CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-455

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21455/N_000
Name of drug:	Bonviva® (ibandronate sodium) Film-Coated Tablets
Applicant:	Hoffmann-La Roche, Inc.
Indication:	Treatment and Prevention of Postmenopausal Osteoporosis
Documents reviewed:	\\CDSESUB1\N21455\2002-07-15\
	and amendments dated 2002-09-04, 2002-09-20, 2002-11-18, 2002-12-11, 2002-12-20, 2003-01-09, 2003-01-17, 2003-01-20, 2003-02-25, and 2003-03-24.
Project manager:	Randy Hedin, R.Ph. (510)
Clinical reviewer:	Theresa Kehoe, M.D. (HFD-510)
Dates:	Submitted: 7/15/02
Statistical reviewer:	Japobrata Choudhury, Ph.D. (HFD-715)
Statistics team leader:	Todd Sahlroot, Ph.D. (HFD-715)
Concurrence by:	Steve Wilson, Dr.P.H. (HFD-715)

Keywords: NDA review, clinical studies, SAS PROC PHREG, interaction, coding

Contents

1 Executive Summary of Statistical Findings 4

1.1 Conclusions and Recommendations 4

1.2 Overview of Clinical Program and Studies Reviewed 4

Treatment of Osteoporosis 4
Prevention of Osteoporosis 4

1.3 Principal Findings 5

2 Statistical Review and Evaluation of Evidence 6

2.1 Introduction and Background 6

2.2 Data Analyzed and Sources 7

2.3 Statistical Evaluation of Evidence on Efficacy / Safety 7

2.3.1 Sponsor's Results and Conclusions 8

Sponsor's Overall Discussion 11
Sponsor's Overall Conclusions 15

2.3.2 Statistical Methodologies 16

Oral Treatment Study MF 4411 16
Oral Prevention Study MF 4499 16

2.3.3 Detailed Review of Individual Studies 16

2.3.3.1 Study MF 4411 17
2.3.3.1.1 Objectives 19
2.3.3.1.2 Disposition of Patients 19
Distribution of Treatment Completion/Withdrawal by Year (ITT/Safety) 19
Figure for Distribution of Treatment Completion/Withdrawal by Year 20
Figure for Distribution of Withdrawals due to Adverse Events by Year (ITT/Safety) 21
2.3.3.1.3 Demographic and Other Baseline Characteristics 22
2.3.3.1.4 Measurements of Treatment Compliance and Other Factors That Could Affect Response 24
2.3.3.1.5.Efficacy Results 26
2.3.3.1.6 Reviewer's Comments and Conclusions on Study MF 4411 44

2.3.3.2 Study MF 4499 46
2.3.3.2.1 Objective 47
2.3.3.2.2 Disposition of Patients 48
Figure for Distribution of Treatment Completion/Withdrawal by Year (Safety) 49

Figure for Distribution of Withdrawals due to Adverse Events by Year (Safety) 50
2.3.3.2.3 Demographic and Other Baseline Characteristics 51
2.3.3.2.4 Measurements of Treatment Compliance and Other Factors That Could Affect Response 53
Calcium Supplement Intake and Concomitant Calcium 53
2.3.3.2.5 Efficacy Results 55
2.3.3.2.6 Reviewer's Comments and Conclusions on Study MF 4499 67

2.4 Findings in Special/Subgroup Populations 68

2.5 Conclusion 69

2.6 Appendix 70

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

Treatment Study MF 4411 and the prevention Study MF 4499 provided statistical evidence in favor of their primary objectives in terms of the respective primary efficacy variable.

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

It appears that the sponsor does not intend to market the 20 mg intermittent dose.

BONVIVA (currently proposed name is Boniva) is proposed to be indicated for the treatment and prevention of osteoporosis in postmenopausal women. The sponsor proposed the following labeling:

Treatment of Osteoporosis
In postmenopausal women with osteoporosis, BONVIVA increases BMD and reduces the incidence of vertebral fractures. Osteoporosis may be confirmed by the presence or history of osteoporotic fracture, or by the finding of low bone mass (T score < -2.0 SD).

Prevention of Osteoporosis
BONVIVA may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of fracture.

The specific Phase II/III clinical therapy studies performed to support the two above indications and the total numbers of patients by treatment per study are shown in Chart 0.1.1 and Tables 0.1.2 to 0.1.4[1] of the Appendix of this document.

§ *Note: In-depth statistical review and analyses have been done only with respect to the primary efficacy variable in the treatment Study MF 4411 and the prevention Study MF 4499 (per consultation with the Medical Team Leader Dr. Eric Colman):*

[1] In the Appendix Table (or Appendix Figure) number i.j.k, i stands for the serial number of the study in the list of studies above (except that 0 indicates overall or "common to all"), j stands for the section or group number for the tables in a particular study, and k stands for the table number in that section. Both tables and figures are under one unique sequence without any distinction between them.

Protocol	Phase	Design	Dose (mg)	Frequency	Patients Treated (N)	Duration	Post-treatment Fasting	Location	Primary efficacy variable
MF 4411 [7009]	3	Multicenter, double-blind, placebo-controlled, parallel	Placebo 2.5 20	daily daily intermittent Total =	975 977 977 2929	3 years	at least 1 hour	Europe North America	New vertebral fractures

Protocol	Phase	Design	Dose (mg)	Frequency	Patients Treated (N)	Duration	Post-treatment Fasting	Location	Stratification	Primary efficacy variable
MF 4499 [7014]	2/3	Multicenter, double-blind, placebo-controlled, parallel, dose-finding	placebo 0.5 1.0 2.5	daily daily daily daily Total =	162 162 166 163 653	2 years	at least, 90 minutes	North America	by baseline L1-L4 BMD and time since menopause	Spine BMD (L1-L4)

1.3 PRINCIPAL FINDINGS

In spite of some statistically significant interactions in Study 4411 [quantitative, i.e., not qualitative (except for Treatment by Baseline BMD T- score only), i.e., better ibandronate treatment response relative to placebo in almost all subgroups, except for BMD T- score >-2.0 SD], both studies reviewed provided statistically significant evidence in favor of their respective primary efficacy conclusion.

In the fracture Study 4411, all the significant treatment by factor interactions occurred for the 2.5mg vs placebo comparisons and the factors were: Baseline lumbar spine T-score, age, weight, years since menopause, and vitamin D status.

In the prevention Study 4499, no significant interaction could be detected (except for the 1.0 mg vs placebo comparison, for which the treatment by weight interaction p-value was 0.0965) from all analyses that could be obtained from the sponsor. Nonetheless, non-significant variation in subgroup results has been discussed in Section 2.3.3.2.6 Reviewer's Comments and Conclusion. There was a linear dose-response relationship. A unit increase in dose resulted, on an average, in 1.2084 fold increase from baseline of BMD (L1- L4) at Month 24.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

(An overview of the whole clinical program for the two indications as provided by the sponsor is in the following Section 2.1.)

2.1 INTRODUCTION AND BACKGROUND

Note: Except where specifically mentioned otherwise (as notes, reviewer's comments, conclusions, etc.), all other results and statements in this document are the sponsor's. The reviewer's silence does not imply his agreement with the sponsor's statements. Whatever the reviewer has verified and believes to be true is specifically stated so. In particular, the material in Sections 2.1 to 2.3.2 (indented) is almost verbatim from the sponsor's submission. Elsewhere, sponsor's statements may be slightly changed for brevity or for clarity.

This application seeks approval for 2.5 mg daily oral ibandronate (Ro 200- 5450) for the treatment and prevention of osteoporosis in postmenopausal women.

Intravenous ibandronate is *(Note: claimed by the sponsor to be)* currently approved in Europe for the treatment of hypercalcemia of malignancy. Ibandronate is being further investigated to determine the efficacy and safety of the compound given using alternative dosing regimens for the treatment and prevention of postmenopausal osteoporosis.

This ISE (*Note: Sponsor's Integrated Summary of Efficacy*) focuses on the studies using oral ibandronate for the treatment and prevention of postmenopausal osteoporosis. However, efficacy data from the key intravenous ibandronate studies in the treatment and prevention of postmenopausal osteoporosis will be presented as they provide supportive evidence for the efficacy of ibandronate in these indications.

As presented in the (*Note: copied from the sponsor's ISE and included in*) Chart 0.1.1 and Tables 0.1.2 to 0.1.4 of the Appendix of this document, the clinical development program comprised five categories of studies investigating:

- the pharmacological properties of oral and intravenous ibandronate (Clinical Pharmacology);

- the efficacy and safety of oral ibandronate in the treatment of postmenopausal osteoporosis (Oral Treatment);

- the efficacy and safety of oral ibandronate in the prevention of postmenopausal osteoporosis (Oral Prevention);

- the efficacy and safety of intravenous ibandronate in the treatment of postmenopausal osteoporosis (Intravenous Treatment);

- the efficacy and safety of intravenous ibandronate in the prevention of postmenopausal osteoporosis (Intravenous Prevention).

2.2 DATA ANALYZED AND SOURCES

Data used by the reviewer are from the electronic document room:
\\CDSESUB1\N21455\N_000\2002-07-15\crt

\\CDSESUB1\N21455\N_000\2002-09-04\crt

2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

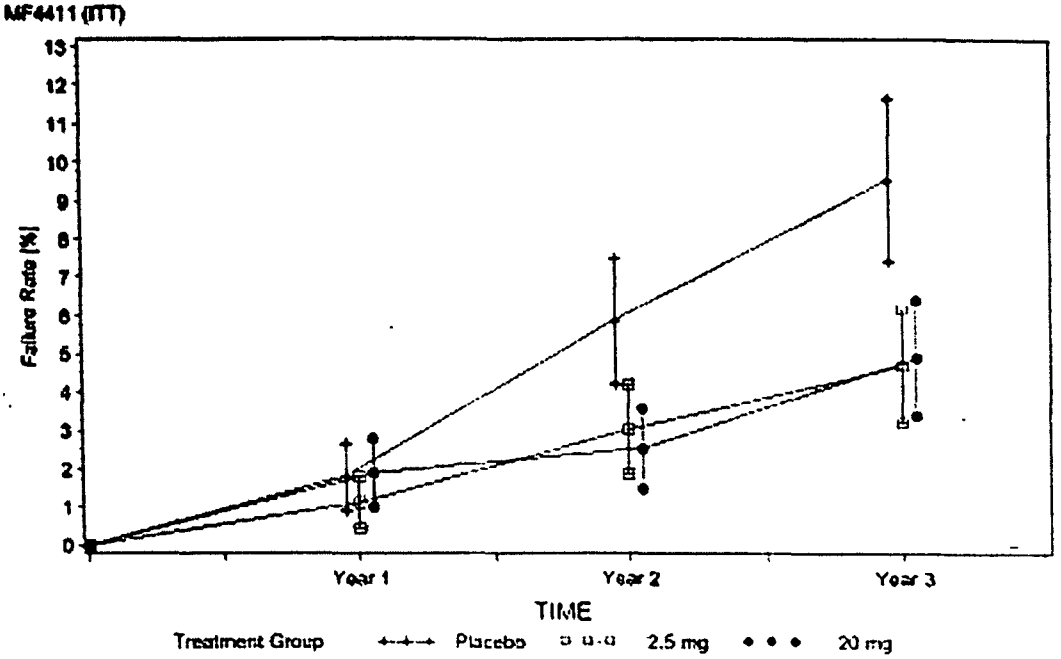
2.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

Primary Endpoint: New Vertebral Fracture– Oral Treatment Study MF 4411

	Placebo (N=975)	Iban 2.5 mg p.o. daily (N=977)	Iban 20 mg p.o. intermit. (N=977)	2.5 mg, 20 mg combined (N=1954)
Primary:				
Through Year 3:				
Patients with first new fracture	73	37	39	76
Estimate for incidence	9.56%	4.68%	4.90%	4.79%
95% CI for estimate	7.47% - 11.66%	3.20% - 6.16%	3.39% - 6.41%	3.74% - 5.85%
Secondary:				
Through Year 2:				
Patients with first new fracture	47	25	22	47
Estimate for incidence	5.87%	3.03%	2.61%	2.78%
95% CI for estimate	4.24% - 7.51%	1.85% - 4.20%	1.49% - 3.58%	2.00% - 3.57%
Through Year 1:				
Patients with first new fracture	16	10	17	27
Estimate for incidence	1.81%	1.11%	1.89%	1.50%
95% CI for estimate	0.93% - 2.69%	0.43% - 1.80%	1.00% - 2.78%	0.94% - 2.06%

Note: One patient in placebo group could not be evaluated for lack of a spine X-ray at baseline.

