease in median urinary CTX values for the 2.5 mg group differed significantly from placebo. Median serum osteocalcin values decreased gradually over the first 6 months for all groups, including placebo, and remained essentially unchanged throughout the remainder of the study. Ibandronate treatment with 2.5mg daily resulted in a significant reduction from baseline in serum osteocalcin concentrations, as compared to placebo ($p < 0.001$).

MF4499: Bone Turnover Markers Relative Change After 24 Mos

		Baseline	Absolute Value	Change (%)
Serum CTX				
Placebo	Median	0.28	0.29	12.43
	p-Value (a)			0.0000*
Iban 0.5 mg	Median	0.24	0.25	8.58
	p-Value (b)			0.6086
Iban 1.0 mg	Median	0.25	0.24	-7.10
	p-Value (b)			0.0935
Iban 2.5 mg	Median	0.27	0.16	-35.14
	p-Value (b)			0.0000*
Urinary CTX/Creatinine				
Placebo	Median	7.12	6.80	-4.44
	p-Value (a)			0.0000*
Iban 0.5 mg	Median	6.56	6.17	-0.53
	p-Value (b)			0.5624
Iban 1.0 mg	Median	7.12	5.66	-19.09
	p-Value (b)			0.0013
Iban 2.5 mg	Median	7.01	4.36	-40.65
	p-Value (b)			0.0000*
Serum Osteocalcin				
Placebo	Median	32.54	27.58	-10.26
	p-Value (a)			0.0000*
Iban 0.5 mg	Median	30.30	23.91	-17.96
	p-Value (b)			0.0374
Iban 1.0 mg	Median	29.58	23.77	-22.08
	p-Value (b)			0.0002*
Iban 2.5 mg	Median	31.59	19.75	-33.66
	p-Value (b)			0.0000*

(a) Kruskal-Wallis-test: all treatment groups versus placebo

(b) Kruskal-Wallis-test: current treatment group versus placebo

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

For serum PTH, all ibandronate dose groups showed varied changes from baseline that were not strictly dose-dependent, as compared to placebo. At Month 24, serum PTH concentrations increased slightly from baseline for the 2.5 mg group, with a median relative change of 1.1%, but the difference from placebo was not statistically significant .

Medical Officer's Conclusions

The results of this study demonstrated a dose-related increase in BMD of the LS and proximal femur, as well as dose-related decreases in biochemical markers of bone turnover. The 2.5 mg dose of ibandronate was clearly the most efficacious dose with a placebo-subtracted increase in LS BMD of 3.1% .

The treatment effect of oral ibandronate in women with normal spine BMD at baseline (T-score >-1 SD) was compared with that seen in osteopenic women (T-score ≥ -2.5 SD and ≤ -1 SD), with a further analysis of these two groups stratified by time since menopause: 1-3 years, and > 3 years. Treatment with 2.5 mg oral ibandronate increased BMD of the LS and total hip in both normal and osteopenic women, with significant effects seen in women at both the early and later stages of menopause. Women who were less than 3 years post-menopause (strata A and B) who received 2.5 mg ibandronate showed smaller increases in spine and total hip BMD than women more than 3 years post-menopause (strata C and D). These results suggest that while ibandronate 2.5 mg daily increases BMD regardless of time since menopause and baseline bone density, greater efficacy may be seen in osteopenic women at later stages of menopause.

VI.C.2.b 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 a weekly oral (5 mg, 10 mg, 20 mg) dosing regimen. The primary objective was to examine the change in LS BMD from baseline to Year 2.

A total of 630 postmenopausal non-osteoporotic women were randomized in equal allocation to placebo, 5 mg, 10 mg or 20 mg ibandronate once-weekly. Baseline demographic characteristics were balanced across the groups: the mean age was 55 years, the mean time since menopause was 4.5 years and the mean LS BMD T-score was –1.1. Approximately 85% of the subjects completed the study.

Over two years, treatment with placebo resulted in an average decrease in LS BMD of 1.1%, while weekly dosing with 10 mg and 20 mg ibandronate significantly increased BMD by 0.7% ($p<0.05$) and 2.9% ($p<0.05$), respectively. Significant increases in BMD at the hip were also seen for the two highest doses of ibandronate compared with placebo. Markers of bone turnover were significantly decreased by Month 3 of treatment with 10 mg and 20 mg ibandronate once-weekly.

Please see Appendix XI.A.5. for the full study summary.

VI.D. Efficacy Conclusions

VI.D.1. Treatment of PMO: The treatment of PMO indication is supported by study MF4411 which enrolled 2946 postmenopausal women with low bone mineral density and prevalent vertebral fractures. Oral ibandronate 2.5 mg daily was efficacious in preventing morphometric vertebral fractures: The number of subjects with new fractures and the corresponding incidence rates estimated by life-table analysis were 37 subjects (4.7%) in 2.5 mg and 39 subjects (4.9%) in 20 mg compared to 73 subjects (9.6%) in placebo. The p-values for the treatment effect in the ITT population were p = 0.0003 for the 2.5 mg group and p = 0.0005 for the 20 mg group. There was also a statistically significant reduction in the incidence of clinical vertebral fractures (fractures diagnosed on the basis of clinical symptoms). However, the incidence of clinical non-vertebral fractures was similar in all treatment groups (placebo: 8.2%; 2.5 mg: 9.1%; 20 mg: 8.9%). Treatment with oral ibandronate 2.5 mg daily produced statistically significant increases in BMD compared to placebo. This was most evident at the lumbar spine. Bone resorption markers were significantly suppressed at 3–6 months into the study and remained suppressed thereafter. Markers of bone formation were also significantly reduced by 3–6 months after initiation of treatment. Histomorphometric data from bone biopsies confirmed that active treatment reduced the rate of bone turnover without evidence of mineralization defects.

VI.D.2. Prevention of PMO: The results of study 4499 demonstrated the 2.5 mg daily oral ibandronate dose was more efficacious than the 0.5 mg and 1.0 mg doses in preventing bone loss of the spine and hip in a population of postmenopausal, non-osteoporotic women. Significant increases in bone mineral density were seen at Month 6 and at all subsequent time points. Treatment with 2.5 mg daily oral ibandronate increased BMD of the lumbar spine and total hip in both normal and osteopenic women, with significant effects seen in women at both the early and later stages of menopause. Biochemical markers of bone turnover supported the BMD data with bone resorption marker suppression achieved at Month 1 and at all subsequent time points. Similar inhibition was observed for markers of bone formation.

Because the women in study 4499 were instructed to fast 30 minutes, as opposed to 60 minutes post-dose, as was done in the pivotal treatment trial 4411, it's safe to conclude that the treatment effects in study 4499 would have been larger if women had fasted for 60 minutes post-dose.

VI.D.3. Appropriate Dose: In study 4348, placebo-subtracted increases in BMD were very similar for the 2.5 mg and 5.0 mg daily doses of ibandronate, but the rate of withdrawal due to adverse events was 2-3 times higher for the 5.0 mg dose group. For these reasons, the 2.5 mg daily dose appears to be the most appropriate dose for marketing for both the treatment and prevention of PMO indications.

VII. Integrated Review of Safety

VII.A. Brief Statement of Conclusions

A total of 3746 subjects received at least one dose of ibandronate and 1401 at least one dose of placebo during the conduct of 7 phase 2/3 postmenopausal osteoporosis prevention and treatment trials ranging in duration from 1 to 3 years. A slightly higher percentage of ibandronate-treated women reported dyspepsia, diarrhea, and esophagitis when compared with placebo-treated subjects. A greater number of ibandronate vs. placebo-treated participants developed low serum phosphate levels in two small studies. The clinical significance of this finding is questionable, however, since the incidence of abnormal laboratory parameters was similar in the active vs. placebo groups from the large, long-term pivotal study MF4411. No abnormalities in bone histomorphometry were noted in a subgroup of subjects who had bone biopsies.

VII.B. Description of Patient Exposure: The tables below outline the cumulative drug exposure for all treatment and prevention trials. The cumulative dose was estimated based on mean days of trial treatment and dose.

Cumulative Patient Drug Exposure – Treatment Trials				
Study	Trial Dose	N	Mean Days	Cumulative dose
MF4411	2.5mg daily	977	905	2262mg
	20mg intermittent	977	898	2395mg
MF4433	Plac/2.5mg daily	37	332	830mg
	Plac/20mg int	35	318	848mg
	2.5mg daily	81	629	1572mg
	20mg intermittent	78	620	1653mg
MF4348	0.25mg daily	30	303	76mg
	0.5mg daily	29	265	132mg
	1.0mg daily	30	299	299mg
	2.5mg daily	28	300	750mg
	5.0mg daily	30	231	1155mg
75003	2.5mg daily	121	305	762mg
	20mg weekly	114	307	819mg
MF4491	2.5mg daily	213	322	805mg

Cumulative Patient Drug Exposure – Prevention Trials				
Study	Trial Dose	N	Mean Days	Cumulative dose
MF4499	0.5mg daily	161	656	328mg
	1.0mg daily	165	662	662mg
	2.5mg daily	163	630	1575mg
MF4500	5mg weekly	155	662	473mg
	10mg weekly	153	670	957mg
	20mg weekly	158	648	1851mg

VII.C. Methods and Specific Findings of Safety Review: Of the 7 phase 2/3 clinical studies conducted to evaluate the efficacy and safety of the 2.5 mg daily oral dose of ibandronate, the vast majority of patient-years of placebo-controlled exposure comes from the treatment trial 4411 and the prevention trial 4499. For this reason, the company did not pool data for analyses of safety, but instead, and we think reasonably, focused attention on the two pivotal trials.

There are currently six bisphosphonates approved by the Agency, with alendronate and risedronate the only two with indications for the treatment and prevention of PMO. The principal safety concerns for bisphosphonates include GI toxicity, inappropriate lowering of serum calcium, phosphorus, and magnesium levels, and abnormal mineralization of bone that would increase risk for fracture.

There were no unexpected safety findings noted in this application. A slightly higher percentage of ibandronate- vs. placebo-treated patients reported upper GI adverse events, but there were no significant differences between groups in reports of abnormal levels of serum calcium or phosphorus. Long-term fracture and bone biopsy data did not indicate any evidence of drug-induced osteomalacia or other mineralization abnormalities.

VII.C.1 Safety Evaluation for the Treatment Trials

VII.C.1.a Study MF 4411: This was a randomized, double-blind, placebo-controlled, 3-year study of postmenopausal osteoporotic women. A total of 982 subjects were enrolled into each treatment group (placebo, 2.5mg ibandronate daily and 20mg ibandronate intermittently). The mean age of the participants was 69 years, and 98% of the subjects were Caucasian. Approximately 64.0% of placebo, 66.3% of ibandronate 2.5mg, and 67.8% of ibandronate 20mg subjects completed the trial

Safety Measurements: Clinical adverse events were monitored continuously throughout the study. Adverse events of special interest included stomach pain, abdominal pain, heartburn, esophagitis (confirmed by endoscopy), fever exceeding 38.5°C, bone pain, muscle ache-like pain, and flu-like symptoms. Laboratory assessments included hemoglobin, hematocrit, erythrocytes, leukocytes, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils serum calcium, phosphate, sodium, potassium, chloride, alanine aminotransferase (ALT), δ-glutamyl transferase (GGT), alkaline phosphatase (AP), creatinine and 25-(OH)-Vitamin D. Transiliac bone biopsies were performed in 110 patients at selected centers and were taken either 22 or 34 months after randomization.

Drug Exposure: The mean total exposure to active drug was 2262 mg in the ibandronate 2.5 mg group and 2395 mg in the ibandronate 20mg intermittent group.

Study MF4411: Drug Exposure (days)			
	Placebo (N=975)	Iban 2.5mg qd (N=977)	Iban 20mg int (N=977)
MEAN	883.3	905.2	897.9
SD	368.6	346.8	357.7

Withdrawals: As shown in the table below, a total of 35.6% of placebo, 33.7% of 2.5 mg, and 32.2% of 20 mg subjects withdrew early from the trial. The majority of withdrawals in each group were secondary to adverse events.