Lifetable Failure Rate Estimates (95% CI) for First New Incident Vertebral Fracture (Study MF 4411)



Sponsor's Summary of Results (Study MF 4411)

In comparison to placebo, ibandronate treatment reduced after 3 years of treatment highly significantly the risk of a new incident vertebral fracture by 61.6% for the 2.5 mg daily and by 49.9% for the 20 mg intermittent group, respectively The p-values for the treatment effect (estimated by a proportional hazards model without an interaction term for the BMD status at baseline) were p = 0.0003 (2.5 mg) and p = 0 0005 (20 mg), respectively. The reduction was robust and was consistently observed in a variety of subgroups.

Significant reductions of new vertebral fractures were observed in both treatment groups also after 2 years of treatment. A strong reduction was already evident in the 2.5 mg group after the first year (reduction of 57.9%; p = 0.0561).

Significant reductions were observed with either regimen in the incidence of new or worsening vertebral fractures.

Reviewer's Note: The rates 61.6% and 57.9% for the 2.5 mg group mentioned by the sponsor above are not appropriate because these are from the proportional-hazards model with the treatment by baseline BMD T-Score interaction. When there is an interaction term in the proportional hazards model, results depend on the coding and so different types of results can be obtained by different coding. These rates should be replaced by 52.2% and 39.8%, respectively, obtained from the proportional-hazards model without interaction (as was done for the p-values). Ref: Table 26 of the ISE (Integrated Summary of Efficacy) Section 9.1.2.1 in the NDA. Ideally, in the case of a serious interaction, especially of a qualitative type as in this case, the

results should be provided separately for the subgroups of the interacting factors. Also, the results were not consistent in all subgroups (significant treatment by factor interaction occurred for the 2.5mg vs placebo comparisons and the factors were: Baseline lumbar spine T-score, age, weight, years since menopause, and vitamin D status). See the subsection "Covariation, Interaction, and Subgroup Results" after the discussion of the main results in the Section 2.3.3.1.5 Efficacy Results.

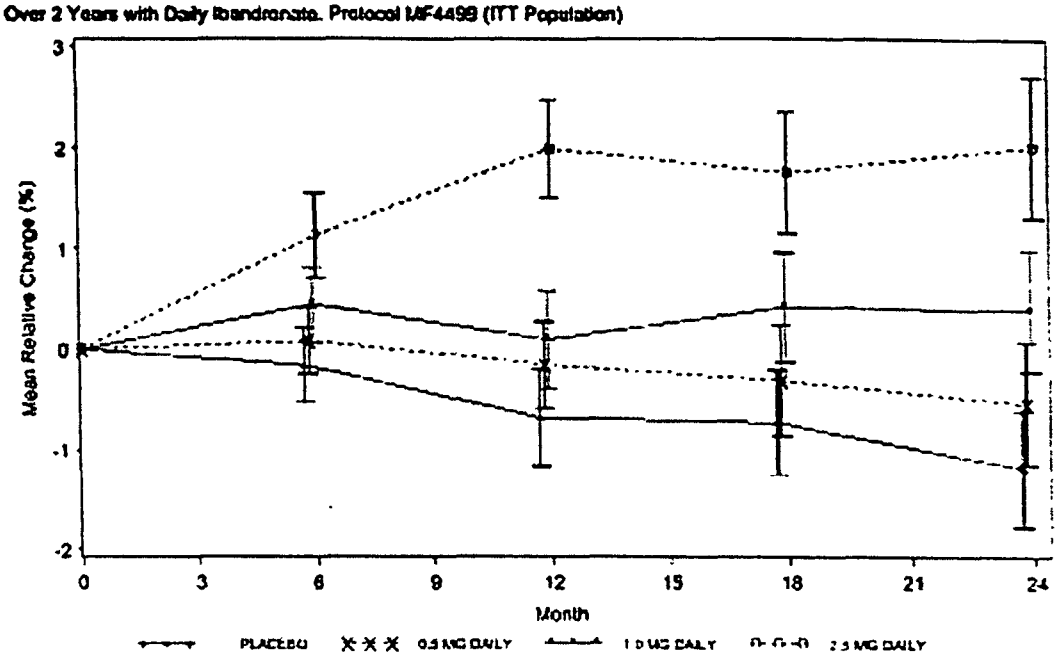
Primary Endpoint: Lumbar Spine BMD [L1 - L4] - Oral Prevention Study MF 4499

Mean Relative Change in Lumbar Spine BMD at Year 1 and Year 2 - LVCF (95% CI) (MF 4499 - ITT)

Dose regimen	MF4499 N=620 Post-dose fasting >=30 min N	Mean	(95% CI)
YEAR 1			
Placebo	141	-0.68	(-1.17, -0.20)
0.5 MG Daily	158	-0.35	(-0.59, 0.28)
1.0 MG Daily	155	0.10	(-0.38, 0.58)
2.5 MG Daily	140	1.99	(1.50, 2.48)
YEAR 2 (LVCF)			
Placebo	150	-1.29	(-1.75, -0.83)
0.5 MG Daily	157	-0.56	(-1.11, -0.02)
1.0 MG Daily	160	0.10	(-0.38, 0.58)*
2.5 MG Daily	154	1.91	(1.30, 2.52)*
Difference in the mean relative change between 2.5mg and placebo			
Year 1		2.67	(2.25, 3.10)
Year 2 (LVCF)		3.19	(2.65, 3.73) *

* Difference between active group and placebo was statistically significant at Year 2 (p < 0.05).
ibebrdtabcrt61, 04APR2002

Time Course of Mean Relative Change (95% CI) from Baseline in Lumbar Spine BMD over 2 Years with Daily Ibandronate (MF 4499 - ITT)



Program SPROD\dp10133\sobmd2yq.sas / Output SPROD\dp10133\reports\sobmd2pg291.opm
05DEC2001 14:56

Sponsor's Summary of Results (MF 4499 - ITT)

Therapy with 2.5 mg daily oral ibandronate in patients at risk of developing postmenopausal osteoporosis was demonstrated to result in:

Significant increases in BMD at the lumbar spine and hip compared to placebo for 2.5 mg daily ibandronate,

Dose- dependent increases in BMD at the lumbar spine, hip and forearm compared to placebo with 2.5 mg daily being the most effective dose;

Effective prevention of bone loss with consistent effects on BMD at the lumbar spine and hip in both early and late postmenopausal women as well as women with normal or low BMD.

Sponsor's Overall Discussion

The data presented in this ISE clearly demonstrate the efficacy of oral ibandronate in reducing the risk of new vertebral fractures and restoring bone mass in postmenopausal women. Additionally, increases in BMD at various skeletal sites and suppression of elevated markers of bone turnover to premenopausal levels clearly reflect the antiresorptive activity of ibandronate. Vertebral fracture study MF 4411 was a large, multicenter, multinational, double- blind, randomized, placebo-controlled study that included two distinct oral dosing regimens of ibandronate, as well as several

clinically important secondary efficacy endpoints. Within this single study, confirmatory evidence was provided for the efficacy of oral ibandronate in the treatment of postmenopausal osteoporosis. MF 4411 demonstrated statistically very robust results for the primary endpoint, the incidence of new vertebral fractures, leading to a clear rejection of the study's null hypothesis of no treatment effect for both ibandronate regimens. Results for both dosing regimens were internally consistent among various relevant population subgroups, and both dosing regimens demonstrated efficacy on a number of key secondary endpoints, such as BMD at various proximal and distal sites, bone markers of resorption and formation, and height. These results further support the conclusions of the primary analysis. Study MF 4411 provided substantial evidence of efficacy of 2.5 mg daily oral ibandronate for the treatment of osteoporosis in postmenopausal women.

Note: See the Reviewer's Note above.

Furthermore, MF 4499, a large, randomized, placebo- controlled, multicenter, two- year study evaluated the effect of oral daily ibandronate on the change in lumbar spine BMD for the prevention of osteoporosis in postmenopausal women. This study clearly demonstrated the efficacy of 2.5 mg daily oral ibandronate in reducing bone turnover and preventing postmenopausal bone loss. The efficacy of ibandronate in preventing bone loss was also confirmed using weekly oral ibandronate in study MF 4500.

Fracture efficacy of ibandronate – vertebral fractures:

The efficacy of ibandronate in fracture risk reduction was demonstrated for two different oral ibandronate treatment regimens. The primary endpoint of a reduction in the incidence of new vertebral fractures was met with a very robust statistical significance for both the daily (p= 0.0001) as well as the intermittent (p= 0.0006) oral ibandronate regimens. The magnitude of the treatment effect at Year 3 was equally strong, with a relative risk reduction of 62% for the 2.5 mg daily administration, and 50% for the intermittent administration. There was no statistical difference between the magnitude of risk reduction induced by either regimen.

Importantly, the effect of treatment with 2.5 mg daily oral ibandronate on fracture risk reduction was of a consistent magnitude throughout the 3 year study period, and no waning of the effect was observed. The relative risk reduction for new vertebral fractures in Year 1 (58%) and Year 2 (61%,) was of a similar magnitude as observed in Year 3 with the 2.5 mg daily oral ibandronate regimen (62%). The statistical significance of the reduction, relative to placebo, was very robust in Year 2 (p= 0.0006) and approached significance at Year 1 (p= 0 0561). The lack of significance at Year 1 was most likely attributable to the unusually low fracture incidence (1.8%) observed in Year 1 for the placebo group.

Note· See Reviewer's Note above about the inappropriateness of the preceding statements.

Fracture efficacy was also consistently shown for new or worsening vertebral fractures, as well as for clinical vertebral fractures and in subgroups of patients at varying fracture risk. The consistency of the fracture efficacy was also confirmed in an analysis on the patient subpopulation with a baseline BMD T- score below -2.5, and therefore fulfilling the BMD criteria for osteoporosis according to the WHO. In addition, study MF 4411 demonstrated for the first time, under adequate and well- controlled trial conditions, the fracture efficacy of an intermittent bisphosphonate regimen having a dose- free interval of up to 10 weeks.