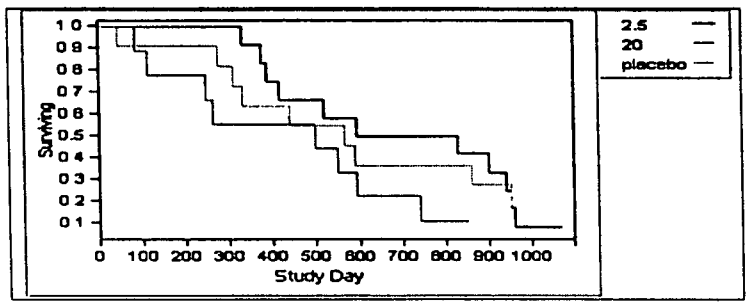
Study MF4411: Withdrawals			
	Year 1 N (%)	Year 2 N(%)	Year 3 N(%)
Placebo (N=975):			
Completed	777 (79.7)	709 (72.7)	628 (64.4)
Withdrew -AE	107 (11.0)	149 (15.3)	180 (18.5)
Withdrew - Other	91 (9.3)	117 (12.0)	167 (17.1)
Iban 2.5mg qd (N=977):			
Completed	805 (82.4)	724 (74.1)	648 (66.3)
Withdrew -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)

Death: As shown in the table below, a total of 29 patients died on-study: 10 in the placebo group, 11 in the 2.5 mg group, and 8 in the 20 mg group. An additional 3 deaths (one in each treatment group) occurred off-study. The majority of deaths were due to cardiovascular events (6 in the placebo group, 6 in the 2.5 mg group and 3 in 20 mg group), followed by malignancies (3 in the placebo group, 3 in the 2.5 mg group and 4 in 20 mg group).

Study MF4411: Deaths					
Subject	Age (yrs)	Dose	Treatment (days)	Day of Onset	Cause
10/6078	70	placebo	589	590	Cerebrovascular Accident
10/6097	63	placebo	564	564	Mesenteric Artery Occlusion
15/6830	76	placebo	953	954	Sudden Death
15/6831	70	placebo	1008	1009	Myocardial Infarction
15/6867	75	placebo	277	278	Myocardial Infarction
15/6879	76	placebo	952	957	Cerebrovascular Accident
36/8281	61	placebo	441	220	CNS Neoplasm
40/8049	75	placebo	334	289	Cerebral Hemorrhage
46/5659	68	placebo	309	299	Lung Carcinoma
54/7652	63	placebo	862	862	Gastrointestinal Carcinoma
66/7793	72	placebo	44	86	Carcinoma
1/8624	75	Iban 2.5mg qd	843	762	Lung Carcinoma
3/7099	\79	Iban 2 5mg qd	760	832	Bladder Carcinoma
11/5794	79	Iban 2.5mg qd	944	944	Sudden Death
12/6984	77	Iban 2.5mg qd	376	376	Acquired Aneurysm
36/5971	65	Iban 2.5mg qd	390	331	Coronary Artery Disorder
36/6624	72	Iban 2 5mg qd	519	338	Endometrial Carcinoma
36/6638	70	Iban 2.5mg qd	595	595	Acquired Aneurysm
36/8242	65	Iban 2.5mg qd	953	954	Myocardial Infarction
36/8354	77	Iban 2.5mg qd	331	331	Accidental Injury
40/8522	79	Iban 2.5mg qd	1076	1076	Cerebrovascular Accident
54/7929	68	Iban 2.5mg qd	964	964	Myocardial Infarction
4/8068	76	Iban 2.5mg qd	418	666	Pneumonia

Study MF4411: Deaths					
12/8009	69	Iban 20mg int	595	595	Accidental Injury
36/6031	75	Iban 20mg int	743	743	Acquired Aneurysm
36/8406	74	Iban 20mg int	855	855	Cerebral Hemorrhage
42/7015	71	Iban 20mg int	65	8	Liver Carcinoma
49/6433	76	Iban 20mg int	251	251	Heart Failure
51/7553	69	Iban 20mg int	551	518	Gastrointestinal Carcinoma
69/5548	69	Iban 20mg int	267	268	Carcinoma
93/7603	77	Iban 20mg int	115	117	Lung Carcinoma
13/5850	76	Iban 20mg int	500	525	Lung Carcinoma

COMMENT: There were no significant imbalances in the rates or causes of death across the three groups, as shown in the following Kaplan Meier survival plot.



Serious Adverse Events: Slightly higher numbers of SAEs were recorded in the ibandronate treatment groups (21.6% of patients with a total of 303 events in the placebo group, 24.0% of patients with a total of 340 events in the ibandronate 2.5mg daily group and 25.3% of patients with a total of 334 events in the ibandronate 20mg intermittent group). The table below outlines the events by body system. Multiple occurrences of the same event in a single individual are counted once.

Study MF4411: Serious Adverse Events			
Body System/Adverse Event	**Placebo**	**Iban 2.5mg qd**	**Iban 20mg int**
	N (%)	**N (%)**	**N(%)**
All Body Systems	**211 (21.6)**	**234 (24.0)**	**247 (25.3)**
Cardiovascular System	70 (7.2)	86 (8.8)	73 (7.5)
Musculoskeletal System	48 (4.9)	53 (5.4)	57 (5.8)
Digestive System	40 (4.1)	39 (4.0)	45 (4.6)
Body as a Whole	28 (2.9)	30 (3.1)	33 (3.4)
Skin and Appendages	23 (2.4)	26 (2.7)	24 (2.5)
Respiratory System	18 (1.8)	21 (2.1)	23 (2.4)
Urogenital System	15 (1.5)	19 (1.9)	23 (2.4)
Nervous System	11 (1.1)	16 (1.6)	8 (0.8)
Special Senses	8 (0 8)	10 (1 0)	13 (1.3)
Endocrine System	5 (0.5)	1 (0.1)	4 (0.4)
Hematologic and Lymphatic System	2 (0.2)	5 (0.5)	2 (0.2)
Metabolic and Nutritional System	1 (0.1)	6 (0.6)	2 (0.2)

Similar to the rates observed for the total number of SAEs, the percentage of SAEs leading to hospitalization was slightly increased in the ibandronate treated groups relative to placebo: 17.8% of patients with a total of 242 events in the placebo group, 19.8% of patients with a total of 271 events in the ibandronate 2.5mg daily group and 20.9% of patients with a total of 270 events in the ibandronate 20mg intermittent group.

Adverse Events Leading to Withdrawal: The breakdown of adverse events leading to withdrawal is presented in the table below. There were no differences between the active-treatment and placebo groups.

Study MF4411: Adverse Events Leading to Withdrawal			
	Placebo	Iban 2.5mg daily	Iban 20mg int
N	975	977	977
	N (%)	N (%)	N (%)
Patients withdrawing due to AE			
Identified by Algorithm	180 (18.5)	175 (17.9)	178 (18.2)
Identified by Review of Comments	3 (0.3)	6 (0.6)	3 (0.3)
Total Pts withdrawing due to AE	183 (18.8)	181 (18.5)	181 (18.5)

Adverse Events: The incidence of the most frequent adverse events occurring at an incidence of ≥ 5% are outlined in the table below. With the exception of some GI adverse events, which occurred more frequently in active vs. placebo-treated subjects, the adverse event rates were similar among the treatment groups.

Study MF4411: Adverse Events			
Adverse Event	**Placebo**	**Iban 2.5mg qd**	**Iban 20mg int**
Upper Respiratory Infection	301 (30.9)	310 (31.7)	298 (30.5)
Accidental Injury	160 (16.4)	146 (14.9)	144 (14.7)
Back Pain	122 (12.5)	139 (14.2)	153 (15.7)
Arthralgia	132 (13.5)	132 (13.5)	145 (14.8)
Osteoporosis Fracture	109 (11.2)	96 (9.8)	102 (10.4)
Dyspepsia	89 (9.1)	111 (11.4)	88 (9.0)
Bronchitis	67 (6.9)	106 (10 8)	89 (9.1)
Hypertension	76 (7.8)	75 (7.7)	82 (8.4)
Pain in Extremity	60 (6.2)	74 (7.6)	77 (7.9)
Diarrhea	52 (5.3)	68 (7.0)	80 (8.2)
Constipation	61 (6.3)	48 (4.9)	68 (7.0)
Cystitis	62 (6.4)	64 (6.6)	51 (5.2)
Arthrosis	65 (6.7)	52 (5.3)	59 (6.0)
Gastroenteritis	54 (5.5)	54 (5.5)	62 (6.3)
Sinusitis	62 (6.4)	57 (5.8)	49 (5.0)
Pneumonia	46 (4.7)	60 (6.1)	61 (6.2)
Nausea	61 (6.3)	41 (4.2)	63 (6.4)
Urinary Tract Infection	39 (4.0)	55 (5.6)	57 (5.8)
Headache	49 (5.0)	58 (5.9)	43 (4.4)
Myalgia	50 (5.1)	49 (5 0)	49 (5 0)
Abdominal Pain	54 (5 5)	45 (4 6)	48 (4.9)
Cataract	56 (5.7)	48 (4.9)	43 (4.4)

COMMENT: The largest differences in rates of AE reporting between ibandronate and placebo-treated patients were for back pain, bronchitis, diarrhea, pneumonia, and urinary tract infection. Based on mechanism of action and safety data from other oral bisphosphonates, it is difficult to conclude that any of these adverse events (except diarrhea) are causally associated with use of ibandronate.

Gastrointestinal Adverse Events: As outlined in the table below, the absolute incidence of GI adverse events was low in all groups. Dyspepsia, diarrhea, and esophagitis were reported more frequently in the ibandronate 2.5 mg-treated groups relative to placebo.

Study MF4411: Gastrointestinal Adverse Events			
Adverse Event	**Placebo**	**Iban 2.5mg qd**	**Iban 20mg int**
Dyspepsia	89 (9.1)	111 (11.4)	88 (9.0)
Nausea	61 (6.3)	41 (4.2)	63 (6.4)
Diarrhea	52 (5.3)	68 (7.0)	80 (8.2)
Gastroenteritis	54 (5.5)	54 (5.5)	62 (6.3)
Abdominal Pain	54 (5.5)	45 (4.6)	48 (4.9)
Gastrointestinal Pain	25 (2.6)	19 (1.9)	24 (2.5)
Esophagitis	10 (1.0)	15 (1.5)	10 (1.0)
Esophageal Ulcer	1 (0.1)	2 (0.2)	1 (0.1)
Esophageal Stenosis	1 (0.1)	2 (0.2)	0 (0.0)
Gastritis	21 (2.2)	22 (2.3)	12 (1.2)
Peptic Ulcer	7 (0.7)	3 (0.3)	7 (0.7)
Duodenitis	3 (0.3)	2 (0.2)	2 (0.2)
Duodenal Ulcer	9 (0.9)	1 (0.1)	1 (0.1)
UGI Hemorrhage	6 (0.6)	5 (0.5)	3 (0.3)
Gastrointestinal Carcinoma	5 (0.5)	7 (0.7)	4 (0.4)

COMMENT: Concomitant use of anti-inflammatory medication was not excluded in this study. Approximately 36% of participants used anti-inflammatory medications (excluding steroids) at some point during the 3 years of the study. Approximately 50% of subjects used anti-peptic and anti-ulcerant medications at some point during the three years of the trial. Subjects with a prior history of gastrointestinal diseases were not excluded from enrollment in this study. Approximately 26% of participants had concomitant gastrointestinal disease. To the extent that this pattern of concomitant drug use mirrors clinical practice, it provides some reassurance regarding the GI toxicity profile of ibandronate.

Safety Laboratories: No major imbalances in mean changes from baseline or the number of abnormal values were found between treatment groups. In particular, there was no increase in abnormalities of hepatic or renal function in the ibandronate groups. Alkaline phosphatase activity decreased in both active-treatment groups, which is consistent with the pharmacological effect of the drug. No clinically relevant differences in high or low shifts in laboratory parameters were observed among the treatment groups.

A summary of markedly abnormal laboratory results is listed in the table below. Four subjects withdrew from the study because of laboratory abnormalities. One placebo subject withdrew because of elevated GGT levels. One ibandronate 2.5 mg subject withdrew because of elevated ALT levels. And two subjects in the 20 mg group withdrew, one because of pre-treatment hypercalcemia and the other because of abnormal LFTs. (Marked laboratory abnormalities are defined in appendix XI.A.1.c)

Study MF4411: Marked Laboratory Abnormalities			
Laboratory	**Placebo**	**Iban 2.5mg**	**Iban 20mg**
N	888	920	906
Hematocrit – low	19 (2.1)	18 (2.0)	16 (1.8)
Hemoglobin – low	10 (1.1)	10 (1.1)	8 (0.9)
Platelets - low	6 (0.7)	4 (0.4)	7 (0.8)
Eosinophils -high	2 (0.2)	3 (0.3)	3 (0.3)
Lymphocytes - low	31 (3.5)	39 (4.2)	46 (5.1)
ALT - high	4 (0.4)	7 (0.8)	4 (0.4)
Alk. Phos. - high	0 (0)	2 (0.2)	2 (0.2)
GGT - high	18 (2.0)	18 (2.0)	29 (3.0)
Creatinine – high	1 (0.1)	2 (0.2)	3 (0.3)
Calcium – high	0 (0)	1 (0.1)	1 (0.1)
Calcium – low	2 (0.2)	3 (0.3)	1 (0.1)
Phosphate – high	7 (0.8)	11 (1.2)	13 (1.4)
Phosphate – low	6 (0.7)	9 (1.0)	9 (1.0)

COMMENT: The finding of an increased percentage of ibandronate-treated subjects who developed elevated levels of serum phosphorus is unexpected – hypophosphatemia would be expected – and likely of no clinical relevance.