Osteoporosis, with associated increased vertebral fracture risk, may also lead to increased loss in stature. Ibandronate treatment significantly reduced the mean loss in stature both annually and after 3 years relative to placebo with both regimens.

Additional information on the fracture efficacy of ibandronate was provided by the I.V. ibandronate study MF 4380. This study investigated the efficacy of ibandronate using an intravenous formulation. Similar to MF 4411, MF 4380 was a large randomized, placebo-controlled, multicenter clinical trial including nearly 3000 patients with near identical inclusion criteria resulting in a study population comparable to that of MF 4411. While the primary endpoint of a significant reduction in the incidence of new vertebral fractures was not met in the MF 4380 ITT analysis, a consistent reduction of new vertebral fractures was demonstrated throughout the study period, and statistical significance was reached in the PP analysis with 1.0 mg quarterly I.V. ibandronate.

The trend towards fracture reduction observed in MF 4380, together with the consistently lower magnitude of BMD gains and suppression of markers of bone turnover, support the interpretation that this study used an insufficient ibandronate dose for the 3- month dosing interval investigated. This is further corroborated by the results of studies MF 4361 and MF 4470, which demonstrated the magnitude of effects on BMD and bone markers to be inferior with 1.0 mg I. V. quarterly when compared with the 2.5 mg daily oral dose explored in study MF 4411. Additional strong support implicating insufficient dosing in MF 4380 was provided by the analysis of the relationship between change in BMD and fracture risk reduction. Although MF 4380 did not meet the predefined primary endpoint, it did, nonetheless, provide additional supportive evidence for the efficacy of treatment with ibandronate.

Fracture efficacy of ibandronate – clinical and nonvertebral fractures:

The efficacy of ibandronate in reducing fracture risk was also evaluated as a secondary endpoint for clinical and nonvertebral fractures in both MF 4411 and MF 4380. Although these studies were not designed to test for statistical significance in the reduction of symptomatic fractures, nominal reductions were shown in MF 4411 in the number of clinical fractures, including clinical vertebral fractures, compared to placebo. The MF 4411 study population showed a baseline BMD profile suggesting that the population was at low risk for fractures. When a subgroup of the population was investigated which was at higher risk for fractures, and which consequently showed a higher incidence of clinical fractures, a clear and statistically significant effect was demonstrated for both the daily and intermittent oral ibandronate regimens.

No apparent treatment effect was observed in the incidence of clinical nonvertebral fractures, including hip fractures, compared to placebo in MF 4411. However, for the population subgroup at higher risk for fractures, a clear treatment effect was also observed which showed a significant reduction in the number of nonvertebral fractures compared to placebo. A clear trend showing a beneficial treatment effect on osteoporotic clinical and nonvertebral fractures (including hip fractures) was also observed in MF 4380.

The effect of ibandronate therapy on the incidence of vertebral fractures, clinical fractures, and nonvertebral fractures is to be viewed in light of the patient population characteristics of the two fracture trials. The design and conduct of the fracture investigations, MF 4411 and MF 4380, closely resembled the large FIT [6007] and VERT [7805, 7802] clinical trials performed for other bisphosphonates. Although there were no major differences in the design of these studies, including the use of similar inclusion criteria, some population characteristics differed considerably between the trials. In particular, the incidence of new vertebral fractures after 3 years in study MF 4411 was approximately 40% lower than observed in the FIT and VERT studies.

A substantial proportion of the patients in MF 4411 had essentially normal femoral neck BMD T-scores at baseline, suggesting that the study population was at low risk of experiencing new fractures. Despite this low risk, ibandronate treatment provided robust fracture efficacy in study MF 4411 as assessed for the primary endpoint of new vertebral fractures. The lack of observation

of a treatment effect on nonvertebral fractures must be considered in the light of the low fracture risk of the study population. This is further supported by the observation of a treatment effect in a subgroup of patients at higher fracture risk.

Bone Mineral Density:

The efficacy of ibandronate on changes in BMD was assessed in study populations with established osteoporosis as well as in study populations at risk for developing osteoporosis. Therapy with 2.5 mg daily oral ibandronate resulted in consistent and progressive BMD increases at the lumbar spine, hip and forearm in all populations assessed. BMD increases were dose-dependent and characteristic of bisphosphonate therapy. In MF 4411, patients with postmenopausal osteoporosis responded to ibandronate therapy with rapid and significant BMD gains in the first 6 months, and gains in BMD that continued progressively throughout the 3- year course of treatment. The progressive pattern of gain in BMD showed a pattern typical of bisphosphonate therapy.

In the prevention studies MF 4499 and MF 4500, therapy with 2.5 mg daily or 20 mg weekly oral ibandronate also resulted in significant increases in BMD at the lumbar spine and hip relative to placebo. Dosing of 2.5 mg daily or 20 mg weekly ibandronate was able to fully prevent bone loss at these sites in early and later postmenopausal women, and in women with normal bone mass or having already reached an advanced osteopenic condition.

Histomorphometric analysis confirmed the normal quality of newly formed bone and the absence of mineralization impairment or marrow abnormalities.

The link between the gains in BMD induced by ibandronate therapy and the associated reduction in fracture risk was analyzed and the strong relationship between the ibandronate- induced BMD gains and fracture risk reduction was validated. Regression analyses and a surrogate marker analysis confirmed ibandronate- induced BMD gains to be predictive of vertebral fracture reduction, both for orally as well as intravenously administered ibandronate.

Markers of Bone Turnover:

Therapy with oral ibandronate led to dose- dependent suppression of markers of bone turnover. The profiles of marker suppression were characteristic of bisphosphonate therapy. A characteristic pattern of suppression was observed for markers of bone resorption in response to therapy with 2.5 mg daily ibandronate. The nadir was reached rapidly after approximately 3 months, and followed by sustained suppression throughout the 3 year period of treatment. Markers of bone resorption responded more rapidly to therapy and showed greater maximal suppression than did markers of bone formation. Greater fluctuation was also observed in markers of bone resorption in response to the drug- free intervals of the intermittent dosing regimen. In osteoporotic populations, the magnitude of resorption marker suppression was sustained at a level between 50% to 80% below baseline with either the daily or intermittent ibandronate regimens. In populations receiving 2.5 mg daily oral ibandronate for the prevention of postmenopausal osteoporosis, the magnitude of the suppression of markers of bone resorption was sustained at a level of between 40% to 50% below baseline.

Suppression of markers of bone formation led to a nadir of approximately 40% relative to baseline after 6 months, with suppression sustained thereafter throughout the remaining 3- year treatment period. The same pattern of suppression, with a similar magnitude, was also observed in the prevention population as a result of therapy with 2.5 mg daily oral ibandronate.

A similar profile of suppression was observed in the prevention studies MF 4499 and MF 4500 as had been observed with the osteoporotic population of MF 4411, albeit with a lower magnitude of suppression reflecting the baseline characteristics of the prevention study populations in MF 4499 and MF 4500.

Sponsor's Overall Conclusions

In summary, treatment with 2.5 mg daily oral ibandronate led to a highly robust reduction in the risk of new morphometric vertebral fractures in patients with postmenopausal osteoporosis (62%, p= 0.0001). This protection was maintained, without waning, over the 3 year period of treatment. A significant reduction in the loss of stature was consistently shown with daily ibandronate therapy, as was a reduction in new or worsening morphometric vertebral fractures and clinical vertebral fractures. In addition, the anti- fracture efficacy of an intermittent bisphosphonate regimen with a drug-free interval of up to 10 weeks was demonstrated for the first time under clinical trial conditions. The risk of clinical fractures was nominally reduced with 2.5 mg daily ibandronate therapy, and a significant reduction in osteoporotic clinical and nonvertebral fractures was observed in a subgroup of the study population at high risk of experiencing such fractures. The lack of an observable treatment effect on the incidence of nonvertebral fractures in the total patient population was probably due to the low- risk patient population included in the study.

Note: See Reviewer's Note above about the inappropriateness of some of the preceding statements.

Daily therapy with 2.5 mg oral ibandronate resulted in consistent and progressive increases in BMD at the lumbar spine, hip, and forearm both in postmenopausal women with established osteoporosis as well as in postmenopausal women at risk of developing osteoporosis. In osteoporotic patients, treatment with 2.5 mg daily oral ibandronate resulted in mean BMD increases of 6.5% at the lumbar spine and 3.4% at the total hip after 3 years. In the prevention of osteoporosis, 2.5 mg oral ibandronate was also observed to be the most efficacious daily dose tested, with significant BMD increases demonstrated relative to placebo. Gains in BMD showed a progressive pattern typical of bisphosphonate therapy. The newly formed bone was shown by histomorphometric analysis to be of normal quality and without mineralization defects.

Ibandronate- induced BMD gains were demonstrated to be predictive of vertebral fracture risk reduction with a strong correlation shown between the change in lumbar spine or hip BMD and the reduction in vertebral fracture rate with ibandronate therapy. Furthermore, a strong correlation was demonstrated for the relative change in BMD between Year 1 and Year 2, Year 2 and Year 3, and Year 1 and Year 3 for BMD of either the lumbar spine or total hip.

Accelerated postmenopausal bone turnover was reduced by ibandronate, with 2.5 mg daily ibandronate significantly suppressing markers of bone resorption and formation compared to placebo in patients with postmenopausal osteoporosis or at risk of developing osteoporosis. The response of markers of bone turnover to treatment was rapid and the effect was sustained throughout the period of treatment.

This integrated summary of efficacy has presented data demonstrating substantial evidence of efficacy for oral ibandronate in reducing the risk of fractures in patients with postmenopausal osteoporosis, and in restoring bone mass in postmenopausal women at risk of developing osteoporosis. Thus the sponsor is seeking approval for 2.5 mg daily oral ibandronate, administered with a post-dose fasting period of 60 minutes, for the treatment and prevention of osteoporosis in postmenopausal women.

2.3.2 STATISTICAL METHODOLOGIES

(Note: Further details are in NDA Section 2.12.6 of the respective Study; some are in Sections 2.3.3.1.5 and 2.3.3.2.5 of this document.)

Oral Treatment Study MF 4411
Primary Endpoint: New Vertebral Fracture – The analysis of the primary endpoint "incidence of new vertebral fractures" was done by testing the homogeneity between the treatment groups of the time-to-event curves with respect to the event 'first new incident vertebral fracture'. All patient withdrawals were considered censored observations in this analysis, unless withdrawal was preceded by a new vertebral fracture.

The time-to-event analysis was done according to the life-table method with events grouped to the first study year, second study year and third study year intervals. The intervals were delineated on the basis of study days. All events that occurred after Year 3 were allocated to the third study year.

Oral Prevention Study MF 4499
Primary Endpoint: Lumbar Spine BMD [L1 - L4] - The primary criterion for the evaluation of relative change in BMD was the mean change in BMD of the non- fractured [L1- L4] lumbar spine vertebrae. The change in BMD was defined as the relative difference between the two-year measurement (either measured or carried forward) and baseline, using the following formula:

Relative change = (2- year value – baseline value) / (baseline value) x 100

The primary model was an ANOVA, which took treatment and allocated stratum of the individual patients into account as independent factors. The primary analysis was the analysis of the intent-to-treat (ITT) population. In the ITT population, a missing BMD value at Month 24 was imputed using the LVCF method.