Bone Histology: Bone biopsies were obtained in 110 subjects (36 in the placebo group, 40 and in the 2.5 mg ibandronate group and 34 in the 20 mg ibandronate group). The primary safety parameter was osteoid thickness. A change of less than 2.5 μm was the safety limit. There was a slight tendency toward reduction in osteoid thickness in the ibandronate groups. This would be expected as a consequence of reduced bone turnover. This reduction was more pronounced for the ibandronate 2.5 mg daily group than for the ibandronate 20 mg intermittent group, consistent with the daily regimen's greater ability to suppress bone turnover. There was no evidence for mineralization defects associated with ibandronate administration. Since the mean value of osteoid thickness did not change by 2.5 μm or more in either ibandronate group vs. placebo, the pre-defined criterion of safety was satisfied.

Study MF4411: Bone Histology			
Parameter	**Placebo**	**Iban 2.5mg qd**	**Iban 20mg int**
Month 22	**14**	**16**	**15**
Osteoid thickness (μm)	5 289 ± 1 625	3.826 ± 0 506	4 567 = 1 005
Osteoid Volume (%)	1 007 ± 0 807	0 454 ± 0.397	0.587 = 0 485
Mineral Apposition Rate (μm/d)	0.428 ± 0 083	0.462 ± 0.091	0 449 = 0.107
Adjusted Apposition Rate (μm/d)	0 201 ± 0 145	0 110 ± 0.115	0.175 = 0 117
Osteoid Surface (%)	9 600 ± 7 078	5.138 ± 4.011	5.387 = 3.612
Activation Frequency (per yr)	0 351 ± 0.375	0 104 ± 0 113	0.223 = 0.306
Osteoclast Number (per mm^2 BS)	0 152 ± 0 144	0 148 ± 0 104	0.160 = 0 164
Bone Formation Rate ($\mu m^3/\mu m^3/d$)	0 025 ± 0 027	0 007 ± 0 007	0.016 = 0.019

Study MF4411: Bone Histology			
Parameter	**Placebo**	**Iban 2.5mg qd**	**Iban 20mg int**
Bone Volume (%)	16.014 ± 6.621	13.444 ± 4.949	16.187 ± 5.425
Trabecular Thickness (μm)	140.71 ± 45.77	108.88 ± 19.66	120.87 ± 27.70
Cortical Thickness (μm)	774.21 ± 260.66	648.36 ± 286.31	601.07 ± 206.53
Month 34	**19**	**20**	**16**
Osteoid thickness (μm)	4.863 ± 0.881	4.579 ± 0.852	4.988 ± 1.030
Osteoid Volume (%)	0.616 ± 0.348	0.750 ± 1.045	0.728 ± 0.556
Mineral Apposition Rate (μm/d)	0.419 ± 0.089	0.550 ± 0.379	0.496 ± 0.076
Adjusted Apposition Rate (μm/d)	0.199 ± 0.115	0.167 ± 0.132	0.139 ± 0.124
Osteoid Surface (%)	6.068 ± 3.328	7.685 ± 9.089	7.481 ± 5.381
Activation Frequency (per yr)	0.258 ± 0.173	0.275 ± 0.438	0.169 ± 0.138
Osteoclast Number (per mm^2 BS)	0.116 ± 0.070	0.170 ± 0.256	0.126 ± 0.191
Bone Formation Rate ($\mu m^3/\mu m^2/d$)	0.018 ± 0.012	0.020 ± 0.032	0.012 ± 0.009
Bone Volume (%)	13.268 ± 4.434	16.055 ± 6.010	16.213 ± 4.885
Trabecular Thickness (μm)	118.05 ± 26.24	128.65 ± 39.07	130.50 ± 36.25
Cortical Thickness (μm)	725.32 ± 260.64	713.05 ± 308.47	785.38 ± 330.86

VII.C.1.b. Study MF4433 - This study was a 2-year, single-center, randomized, double-blind, placebo-controlled study. Placebo patients were crossed over to active treatment after 1 year. A total of 240 patients were enrolled into the study (year 1 – 81 in placebo, 81 in 2.5 mg daily, 78 in 20 mg intermittently). Subjects were at least 5 years post last menstruation, aged 55 - 75 years and had LS BMD T-scores ≤-2.5. The treatment groups were well-balanced with respect to age, height, and body weight. The average age of participants was 66.5 years.

Safety Measurements: Clinical adverse events were monitored continuously throughout the study. Adverse events of special interest included stomach pain, abdominal pain, heartburn, esophagitis (confirmed by endoscopy), fever exceeding 38.5°C, bone pain, muscle ache-like pain, and flu-like symptoms. Laboratories for safety analysis included red blood cell count, white blood cell count (neutrophils, lymphocytes, monocytes, basophils, eosinophils), hemoglobin, hematocrit, and platelet count and blood chemistries - calcium, potassium, and sodium, total alkaline phosphatase, SGOT (AST), SGPT (ALT), and creatinine.

Withdrawals: A total of 53 (22.1%) subjects withdrew from the study for any reason. During the placebo-controlled period, 32 subjects (13.3%) withdrew prematurely. The majority of the subjects withdrew because of adverse events. The table below outlines the patient disposition of the study.

Study MF4433: Withdrawals				
Year 1	**Placebo**		**2.5mg daily**	**20mg int**
N	81		81	78
W/D AE	8		8	11
W/D Other	1		3	1
Completed	72		70	66
Year 2	**2.5mg daily**	**20 mg int**	**2.5 mg daily**	**20 mg int**
N	37	35		
W/D AE	2	5	5	5
W/D Other	2	2	0	0
Completed	33	28	65	61

Patient Exposure: The mean total exposure to active drug was 1572 mg in the ibandronate 2.5 mg daily group, 1653 mg in the ibandronate 20 mg intermittent group, 830 mg in the placebo/ibandronate 2.5 mg daily group and 848 mg placebo/ibandronate 20 mg intermittent group (Table below).

Study MF4433: Drug Exposure					
	Placebo	Placebo/ 2.5 mg	Placebo/ 20 mg	2.5 mg	20 mg
N	81	37	35	81	78
MEAN	334.78	331.73	317.86	629.11	619.78
SD	93.70	89.30	103.04	222.13	220.15

Death: During the study, four subjects died. Three of the deaths occurred while the subjects were on-study and one death occurred 363 days after the patient had withdrawn from treatment (Table below).

Study MF4433: Deaths					
Subject	Age (yrs)	Dose	Treatment (days)	Day of Onset	Cause
1/003	68	placebo	104	467	Gastrointestinal carcinoma
1/011	65	plac/ iban 20	453	475	Heart arrest
1/066	62	plac/ iban 20	549	549	Bronchitis
1/100	70	iban 20	443	443	Heart arrest

Serious Adverse Events A total of 33 subjects reported SAEs with 17 subjects reporting SAEs in Year 1 and an additional 16 subjects reporting SAEs in Year 2. Events are outlined in the table below. One subject had more than one adverse event during the trial.

Study MF4433: Serious Adverse Events					
Event	Placebo	Iban 2.5mg qd		Iban 20mg int	
	year 1	year 1	year 2	year 1	year 2
All Body Systems	7	6	5	4	12
Cardiovascular System	-	-	1	1	4
Musculoskeletal System	1	-	1	-	3
Digestive System	3	3	1	-	1
Body as a Whole	-	-	-	1	-
Skin and Appendages	-	2	-	-	-
Respiratory System	-	1	-	1	1
Urogenital System	1	-	-	1	2
Nervous System	2	-	1	-	1
Special Senses	-	-	1	-	-
Endocrine System	-	-	-	-	-

Adverse Events Leading to Withdrawal A total of 45 subjects experienced AEs, which led to withdrawal from treatment (Table below). Of these, 31 patients had an AE in Year 1 and 14 during Year 2. A slightly higher incidence of withdrawals due to AEs during Year 1 was observed in the ibandronate 20 mg intermittent group (14%) and the ibandronate 2.5 mg daily group (13%) compared to the placebo group (11%). The most frequently reported AE leading to withdrawal from treatment in Year 1 was diarrhea in the ibandronate 2.5 mg daily group (4%).

Study MF4433: Adverse Events Leading to Withdrawal			
Event	Placebo	Iban 2.5mg	Iban 20mg
	year 1	year 1 + 2	year 1 + 2
All Body Systems	9 (11.1)	13 (16.0)	16 (20.5)
Cardiovascular System	-	2	4
Musculoskeletal System	2	2	2
Digestive System	6	7	7
Body as a Whole	1	-	-
Skin and Appendages	-	-	1
Respiratory System	-	-	-
Urogenital System	-	-	1
Nervous System	2	3	3
Special Senses	-	-	1
Endocrine System	-	2	-

Adverse Events: Overall, the adverse event rates were similar among the treatment groups. Gastrointestinal adverse events were slightly more frequent in the ibandronate 2.5 mg group, as shown in the table below. In the placebo group respiratory infection (28%), nausea (11%), infection (10%), and cystitis (10%) were the most frequently reported events. In the ibandronate 2.5 mg daily group, upper respiratory tract infection (21%), infection (17%), diarrhea (11%) and headache (14%) were the most common events. In the ibandronate 20 mg intermittent group, upper respiratory tract infection (18%), infection (9%), and diarrhea (10%) were most common.

Study MF4433: Adverse Events					
Event	Placebo	Iban 2.5mg qd		Iban 20mg int	
	year 1	year 1	year 1 + 2	year 1	year 1 + 2
At Least One AE	74 (91.4)	72 (88.9)	77 (95.1)	61 (78.2)	71 (91.0)
Cardiovascular System	8 (9.9)	8 (9.9)	13 (16.0)	8 (10.3)	11 (14.1)
Musculoskeletal System	19 (23.5)	19 (23.5)	26 (32.1)	11 (14.1)	17 (21.8)
Digestive System	29 (35.8)	33 (40.7)	41 (50.6)	26 (33.3)	33 (42.3)
Body as a Whole	25 (30.9)	28 (34.6)	40 (49.4)	21(26.9)	30 (38.5)
Skin and Appendages	9 (11 1)	10 (12.3)	14 (17.3)	1 (1.3)	2 (2.6)
Respiratory System	34 (42.0)	1 (1.2)	37 (45.7)	1 (1.3)	39 (50.0)
Urogenital System	10 (12 3)	6 (7.4)	9 (11 1)	8 (10.3)	13 (16.7)
Nervous System	16 (19 8)	19 (23.5)	22 (27.2)	14 (17.9)	16 (20.5)
Special Senses	4 (4 9)	6 (7.4)	8 (9.9)	4 (5.1)	6 (7.7)
Endocrine System	1 (1.2)	2 (2.5)	2 (2.5)	0 (0.0)	0 (0.0)
Heme and Lymphatic System	1 (1.2)	0 (0 0)	1 (1.2)	1 (1.3)	1 (1.3)
Metab and Nutrition System	1 (1.2)	1 (1.2)	3 (3 7)	4 (5.1)	5 (6.4)

Gastrointestinal Adverse Events As shown in the table below, little difference was observed in the rate of gastrointestinal AEs reported by patients in the placebo group (35%), the ibandronate 2.5 mg daily group (35%), or the ibandronate 20 mg intermittent group (30%). During Year 1, diarrhea and constipation were more frequently reported in the ibandronate groups than in the placebo group, whereas, nausea and gastrointestinal disorder were less frequently reported in the ibandronate-treated patients than in the placebo patients. The majority of the gastrointestinal adverse events were reported in Year 1. Nine additional events were reported in the subjects who crossed over to ibandronate in Year 2: 3 (8.1%) in the ibandronate 2.5 mg daily group and 6 (17.1%) in the ibandronate 20 mg intermittent group.

Study MF4433: Gastrointestinal Adverse Events –Year 1			
Adverse Event	Placebo	Iban 2.5mg qd	Iban 20mg int
At least 1 GI AE	28 (34.6)	28 (34.6)	23 (29.5)
Dyspepsia, Dysphagia	2 (2.5)	3 (3.7)	1 (1.3)
Nausea	9 (11.1)	3 (3.7)	5 (6.4)
Diarrhea	1 (1.2)	9 (11.1)	8 (10.3)
Gastroenteritis	2 (2.5)	3 (3.7)	1 (1.3)
Abdominal Pain	2 (2.5)	0 (0.0)	1 (1.3)
Gastrointestinal Pain	1 (1.2)	2 (2.5)	4 (5.1)
Esophagitis	0 (0.0)	0 (0.0)	1(1.3)
Esophageal Ulcer	0 (0.0)	0 (0.0)	0 (0.0)
Esophageal Stenosis	0 (0.0)	0 (0.0)	0 (0.0)
Gastritis	0 (0.0)	2 (2.5)	1(1.3)
Peptic Ulcer	1 (1.2)	0 (0.0)	0 (0.0)
Gastrointestinal Carcinoma	1 (1.2)	2 (2.5)	0 (0.0)
Other GI disorder	13 (16.0)	13 (16.0)	8 (10.2)

Safety Laboratories No major imbalances in laboratory abnormalities were noted between treatment groups. In particular, there was no increase in abnormalities of hepatic or renal function in the ibandronate groups. Alkaline phosphatase levels decreased in both active-treatment groups, which is consistent with the treatment effect of the drug and reflects the reduction in bone-specific alkaline phosphatase. No clinically relevant differences in shifts in laboratory parameters were observed among the 3 groups. Twelve subjects experienced marked laboratory abnormalities during the study. A summary of markedly abnormal laboratory results is listed in the table below.