2.3.3 DETAILED REVIEW OF INDIVIDUAL STUDIES

Note: If statistical significance is not mentioned, then the comparison is only numerical.

The following two studies have been reviewed in depth with a focus on the primary efficacy variable and analysis:

Protocol	Phase	Design	Dose (mg)	Frequency	Patients Treated (N)	Duration	Post-treatment Follow	Location	Primary efficacy variable
MF 4411 [1004]	3	Multicenter, double-blind, placebo-controlled, parallel	Placebo 2.5 20	daily daily maximum Total	475 477 477 2429	3 years	at least 1 year	Europe South America	New vertebral fractures

Protocol	Phase	Design	Dose (mg)	Frequency	Patients Treated (N)	Duration	Post-treatment Follow	Location	Stratification	Primary efficacy variable
MF 4499 [7014]	3	Multicenter, double-blind, placebo-controlled, parallel dose finding	placebo 0.5 1.0 2.5	daily daily daily daily Total	162 162 160 163 647	2 years	at least 6 months	North America	by baseline L1-L4 BMD and time since menopause	Spine BMD [L1-L4]

2.3.3.1 *Study MF 4411*

Synopsis of the Study follows:

TITLE OF THE STUDY: Clinical Study Report - Protocol MF 4411: Multicenter, double-blind, placebo controlled, randomized study on the efficacy and safety of ibandronate over 3 years in patients with postmenopausal osteoporosis using a continuous oral and an intermittent oral dosing regimen.

INVESTIGATORS / CENTERS AND COUNTRIES: 73 Centers in Canada, Denmark, France, Germany, the Netherlands, Norway, Poland, Russia, the United Kingdom, and the United States.

PERIOD OF TRIAL: Nov. 22, 1996 – Aug. 29, 2000

CLINICAL PHASE: III

OBJECTIVES: To investigate the long- term efficacy and safety of continuous and intermittent oral administration of ibandronate in the long-term treatment of postmenopausal osteoporosis, using the incidence of new vertebral fractures as the primary efficacy variable.

STUDY DESIGN: 3-year, multicenter, double-blind, randomized, placebo-controlled study with 3 parallel treatment groups.

NUMBER OF SUBJECTS: A total of 2946 patients were randomized. The 3 treatment groups of the ITT/ Safety population were composed as follows: 975 patients on placebo, 977 on 2.5 mg daily ibandronate, and 977 on 20 mg intermittently ibandronate.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Women with postmenopausal osteoporosis aged 55-80 years, with time since menopause ≥5 years. Bone- mineral density T-score in at least one vertebra of the lumbar spine (L1–L4) between -2.0 and -5.0, and with 1- 4 prevalent vertebral fractures (T4–L4).

DOSE / ROUTE / REGIMEN / DURATION: Treatment was given orally over a period of 3 years. Patients in the 2.5 mg group received daily doses of 2.5 mg ibandronate. Patients receiving intermittent treatment were administered 12 doses of 20 mg ibandronate every other day at the start of each 3 month cycle. On days without active study medication they were given an identically looking placebo. All patients received oral doses of calcium (500 mg/ day) and vitamin D3 (400 IU/ day) as supplements.

CRITERIA FOR EVALUATION

EFFICACY: The primary efficacy parameter was the incidence of new vertebral fractures, defined as the proportion of patients with at least one new fracture. Secondary variables included: general incidence of clinical fractures, bone mineral density (BMD) of the lumbar spine, proximal femur, and distal forearm; height, pain and disability; urinary calcium, CTx and NTx; serum osteocalcin, bone-specific alkaline phosphatase, and parathyroid hormone concentrations.

SAFETY: Incidence of clinical adverse events, concomitant medications, clinical laboratory assessments (hematology and blood chemistry), laboratory abnormalities. Bone biopsy histomorphometry assessments were performed in a subgroup of patients.

STATISTICAL METHODS: All efficacy parameters were summarized for both the ITT and PP populations. The primary analysis group for all fracture analyses was the ITT population; for BMD and biochemical markers of bone turnover, the PP population was primary. Subgroup analyses were conducted for the new vertebral fractures, osteoporotic clinical fractures, and BMD variables.

Analysis of the primary efficacy variable was performed using the life-table survival method. A confirmatory analysis of the primary endpoint was done by testing the homogeneity of the time-to-event curves. The reduction in relative risk was estimated by using a proportional hazards model considering an interaction between treatment and 'high' or 'low' lumbar spine BMD at baseline. Analyses of time-to-event for clinical fractures, used Kaplan Meier survival analysis to evaluate pairwise differences between treatment groups.

An ANOVA was used to investigate the treatment effect on the relative 3- year BMD changes, adjusting for baseline BMD as a covariate. Kruskal-Wallis tests were used for the comparison of treatment groups, based on 3-year data, for relative changes in markers of bone turnover. Differences in the reduction of height were assessed by a Wilcoxon test.

METHODOLOGY:

After a screening visit within 3 months prior to study start patients attended regular visits at 3 months intervals during the 3-year study. Lateral radiographs of the thoraco-lumbar spine were taken annually for the assessment of vertebral fractures. Evaluation of the X-rays was performed by 2 central reading facilities. BMD measurements of the lumbar spine, the hip, and of the distal forearm (for a subset of patients) were carried out every 6 months during the first 2 years and then again at the final visit. Two central quality assurance centers calibrated and corrected all data before transfer to the sponsor. Height and bone pain were recorded at each visit. Laboratory assessments were done at 3-month intervals during the first half year and then every 6 months until the end of the second

year and then once more at the final visit. All collected laboratory samples were used for the analysis of safety parameters, while samples of subset of patients were also used to assess efficacy parameters. Disability/ physical activity were recorded annually. Safety information regarding adverse events and concomitant medications were recorded continuously throughout the study.

2.3.3.1.1 Objectives

To investigate the long-term efficacy and safety of continuous and intermittent oral administration of ibandronate in the long-term treatment of postmenopausal osteoporosis, using the incidence of new vertebral fractures as the primary efficacy variable.

2.3.3.1.2 Disposition of Patients

From the 2946 patients originally randomized, 17 patients were excluded from the ITT and Safety analyses because they did not take any study medication. The composition of both the ITT and the Safety populations was identical.

The distribution over time of withdrawals did not differ considerably between treatment groups (Table below). The highest rate of withdrawal was observed in the first year (up to Visit 5) in all groups and irrespective of whether the withdrawals were due to AEs or due to other reasons. In the subsequent 2 years (up to Visit 9 and Visit 13, respectively) the withdrawal rates were markedly lower than in the first year but there were no consistent differences between treatment groups (which might potentially affect the results).

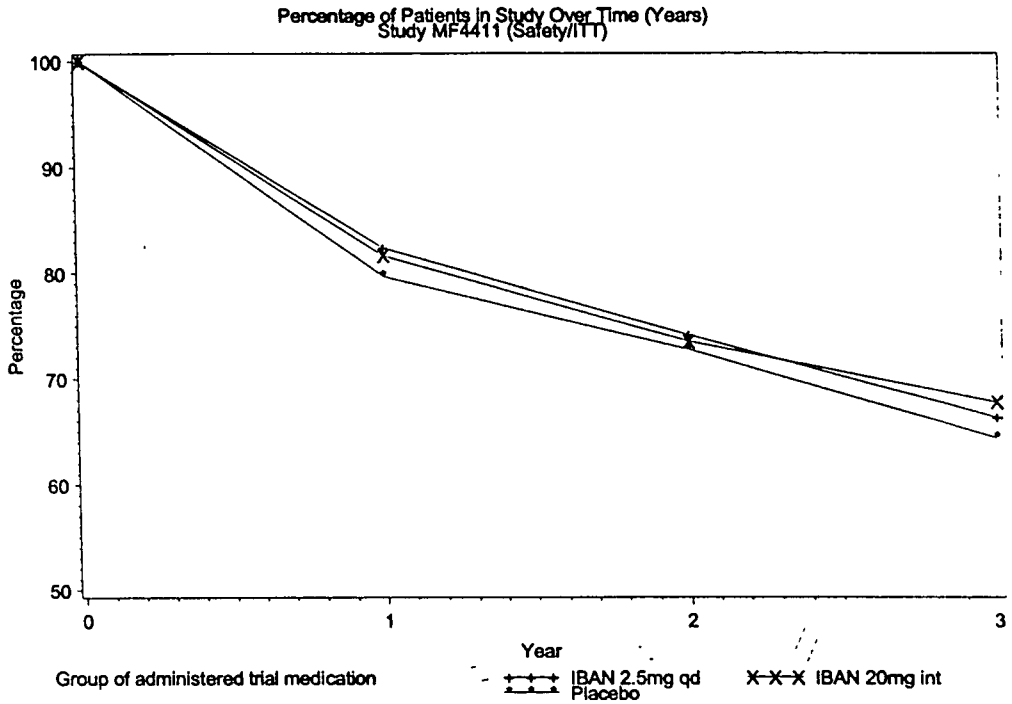
Distribution of Treatment Completion/Withdrawal by Year (ITT/Safety)

	Year 1		Year 2		Year 3	
	N	PCT	N	PCT	N	PCT
Placebo (N=975):						
COMPLETED TREATMENT AND STUDY	777	79.69	709	72.72	628	64.41
WITHDRAWN DUE TO AE	107	10.97	149	15.28	180	18.46
OTHER WITHDRAWALS	91	9.33	117	12.00	167	17.13
IBAN 2.5mg qd (N=977):						
COMPLETED TREATMENT AND STUDY	805	82.40	724	74.10	648	66.33
WITHDRAWN DUE TO AE	103	10.54	143	14.64	177	17.91
OTHER WITHDRAWALS	69	7.06	110	11.26	154	15.76
IBAN 20mg int (N=977):						
COMPLETED TREATMENT AND STUDY	798	81.68	718	73.49	663	67.76
WITHDRAWN DUE TO AE	114	11.67	156	15.97	178	18.22
OTHER WITHDRAWALS	63	6.45	103	10.54	137	14.02

'Year 1': At visit 5
'Year 2': At visit 9
'Year 3': At visit 13

The following graph summarizes the percentage of patients continuing with treatment over time.

Figure for Distribution of Treatment Completion/Withdrawal by Year

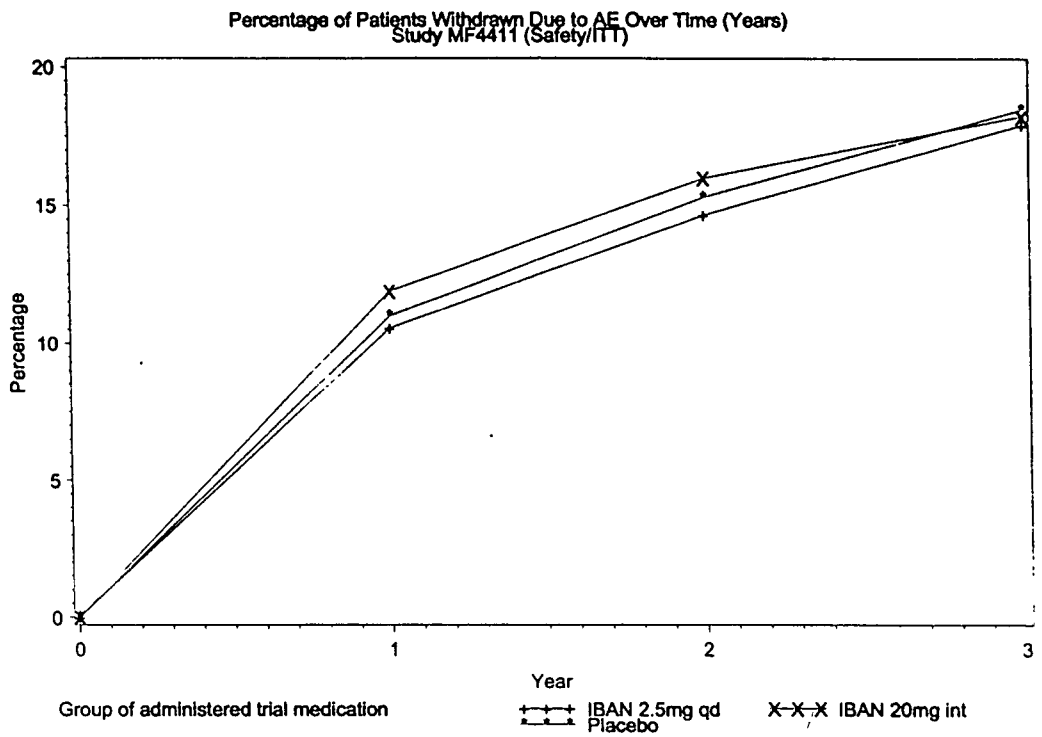


Program $PROD/cd10133a/complete sas / Output . $PROD/cd10133a/reports/completeall cgm
13NOV2002 18 09

In addition, the graph below also shows the percentage of patients withdrawing from treatment due to adverse events at 1, 2 and 3 years.

APPEARS THIS WAY
ON ORIGINAL

Figure for Distribution of Withdrawals (Cumulative) due to Adverse Events by Year (ITT/Safety)



Program $PROD/cd10133a/complete.sas / Output · $PROD/cd10133a/reports/completeae cgm
13NOV2002 18 09

2.3.3.1.3 Demographic and Other Baseline Characteristics

Summary of Baseline Demographic Characteristics (Safety/ ITT):

	Placebo (N=975)	Iban 2.5 mg p.o. daily (N=977)	Iban 20 mg p.o. intermit. (N=977)
Age (yrs.)			
N	975	977	977
MEAN	68.8	68.7	68.7
SD	6.0	6.2	6.2
MIN	54.0	55.0	55.0
MEDIAN	69.0	69.0	69.0
MAX	80.0	81.0	80.0
Body Weight (kg)			
N	974	977	977
MEAN	66.8	66.6	66.7
SD	11.1	10.9	10.9
MIN	36.5	40.8	36.3
MEDIAN	65.4	65.2	65.5
MAX	118.4	142.0	108.9
Body Height (cm)			
N	974	977	977
MEAN	159.7	160.2	160.3
SD	6.1	6.3	6.1
MIN	141.5	139.7	137.2
MEDIAN	159.9	160.0	160.3
MAX	177.6	179.1	177.3
BMI (kg/m2)			
N	974	977	977
MEAN	26.2	26.0	26.0
SD	[illegible]	[illegible]	[illegible]
MIN	[illegible]	[illegible]	[illegible]
MEDIAN	[illegible]	[illegible]	[illegible]
MAX	[illegible]	[illegible]	[illegible]
Race			
N	975 (100.0%)	977 (100.0%)	977 (100.0%)
CAUCASIAN	968 (99.3%)	964 (98.7%)	968 (99.1%)
ASIAN	8 (0.8%)	6 (0.6%)	7 (0.7%)
BLACK	3 (0.3%)	6 (0.6%)	3 (0.3%)
HISPANIC		1 (0.1%)	1 (0.1%)
OTHER	4 (0.4%)	2 (0.2%)	6 (0.6%)

The mean time since menopause was between 20.8 and 20.9 years in all treatment groups. A slightly higher proportion of patients in the ibandronate groups had undergone an oophorectomy (14.7% and 16.1%) compared to placebo (12.4%). The numbers of hysterectomies were more similar (20.4% and 19.2% for ibandronate) in comparison to placebo (18.1%). The proportion of patients that had received post-menopausal hormone replacement therapy was between 20.8% and 21.9%.

Summary of Fracture History at Baseline (Safety/ ITT):

	Placebo (N=975)	Ibandronate 2.5 mg p.o. daily (N=977)	Ibandronate 20 mg p.o. intermit. (N=977)
Number of prevalent vertebral fractures:			
n	975 (100.0%)	977 (100.0%)	977 (100.0%)
0	68 (7.0%)	57 (5.8%)	60 (6.1%)
1	485 (49.7%)	487 (49.9%)	504 (51.6%)
2	242 (24.8%)	254 (26.0%)	244 (25.0%)
3	110 (12.1%)	125 (12.8%)	120 (12.3%)
4	53 (5.4%)	45 (4.6%)	42 (4.4%)
5	4 (0.4%)	9 (0.9%)	5 (0.5%)
6	4 (0.4%)	.	1 (0.1%)
no data available	1 (0.1%)	.	.
Number of other ("clinical") previous fractures in the last 5 years:			
n	975 (100.0%)	977 (100.0%)	977 (100.0%)
0	765 (78.5%)	716 (73.3%)	756 (77.4%)
1	167 (17.1%)	214 (21.9%)	179 (18.3%)
2	34 (3.5%)	40 (4.1%)	34 (3.5%)
3	7 (0.7%)	7 (0.7%)	6 (0.6%)
4	2 (0.2%)	.	1 (0.1%)
5	.	.	1 (0.1%)
Number of other ("clinical") previous fractures since age 45:			
n	975 (100.0%)	977 (100.0%)	977 (100.0%)
0	538 (55.2%)	510 (52.2%)	529 (54.1%)
1	281 (28.8%)	303 (31.0%)	307 (31.4%)
2	95 (9.7%)	102 (10.4%)	85 (8.7%)
3	41 (4.2%)	41 (4.2%)	34 (3.5%)
4	19 (2.0%)	15 (1.5%)	16 (1.6%)
5	1 (0.1%)	6 (0.6%)	3 (0.3%)
6	.	.	1 (0.1%)
7	.	.	1 (0.1%)
8	.	.	1 (0.1%)

For some patients there were violations of inclusion and/ or exclusion criteria. The most significant deviation was the absence of any prevalent vertebral fractures in 185 patients (6.3% of the ITT population, see Table 10 of the study report in the NDA), although the inclusion criteria required 1-4 such fractures. The reason for this discrepancy is that during the screening period, all baseline vertebral radiographs were evaluated only morphometrically, without any qualitative assessment by a radiologist. When radiologists reassessed the vertebral radiographs during the further course of the study, the radiologists downgraded a considerable number of conditions initially considered to be prevalent vertebral fractures. A listing of patients without or with more than 4 baseline fractures is provided in NDA Appendix 13 of the study report.

Five variables were found to have a significant imbalance (without multiple comparison adjustments) between at least one of the active treatment groups versus placebo at baseline. Three of those variables (body height, clinical fractures in last 5 years, and serum bone- specific alkaline phosphatase) were for differences between the 2.5mg group versus placebo.

Baseline Variable		Placebo	2.5mg	20mg
Body Height (cm)	n	974	977	977
	mean	159.[illegible]	160.2	160.3
	p-value		0.0764	0.0300

History of Oophorectomy	n yes no no data p-value	975 121 (12.4%) 852 (87.4%) 2 (0.2%)	977 144 (14.7%) 833 (85.3%) 0 (0%) 0.1378	977 157 (16.1%) 820 (83.9%) 0 (0%) 0.0217
Number of Other ("clinical") Previous Fractures in the Last 5 Years	n 0 1 2 3 4 5 p-value	975 765 (78.5%) 167 (17.1%) 34 (3.5%) 7 (0.7%) 2 (0.2%) 0 (0%)	977 716 (73.3%) 214 (21.9%) 40 (4.1%) 7 (0.7%) 0 (0%) 0 (0%) 0.0421	977 756 (77.4%) 179 (18.3%) 34 (3.5%) 6 (0.6%) 1 (0.1%) 1 (0.1%) 0.9690
Serum Bone-Specific Alkaline Phosphatase (U/L)	n mean p-value	224 40.93	223 44.42 0.0592	229 44.54 0.0399
Urinary Calcium* (mmol/mmol)	n mean p-value	219 0.37	217 0.41 0.1159	223 0.43 0.0307

Alternative analyses for efficacy were done adjusting for these imbalances (see the subsection "Covariation, Interaction, and Subgroup Results" after the discussion of the main results in the Section 2.3.3.1.5 Efficacy Results).

2.3.3.1.4 Measurements of Treatment Compliance and Other Factors That Could Affect Response

Summaries of Gynecological History and Other Baseline Characteristics, Bone Mineral Density at Baseline, Values for Markers of Bone Turnover at Baseline, Previous and Concomitant Medical Disorders at Baseline, etc. are in NDA Section 3.1.4 to 3.1.6 of the study report.

Mean Time Spent in Study:

The mean time of patient participation in the study was well balanced between the treatment groups, and ranged from 2.42 to 2.48 years (Table below). Similarly, the duration of the period during which patients received study medication was similar between treatment groups, ranging from a mean of 2.25 to 2.31 years (NDA Appendix 16).

	Placebo (N=975)	Ibandronate 2.5 mg p.o. daily (N=977)	Ibandronate 20 mg p.o. intermit. (N=977)
MEAN	2.42	2.43	2.46
SD	0.96	0.96	0.94
MIN			
Q1	2.09	2.08	2.16
MEDIAN	2.37	2.36	2.44
Q3	3.00	3.00	3.00
MAX			

Previous Treatments:

From the ITT population, 276 patients indicated the absence of any medications prior to study start or at baseline. The percentages of patients receiving at least one previous treatment was evenly distributed among treatment groups. However, the actual number of previous treatments was slightly higher in the ibandronate groups (3691 for 2.5 mg and 3673 for 20 mg) than in placebo (3527), thereby, mirroring the somewhat higher number of previous disorders in the two ibandronate groups (see 3.1.5). Also, on the level of the individual superclass terms, there were no obvious imbalances in the distribution of previous treatments among the three treatment groups. Apart from various vitamin and calcium preparations, the most frequent previous medications included analgesics / antipyretics, antiinflammatory / antirheumatic agents, anticoagulants, β-blockers, and cholesterol reducers/ antiatheroma preparations.

Concomitant Treatments:

A full summary of all concomitant medications taken during the period in which the patients received study medication is provided in NDA Appendix 29. Every patient in the Safety population received at least one concomitant treatment. The overall distribution of the number of treatments was very similar between placebo (8621 treatments) and the 20 mg ibandronate group (8669 treatments) but was slightly higher in the case of the 2.5 mg ibandronate group (9377 treatments). The most frequent concomitant medications were calcium and vitamin D as adjuvant therapy for osteoporosis. The most frequently administered other concomitant medications were those used to treat digestive disorders (antacids, antiflatulents, antipeptic ulcerants), musculoskeletal disorders (analgesics, antiinflammatories), and cardiovascular disorders (anticoagulants, beta blockers, cholesterol reducers, arteriolar smooth muscle agents, renin-angiotensin system agents, myocardial agents). Only minor differences were observed between treatment groups, and these were not considered to indicate any safety issue undetected by the analysis of the safety/ tolerability profile as presented in 3.4.