Study MF4433: Marked Laboratory Abnormalities				
Subject	Laboratory	Study Day	Change from baseline	Treatment group
YEAR 1				
245	MCH	29	+ 15%	Placebo
192	SGPT	123	+ 251%	Placebo
49	Potassium	62	- 18%	Iban 2.5mg qd
176	% Neutrophils	92	+ 58%	Iban 2.5mg qd
64	Alkaline Phos	179	+ 248%	Iban 2.5mg qd
6	% Neutrophils	356	+ 75%	Iban 2.5mg qd
20	Platelets	363	- 50 %	Iban 2.5mg qd
215	MCH	124	- 12 %	Iban 20mg int
27	% Lymphocytes	185	+ 80%	Iban 20mg int
YEAR 2				
231	Sodium	453	- 10%	Iban 2.5mg qd
19	SGPT	545	+ 483%	Iban 2.5mg qd
206	MCH	727	+ 10%	Iban 2.5mg qd

VII.C.1.c. Study MF4348: This was a randomized, placebo-controlled, double blind, single-center, dose-finding study of different daily oral doses (0.25, 0.5, 1.0, 2.5 and 5 mg) of ibandronate during 12 months' treatment in patients with postmenopausal osteoporosis. A total of 180 (30 in each group) subjects were enrolled in the trial. All demographic parameters were balanced between groups. The mean age of the subjects was 63 years.

Safety Measurements All AEs were reported continuously during the study. Laboratories for safety analysis included - hemoglobin, hematocrit, erythrocytes, leukocytes, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils and - serum calcium, phosphate, sodium, potassium, chloride, alanine aminotransferase (ALT), aspartate aminotransferase (AST), δ-glutamyl transferase (GGT), alkaline phosphatase (AP), serum albumin, blood urea nitrogen, and creatinine.

Withdrawals: Of the 180 subjects enrolled in the study, 41 withdrew prematurely [6 (20%) from placebo, 5 (17%) from 0.25 mg, 8 (27%) from 0.5 mg, 4 (13%) from 1.0 mg, 6 (20%) from 2.5 mg and 12 (40%) from 5.0 mg](Table below).

Study MF4348: Withdrawals						
	Placebo	0.25 mg	0.5 mg	1.0 mg	2.5 mg	5.0 mg
Randomized	30	30	30	30	30	30
Completed	24	25	22	26	24	18
W/D AE	5 (16.7)	3 (10.0)	4 (13.3)	3 (10.0)	4 (13.3)	9 (30.0)
W/D Other	1 (3.3)	2 (6.7)	4 (13.3)	1 (3.3)	2 (6.7)	3 (10.0)

Patient Exposure The mean total exposure to active drug was 76 mg in the 0.25 mg ibandronate group, 132 mg in the 0.5 mg group, 299 mg in the 1.0 mg/group, 750 mg in the 2.5 mg group and 1155 mg in the 5.0 mg group.

Study MF4348: Summary of Exposure (days)						
	Placebo	0.25 mg	0.5 mg	1.0 mg	2 5 mg	5.0 mg
N	30	30	29	30	28	30
MEAN	291.70	302.77	265.28	299.40	300.43	230.90
SD	104.90	93.13	133.19	102.51	97.56	139.57

Death: Two subjects died during the course of treatment: a 67-year-old woman on placebo suffered a cerebral hemorrhage on Day 82, was hospitalized and died 6 days later and a 75-year-old woman with a history of coronary artery disease who was randomized to ibandronate 2.5 mg died suddenly on Day 326.

Serious Adverse Events: Eight subjects, including the two who died, experienced nine serious AEs during the study. The highest incidence was in the placebo group. Of the eight subjects with serious AEs, seven were hospitalized due to serious AEs, and two withdrew from the study. Serious AEs reported during treatment comprised accidental injury (ankle fracture), spontaneous bone fracture, colitis, enteritis, and arterial thrombosis of the leg leading to surgery and consecutive wound infection, and breast carcinoma.

Adverse Events Leading to Withdrawal Twenty-eight (15.6%) subjects were withdrawn from treatment because of an AE. Withdrawals due to AEs were more frequent in the 5.0 mg ibandronate group (30%) than in the other treatment groups (10-16.7%). The most frequent reasons for withdrawal were gastrointestinal complaints (diarrhea, nausea, dyspepsia, and constipation).

Study MF4348: Adverse Events Leading to Withdrawal						
Event	Placebo	0.25mg	0.5mg	1.0mg	2.5mg	5.0mg
N	30	30	30	30	30	30
All Body Systems	**5 (16.7)**	**3 (10.0)**	**4 (13.3)**	**3 (10.0)**	**4 (13.3)**	**9 (30.0)**
Cardiovascular System	1 (3.3)	1 (3.3)	-	1 (3.3)	1 (3.3)	-
Musculoskeletal System	-	1 (3.3)	-	1 (3.3)	-	2 (6.7)
Digestive System	2 (6.7)	-	2 (6.7)	1 (3.3)	-	5 (16.7)
Body as a Whole	-	-	1 (3.3)	-	2 (6.7)	-
Skin and Appendages	-	1 (3.3)	-	-	-	1 (3.3)
Respiratory System	-	-	-	-	-	-
Urogenital System	-	-	-	-	-	-
Nervous System	1 (3.3)	-	1 (3.3)	-	1 (3.3)	1 (3.3)
Special Senses	-	-	-	-	-	-
Endocrine System	-	-	-	-	-	-
Heme and Lymphatic system	1 (3.3)	-	-	-	-	-
Metabolic and Nutr system	-	-	-	-	-	-

Adverse Events: Of the 150 subjects who received ibandronate, 77.3% reported at least one AE during the study, compared with 76.7% in the placebo group. The AEs reported most often were gastrointestinal, followed by respiratory tract infections, musculoskeletal symptoms (arthralgia and back pain), urogenital symptoms (cystitis), and the nervous system related events. There was no clear relationship between ibandronate dose and any specific AE.