The patients were prescribed, or distributed directly, concomitant calcium and vitamin D (see 2.6.5 and 2.6,7). The summaries in NDA Appendix 30 and Appendix 31 of the various types of calcium and vitamin D treatments show that at least 99% of patients in each treatment group were administered at least one medication with calcium and one with vitamin D. The average duration of calcium and vitamin D prescription was very similar among treatment groups (ranging between 2.38 and 2.43 years). The compliance (calculated based on the time the patients were on study) was also very similar, being between 96 and 97% for all treatment groups, both for calcium and vitamin D (Appendix 32 and Appendix 33).

2.3.3.1.5 Efficacy Results

(Sponsor's Analyses)

The Data Analysis Plan (DAP) differed substantially from the protocol. In the presence of a Data Analysis Plan (DAP), in general, sponsors no longer follow the protocol with respect to statistical analyses.

Date of finalization of DAP: 14th December 2000 (attachment to DAP finalized)

Date of Database Closure: 14th December 2000

Date of Randomization Code Release: 14th December 2000

The Data Analysis Plan (DAP) stated:

> **Primary Model for the Confirmatory Approach**
>
> The confirmatory analysis of the primary endpoint "incidence of new vertebral fractures" (as observed) will be done by testing, between the treatment groups, the homogeneity of the time-to-event curves with respect to the event 'first new incident vertebral fracture'. In the confirmatory analysis, all patient withdrawals will be considered censored observations, unless withdrawal was preceded by a new vertebral fracture.
>
> Events will be grouped to the first study year, second study year and third study year intervals. The intervals will be delineated on the basis of study days (see below). All events that occur after 3 years will be allocated to the third study year.
>
> The time- to- event analysis will be done according to the Cox regression method including the covariate BMD at baseline, to control for possible inhomogeneities between the treatment groups with respect to the number of "high" BMD patients and "low" BMD patients. The BMD criterion is selected to reflect the upper threshold for the definition of osteoporosis used in corresponding fracture studies with other agents and in osteoporosis guidelines.
>
> The covariate will be defined as a binary variable on the levels 0 and 1 as follows:
>
> 1) (High BMD): Baseline BMD at lumbar spine [L2- L4]: > -2.0 SD T- score ,
>
> 0) (Low BMD): Remainder (this group includes specifically those with missing values for lumbar spine [L2- L4] BMD at baseline).

The p- value of the Wald statistics from this cox regression model will be decisive for the assessment of the treatment effects.

The relative risk reduction and corresponding confidence intervals of the first new incident vertebral fracture associated with placebo will be calculated by means of an appropriate adjusted Cox regression analysis for the individual ibandronate treatment groups.

In a first step, the cox regression model specified above will be extended by the interaction between treatment and BMD-covariate. In the event that this analysis does not reveal concerns with respect to different treatment effects in the two BMD subgroups, the estimate of the model without interaction (i. e. the model of the confirmatory p- value) will be used to give an estimate of the risk reduction. Otherwise, due to the definition of the covariate, the cox model with interaction allows for a specific investigation of the effect of the drug in the population defined by a BMD criterion of osteoporosis.

The proportional hazard analysis will be applied to a data-model adapted to a life-table approach with yearly intervals.

Details on how patients will be considered in the model of the life-table approach are in the Data Analysis Plan.

Statistical Hypotheses

The confirmatory efficacy analysis follows a set of partial a-priori defined and ordered hypotheses. The statistical hypotheses are ordered to investigate the difference in fracture incidences over three years between treatment groups at the same level of alpha. This ordering of hypotheses will allow for a test at the level of alpha = 5% each for each of the individual hypotheses, unless the previous hypothesis could not be rejected.

The partial a priori ordering of hypotheses is formally defined as follows:

Set 1:

H01: "There is no difference between placebo and the pooled ibandronate groups in the incidence of new incident vertebral fractures".

Set 2:

H02: "There is no difference between placebo and continuous daily administered 2.5 mg ibandronate in the incidence of new incident vertebral fractures".

H03: "There is no difference between placebo and intermittently administered 20 mg ibandronate in the incidence of new incident vertebral fractures".

Note: The reviewer commented during the protocol stage, "The sponsor must submit for review the proof, and not just some statements made in literature, that their set of a-priori defined and ordered hypotheses, each tested at the 5% level, controls the overall Type I error at 5% level." The sponsor did not respond. Fortunately, multiple-dose is not an issue now.

Set 3:

H04: "There is no difference between continuously daily administered 2.5 mg ibandronate and intermittently administered 20 mg ibandronate in the incidence of new incident vertebral fractures".

H02 and H03 are classified in one set of hypotheses.

The test procedure will first investigate, at the level of α=5%, whether H01 can be rejected. In case H01 is rejected, the hypotheses H02 and H03 will each be tested simultaneously at α=5%. If H02 and H03 are rejected, H04 will be tested at =5%.

Efficacy Results, Primary Analysis

In comparison to placebo, ibandronate treatment reduced after 3 years of treatment highly significantly the risk of a new incident vertebral fracture by 61.6% for the 2.5 mg daily and by 49.9% for the 20 mg intermittent group, respectively. The p-values for the treatment effect (estimated by a proportional hazards model without an interaction term for the BMD status at baseline) were p = 0.0003 (2.5 mg) and p = 0.0005 (20 mg), respectively. The reduction was robust and was consistently observed in a variety of subgroups.

Significant reductions of new vertebral fractures were observed in both treatment groups also after 2 years of treatment. A strong reduction was already evident in the 2.5 mg group after the first year (reduction of 57.9%; p = 0.0561).

Reviewer's Note: The rates 61.6% and 49.9% for the 2.5 mg group mentioned by the sponsor above are not appropriate because these are from the proportional-hazards model with the treatment by baseline BMD T-Score interaction. When there is an interaction term in the proportional hazards model, results depend on the coding and so different types of results can be obtained by different coding. These rates should be replaced by 52.2% and 49.1% obtained from the proportional-hazards model without interaction (as was done for the p-values). Ref: NDA Table 26 of the ISE (Integrated Summary of Efficacy) Section 9.1.2.1. Ideally, in the case of a serious interaction,

especially of a qualitative type as in this case, the results should be provided separately for the subgroups of the interacting factors. Also, the results were not consistent in all subgroups (significant treatment by factor interaction occurred for the 2.5mg vs placebo comparisons and the factors were: Baseline lumbar spine T-score, age, weight, years since menopause, and vitamin D status). See the subsection "Covariation, Interaction, and Subgroup Results" after the discussion of the main results in this section.

Significant reductions were observed with either regimen in the incidence of new or worsening vertebral fractures.

New Incident Vertebral Fractures

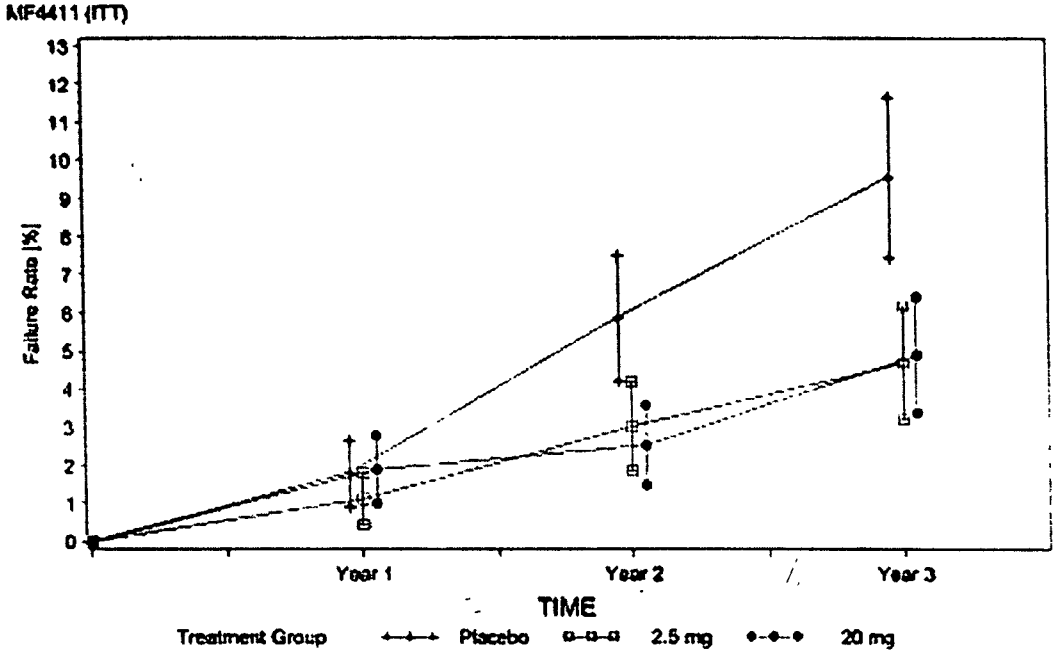
A total of 149 patients suffered at least one new vertebral fracture during the 3 years course of the trial. Such fractures were experienced by 73 patients on placebo, but only by 37 patients (2.5 mg) and 39 patients (20 mg) of the ibandronate groups. By a life-table approach, the rate over 3 years of ITT patients with new incident vertebral fractures was estimated to be 9.6% for the placebo group and 4.7% (2.5 mg) or 4.9% (20 mg) for the ibandronate treatment groups.

Primary Endpoint: New Vertebral Fracture– Oral Treatment Study MF 4411

	Placebo (N=975)	Iban 2.5 mg p.o. daily (N=977)	Iban 20 mg p.o. intermit. (N=977)	2.5 mg, 20 mg combined (N=1954)
Primary:				
Through Year 3:				
Patients with first new fracture	73	37	39	76
Estimate for incidence	9.56%	4.68%	4.90%	4.79%
95% CI for estimate	7.47% - 11.66%	3.20% - 6.16%	3.39% - 6.41%	3.74% - 5.85%
Secondary:				
Through Year 2:				
Patients with first new fracture	47	25	22	47
Estimate for incidence	5.87%	3.03%	2.61%	2.78%
95% CI for estimate	4.24% - 7.51%	1.85% - 4.20%	1.49% - 3.58%	2.00% - 3.57%
Through Year 1:				
Patients with first new fracture	16	13	17	27
Estimate for incidence	1.91%	1.11%	1.89%	1.50%
95% CI for estimate	0.93% - 2.69%	0.49% - 1.80%	1.00% - 2.98%	0.94% - 2.05%

Note: One patient in placebo group could not be evaluated for lack of a spine X ray at baseline.

Lifetable Failure Rate Estimates (95% CI) for First New Incident Vertebral Fracture (Study MF 4411)



§ Covariation, Interaction, and Subgroup Results

Note: The synopsis of this large subsection is provided in Section 2.3.3.1.6 Reviewer's Comments and Conclusions.

BMD was the only covariate pre-specified in the Data Analysis Plan, for inclusion in the Cox regression model, for primary analysis. The table below summarizes the covariation and interaction p-values from the Cox regression model fitted to the primary efficacy parameter, incidence of New Vertebral Fracture (based on the ITT population).

Covariation and Interaction P- values from Cox Regression Model Fitted to the Primary Efficacy Parameter (ITT)

	2.5mg vs. placebo		20mg vs. placebo	
	RRR	P-value	RRR	P-value
Treatment	61.62%	0.0001	49.87%	0.0006
BMD T-score	88.53%	0.0025	88.50%	0.0026
Treatment*BMD T-score	-940.53%	0.0043	-3.72%	0.9765

Note 1) BMD T- score has been classed as a binary covariate, 0= '≤ -2.0 SD' and 1= '>- 2.0 SD'.
2) RRR - Relative Risk Reduction

Note: See Reviewer's note above about the inappropriateness of the results for the 2.5 mg vs placebo comparison from this model with the interaction term.

The distribution of the small number of new fractures in the low risk group of patients with a BMD T- score > –2.0 was different to the new fractures found in the majority of patients with a T- score ≤-2.0. As a consequence, the interaction test between treatment and BMD T- score was significant for the 2.5 mg daily ibandronate treatment group (p= 0.0043), but not for the intermittent treatment group (p= 0.9765). This interaction is qualitative.

The following table presents the fracture incidence and relative risk reductions for the primary efficacy parameter for each BMD lumbar spine T-score level and each treatment group.

Lifetable Analysis for the First New Incident Vertebral Fracture and Estimate of Relative Risk Reduction through Year 3 by BMD Lumbar Spine L2-L4 T-score (ITT)

	Fracture Incidence			Relative Risk Reduction			
	Placebo	2.5mg	20mg	2.5mg vs. Placebo	p-value	20mg vs. Placebo	p-value
BMD Lumbar Spine (L2-L4)							
T-score ≤-2.0SD	11.47% (n=778)	4.55% (n=791)	5.85% (n=783)	61.63%	<0.0001	49.87%	0.0006
T-score >-2.0SD	1.44% (n=196)	5.28% (n=186)	0.58% (n=194)	-298.25%	0.0805	48.02%	0.5933

The treatment comparison p-values show that there was a greater treatment effect between 2.5mg versus placebo and 20mg versus placebo in the high-risk patients (i. e. BMD T- score <= -2.0 SD) than in the low-risk patient subgroup. In fact, in the low risk patient subgroup, the 2.5mg group was numerically far inferior to placebo and statistically nearly significantly inferior to placebo. That is, the interaction was

qualitative. The sponsor's p-value was 0.081 for this comparison in the low risk patient subgroup. By the reviewer's analysis, using SAS PROC LIFETEST, the p-value was 0.0587 (0.0591, when adjusted for "continent").

The distribution of fractures in the two subgroup-BMD levels was not consistent across all treatment groups. In the placebo and 20mg intermittent groups, the incidence of fractures in the high risk patients, namely patients with BMD T- score ≤-2.0 SD, was higher than that in the low risk patients, whereas a somewhat similar incidence was observed in the 2 levels of BMD T-score for the 2.5mg.

§ The following subgroup (or factors to be considered potential risk factors for fracture) analyses were exploratory:

All patients were female. Over 98% of all patients were Caucasians. Therefore, subgroup analyses were not applicable for these factors.

Seventy-three centers enrolled patients in MF4411, so a sub-group analysis with 73 levels would not be practical, instead the centers were grouped into continents (Europe, North America) and regions (Canada/ Montana/ Seattle, Other North America, Norway, Other European). In the model containing patients from the placebo and 2.5mg groups, the risk of a fracture in Europe is 41% higher than in North America, however the covariate 'Continent' is not significant at the 5% level. When Region was included in the model, 20mg result was non-significant.

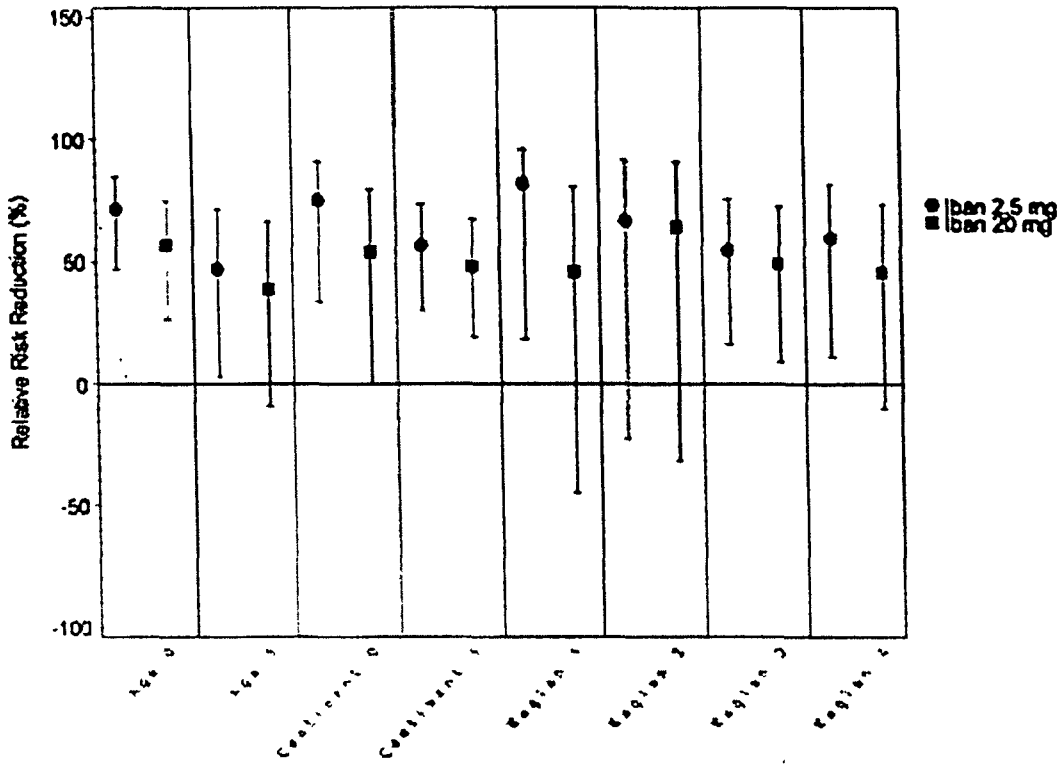
There was a statistically significant Age (<70 (Age 0) or ≥70 (Age 1)) by Treatment interaction (p= 0.0747) for the 2.5mg vs placebo comparison. The treatment benefit was more in the age group <70:

Lifetable Analysis for the First New Incident Vertebral Fracture and Estimate of Relative Risk Reduction through Year 3 by Age Group (ITT)

	Fracture Incidence			Relative Risk Reduction			
	Placebo	2.5mg	20mg	2.5mg vs. Placebo	p-value	20mg vs. Placebo	p-value
Age							
<70	10.96% (n=501)	3.88% (n=510)	4.78% (n=510)	71.48%	<0.0001	56.97%	0.0019
≥70	7.99% (n=473)	5.56% (n=467)	5.06% (n=467)	47.08%	0.0410	39.42%	0.0949

Note: 1) The Cox regression model also contained baseline lumbar spine t- score (≤-2.0 SD, >- 2.0 SD) as a covariate and the interaction between baseline lumbar spine t- score and treatment.

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



[<70 (Age 0), >=70 (Age 1), North America (Continent 0), Europe (Continent 1), Canada/Montana/Seattle (Region 1), Other North America (Region 2), Norway (Region 3), Other European (Region 4)]

The risk of the first new vertebral fracture is over 47% and over 39% less compared to placebo for all subgroup levels in the 2.5mg and the 20mg groups, respectively.

The relative risk reduction is higher for the 2.5mg group compared to the 20mg group for all subgroup levels.

The most relevant (thought by the sponsor) subgroup analyses (continent, BMI at baseline, age at baseline, time since menopause, number of prevalent fractures, lumbar spine BMD at baseline) are summarized in the Table and Figure below. The overall incidence of new vertebral fractures varied depending on the subgroup. Nevertheless, all subgroup analyses showed a robust trend to a reduction in fracture risk in both ibandronate treatment groups. These trends often reached statistical significance despite the fact that the study was not powered to show this for these sub-populations.

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

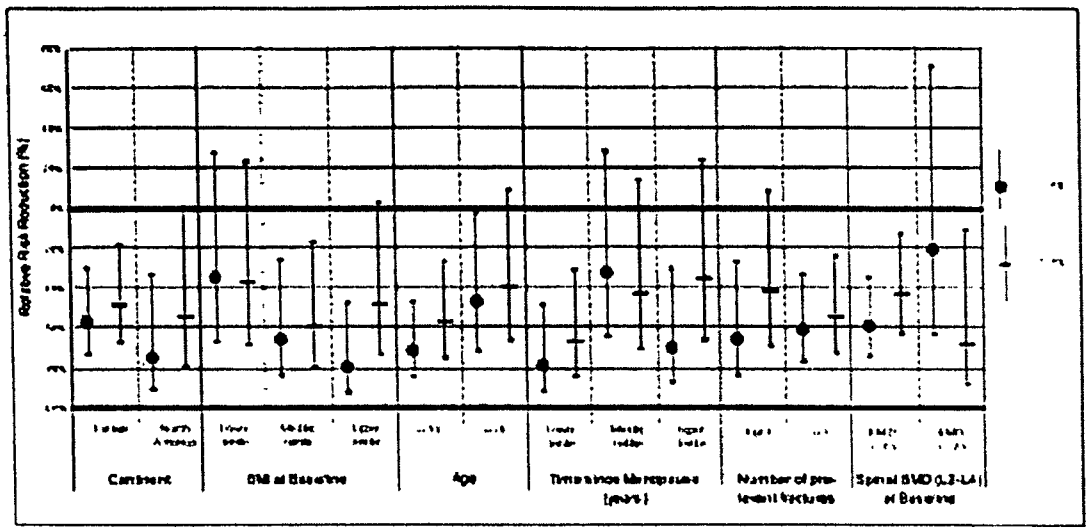
	Fracture Incidence			Relative Risk Reduction			
	Placebo	2.5 mg	20 mg	2.5 mg vs. Placebo	p-value	20 mg vs. Placebo	p-value
Continent:							
Europe	10.34%	5.37%	5.48%	56.86%	0.0007	48.47%	0.0044
North America	7.97%	3.22%	3.73%	75.12%	0.0054	54.44%	0.0522
BMI at Baseline:							
Lower tertile (≤ 23.96)	8.77%	5.76%	5.27%	34.79%	0.2107	37.85%	0.1721
Middle tertile (23.97-27.42)	10.04%	4.27%	3.98%	65.46%	0.0060	59.20%	0.0127
Upper tertile (≥ 27.43)	9.47%	3.94%	5.40%	79.90%	0.0011	47.69%	0.0564
Age (years):							
< 70	10.96%	3.88%	4.78%	71.48%	<0.0001	56.97%	0.0019
≥ 70	7.99%	5.56%	5.06%	47.08%	0.0410	39.42%	0.0949
Time since Menopause (years):							
Lower tertile (≤ 17)	10.40%	2.16%	3.78%	78.88%	0.0006	66.79%	0.0031
Middle tertile (18-24)	8.21%	8.20%	4.77%	32.67%	0.2287	42.67%	0.1117
Upper tertile (≥ 25)	10.20%	3.62%	6.48%	70.05%	0.0052	35.51%	0.1863
Number of prevalent fractures:							
0 or 1	6.21%	2.43%	3.54%	65.76%	0.0056	41.97%	0.0868
≥ 2	14.00%	7.46%	6.76%	60.91%	0.0005	54.62%	0.0024
Spinal BMD (L2-L4) at Baseline:							
BMD < -2.5	12.54%	5.36%	7.28%	58.97%	0.0002	42.93%	0.0252
BMD ≥ -2.5	4.89%	3.71%	3.54%	20.99%	0.5492	67.67%	0.0221

Note: One patient in placebo group could not be evaluated for lack of a spine X-ray at baseline.