Study MF4348: Adverse Events						
Event	Placebo	0.25mg	0.5mg	1.0mg	2.5mg	5.0mg
N	30	30	30	30	30	30
All Body Systems	**23 (76.7)**	**21 (70.0)**	**20 (66.7)**	**26 (86.7)**	**24 (80.0)**	**25 (83.3)**
Cardiovascular System	2 (6 7)	1 (3 3)	1 (3 3)	2 (6 7)	6 (20 0)	2 (6.7)
Musculoskeletal System	5 (16.7)	2 (6 7)	1 (3.3)	4 (13 3)	3 (10 0)	4 (13.3)
Digestive System	12 (40 0)	9 (30 0)	15 (50.0)	8 (26 7)	6 (20.0)	18 (60 0)
Body as a Whole	6 (20 0)	4 (13.3)	10 (33 3)	6 (20 0)	9 (30 0)	6 (20 0)
Skin and Appendages	4 (13.3)	1 (3 3)	1 (3 3)	2 (6 7)	3 (10.0)	3 (10 0)
Respiratory System	7 (23 3)	9 (30 0)	3 (10.0)	10 (33.3)	2 (6.7)	2 (6 7)
Urogenital System	4 (13.3)	4 (13 3)	6 (20.0)	5 (16.7)	7 (23.3)	1 (3.3)
Nervous System	5 (16 7)	5 (16 7)	4 (13.3)	5 (16.7)	5 (16 7)	3 (10 0)
Endocrine System	-	-	-	1 (3.3)	-	-
Heme and Lymphatic system	1 (3.3)	1 (3.3)	-	1 (3.3)	1 (3.3)	-
Metabolic and Nutr system	2 (6.7)	4 (13 3)	-	1 (3 3)	2 (6.7)	-

Gastrointestinal Adverse Events: Overall, 36% of subjects in the ibandronate groups experienced gastrointestinal AEs compared with 40% in the placebo group. The frequency of gastrointestinal AEs was lower in the 0.25 mg, 1.0 mg, and 2.5 mg ibandronate groups than in the placebo group and the 0.5 mg and 5.0 mg ibandronate groups. Diarrhea was reported in 30% of subjects in the 5.0 mg ibandronate and in 6.7-13.3% of subjects in the placebo and lower dose ibandronate groups. There was otherwise no clear relationship between ibandronate dose and any specific AE.

Study MF4348: Gastrointestinal Adverse Events						
Event	Placebo	0.25mg	0.5mg	1.0mg	2.5mg	5.0mg
N	30	30	30	30	30	30
Digestive System	12 (40.0)	9 (30.0)	15 (50.0)	8 (26.7)	6 (20.0)	18 (60.0)
Dyspepsia, Dysphagia	1 (3.3)	3 (10.0)	2 (6.7)	1 (3.3)	-	2 (6.7)
Diarrhea	2 (6.7)	4 (13.3)	4 (13.3)	2 (6.7)	2 (6.7)	9 (30.0)
Nausea	1 (3.3)	1 (3.3)	4 (13.3)	2 (6.7)	-	-
Gastroenteritis	1 (3.3)	-	-	2 (6.7)	-	-
Enteritis	1 (3.3)	-	-	-	-	-
Gastritis	1 (3.3)	-	-	-	-	-
Other Gastrointestinal d/o	7 (23.3)	4 (13.3)	8 (26.7)	3 (10.0)	5 (16.7)	7 (23.3)

Laboratories: No differences were observed between placebo and the different ibandronate groups in the frequency of subjects with elevated liver enzymes. Renal function tests remain stable throughout the study. Clinically relevant decreases in phosphate level were observed in 11 patients. The numbers of patients with clinically relevant decreases were small, and no clear conclusion can be drawn from the data. Liver function tests remain stable throughout the study.

Study MF4348: Relevant Laboratory Abnormalities						
Laboratory	plac	0.25mg	0.5mg	1.0mg	2.5mg	5.0mg
Phosphate – low	1	1	1	3	3	2
White blood cell – low	-	-	-	1	1	-
White blood cell – high	-	-	-	-	1	-
Platelets - high	1	-	-	-	-	-
Neutrophils -high	-	-	-	-	1	-
ALT - high	1	-	-	-	-	-
AST - high	-	-	-	-	-	1
Alk. Phos. - high	-	-	-	-	1	-
GGT - high	-	-	-	-	-	1
Blood Urea Nitrogen – high	1	1	-	-	-	-
Potassium – low	-	-	-	-	-	1

VII.C.1.d. Study 75003: This was a randomized, double-blind, comparative study on 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. A total of 235 (121 in 2.5 mg daily, 114 in 20 mg weekly) subjects were enrolled in the trial. All demographic parameters were balanced between groups. The mean age of subjects was 65.7 years, the mean time since menopause was 17.5 years and the mean LS T-score was – 2.9.

Safety Measurements: Laboratory parameters that were assessed included serum electrolytes (chloride, potassium, sodium, calcium, phosphorus) and hematology (white cells, red cells, neutrophils, lymphocytes, monocytes, basophils, eosinophils, hemoglobin, hematocrit, and platelet count). Biochemical assessments of hepatic function consisted of total alkaline phosphatase, AST (SGOT), ALT (SGPT), and GGT, while creatinine and blood urea nitrogen were assessed for renal function.

Withdrawals: 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 20mg weekly group]. Withdrawals were evenly distributed among both groups.

Study 75003: Withdrawals		
	2.5mg daily	20 mg qweek
N	121	114
W/D AE	10	10
W/D Other	2	2
Completed	109	102

Patient Exposure: The mean total exposure to active drug was 305.2mg in the 2.5mg group and 307.2mg in the 20mg weekly group.

Study 75003: Exposure (days)		
	2.5mg daily	20 mg qweek
N	121	114
mean	305.2	307.3
SD	80.16	74.64
median	332	333.0

Death: No deaths were reported during this study.

Serious Adverse Events: Serious adverse events were reported for 12 (10%) patients in the daily and 9 (8%) patients in the weekly ibandronate treatment groups. Osteoporotic fractures were reported in two of the daily and five of the weekly subjects. All other SAEs were reported for a single patient only.

Adverse Events Leading to Withdrawal: Ten subjects in each group withdrew due to an AE. The most commonly reported AE leading to withdrawal was dyspepsia. Dyspepsia led to the withdrawal of 3 patients from the daily treatment arm and 1 patient from the weekly treatment arm. Vomiting and depression each led to the withdrawal of two patients from the daily