Relative risk reduction estimated by proportional hazard model with interaction (treatment * baseline T-Score ≤-2) for all subgroups, except for lumbar spine BMD, for which the interaction term is not applicable.

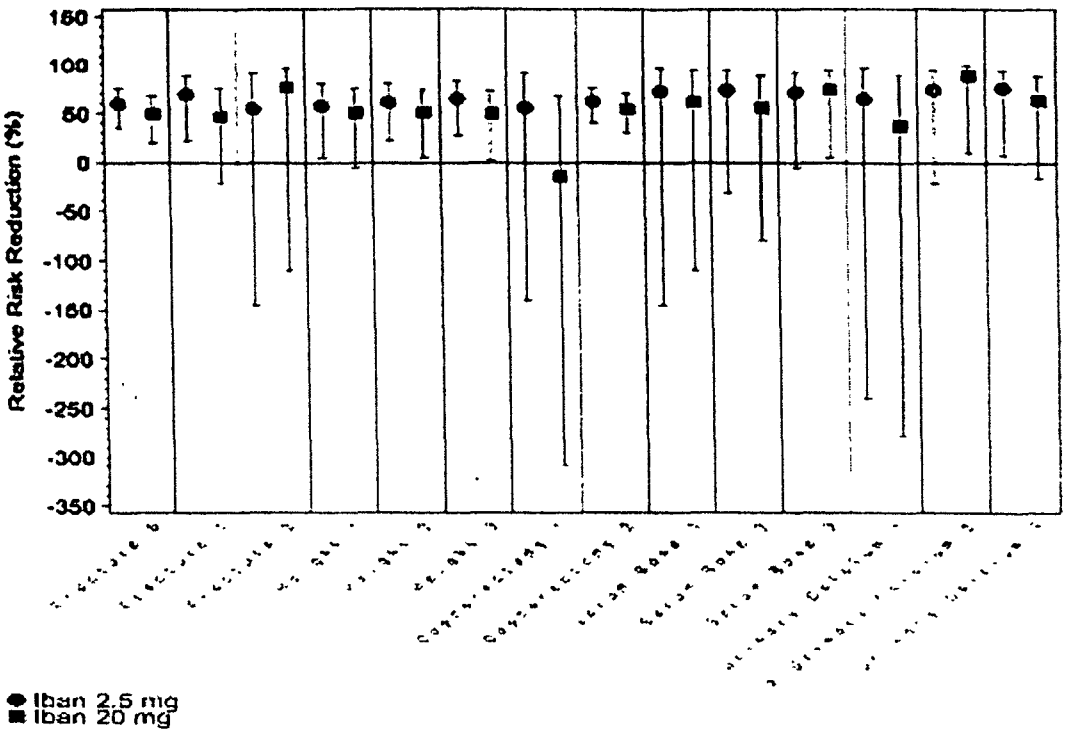
APPEARS THIS WAY
ON ORIGINAL

Figure for Reduction in Relative Risk (with 95% CI) of First New Incident Vertebral Fracture Through Year 3 in Selected Subgroups (ITT):



APPEARS THIS WAY
ON ORIGINAL

§ Figure for Reduction in Relative Risk (with 95% CI) of First New Vertebral Fracture Through Year 3 in Selected Subgroups (ITT):



For both active treatment groups, the reduction in the relative risk of the first new vertebral fracture for all subgroup levels is greater than 35% except for "History of Oopherectomy= Yes" for the 20mg group. The risk of a new vertebral fracture in the "History of Oopherectomy= Yes" subgroup level is higher in the 20mg group compared to placebo.

The risk of the first new vertebral fracture in the 2.5mg group is over 54% less compared to placebo for all subgroup levels.

The relative risk reduction is higher for the 2.5mg group compared to the 20mg group for all subgroup levels except, Fracture 2 (≥2 clinical fractures), Serum Bone 3 (serum bone-specific alkaline phosphatase > 48 U/ L) and Urinary Calcium 2 (urinary calcium between 0.255 and 0.424 mmol/ mmol).

Numerical Results:

	Fracture Incidence			Relative Risk Reduction			
	Placebo	2.5mg	20mg	2.5mg vs. Placebo	p-value	20mg vs. Placebo	p-value
Baseline Height (cm)							
Lower Tertile (< 157.48) (Height 1)	8.35% (n= 332)	4.06% (n=301)	3.82% (n=308)	57.7%	0.0382	50.2%	0.0695
Middle Tertile (157.48-162.56) (Height 2)	9.75% (n=346)	4.51% (n=337)	5.45% (n=328)	61.4%	0.0082	50.2%	0.0354
Upper Tertile (> 162.56) (Height 3)	10.4% (n=296)	5.38% (n=339)	5.34% (n=341)	65.1%	0.0054	49.2%	0.0458
History of Oopherectomy							
Yes (Oopherectomy 1)	4.30% (n=121)	2.83% (n=144)	4.44% (n=157)	55.9%	0.3448	-15.0%	0.8287
No (Oopherectomy 2)	10.30% (n=852)	5.00% (n= 833)	4.98% (n=820)	61.8%	<0.0001	54.0%	0.0003
Clinical Fractures in Last 5 Years							
0 (Fracture 0)	8.87% (n=765)	4.44% (n=716)	4.76% (n=756)	59.8%	0.0004	49.0%	0.0041
1 (Fracture 1)	11.25% (n=167)	4.66% (n=214)	5.97% (n= 179)	69.3%	0.0145	46.5%	0.1386
2 or more (Fracture 2)	14.65% (n=43)	8.31% (n=47)	2.60% (n=42)	54.8%	0.3593	76.4%	0.1965
Serum Bone Specific Alkaline Phosphatase (U/L)							
Lower Tertile (< 32) (Serum Bone 1)	6.65% (n=81)	4.01% (n=59)	4.00% (n=67)	72.5%	0.2481	61.6%	0.2685
Middle Tertile (32-48) (Serum Bone 2)	9.62% (n=81)	4.23% (n=91)	5.95% (n=81)	73.5%	0.1042	55.3%	0.2551
Upper Tertile (> 48) (Serum Bone 3)	17.17% (n=62)	5.48% (n=73)	4.44% (n=81)	71.4%	0.0608	74.1%	0.0429
Urinary Calcium/Creatinine (mmol/mmol)							
Lower Tertile (< 0.255) (Urinary Calcium 1)	5.31% (n=78)	3.88% (n=64)	3.51% (n=74)	64.6%	0.3687	37.0%	0.6135
MiddleTertile (0.255-0.424) (Urinary Calcium 2)	13.42% (n=80)	4.71% (n=77)	1.94% (n=63)	73.9%	0.0859	88.4%	0.0410
Upper Tertile (> 0.424) (Urinary Calcium 3)	14.95% (n=61)	5.31% (n=76)	8.63% (n=86)	75.9%	0.0395	63.2%	0.0882

Following is a Table for factor-Covariation, treatment, and treatment by factor interaction p-values for some factors:

P- Values from Cox's Proportional Hazards Model

	2.5mg vs. placebo P-value	20mg vs. placebo P-value
Low Weight	0.1927	0.1999
Medium Weight	0.3986	0.3923
Treatment	0.0001	0.0143
Low Weight*Treatment	0.0468	0.3482
Medium Weight*Treatment	0.2585	0.9406
Low BMI	0.4266	0.4224
Medium BMI	0.8362	0.8308
Treatment	0.0011	0.0527
Low BMI*Treatment	0.1838	0.8082
Medium BMI*Treatment	0.7354	0.6147
Low Years Since Menopause	0.9399	0.9218
Medium Years Since Menopause	0.4669	0.4755
Treatment	0.0019	0.1506
Low Years*Treatment	0.2961	0.2426
Medium Years*Treatment	0.0440	0.8677
No of Prevalent Fractures	0.0005	0.8006
Treatment	0.2929	0.1148
No of Prevalent Fractures*Treatment	0.3533	0.6510
History of Osteoporotic Fractures	0.2549	0.2579
Treatment	0.1058	0.2016
History of Osteoporotic Fractures*Treatment	0.8992	0.8484
Low BMD T-score of the HIP	0.4756	0.4800
Medium BMD T-score of the HIP	0.6615	0.6621
Treatment	0.0046	0.0654
Low BMD T-score*Treatment	0.6964	0.5846
Medium MD T-score*Treatment	0.8047	0.8138

Note: 1) The Cox regression model also contained baseline lumbar spine t-score (<-2.0SD, ≥-2.0SD) as a covariate and the interaction between baseline lumbar spine t-score and treatment.
2) Weight, BMI, Years sine Menopause and Baseline BMD T-scores have been split into 3 catergories using tertiles based on the following rules:
Low Weight: <= 61.2 Kg, Medium Weight: 61.2 Kg < Weight < 70 Kg, High Weight: >= 70 Kg
Low BMI:<= 24 Kg/M^2, Medium BMI:24 Kg/M^2<BMI<27.4 Kg/M^2, High BMI:>= 27.4 Kg/M^2
Low Meno: <= 17 yrs, Medium Meno:17 yrs< Meno <24 yrs, High Meno: >= 24 yrs
Low BMD: <= -2.1 g/cm^2, Medium BMD:-2.1 g/cm^2< BMD<-1.4 g/cm^2, High BMD:>=-1.4 g/cm^2
3) Number of Prevalent Fractures at baseline has been classed as a binary covariate. 1=none or 1 and 2=2 or more
4) History of osteoporotic fractures has been classed as a binary covariate. 1=YES and 2=NO.

The non-significant treatment p-values corresponding to factors/covariates "No of Prevalent Vertebral Fractures" and "History of Osteoporotic Fractures" turned significant by the reviewer's analyses excluding the interaction term (this is appropriate because the interaction is not significant) and excluding baseline lumbar spine T-score (otherwise multi-collinearity may occur). The sponsor also provided significant p-values later in the 3-24-03 submission. However, their following argument may be controversial:

> "Please note that the coding used to represent the 'number of prevalent fractures' has changed (footnote marked in bold). The original coding used was 1 and 2 to represent the two levels, it has now been changed to 0 and 1 in order to help interpret the interaction term more easily. As you can see the p- values for the number of prevalent fractures and the interaction term in Table 13 have not

changed from the previous values sent, however the treatment term is now significant.

By using the original coding, the interaction term was acting as a covariate describing the 2.5mg group (over parameterisation). This was reducing the treatment effect accordingly. The new coding now represents the interaction between the number of prevalent fractures and treatment group correctly."

When only the 2.5mg and placebo arms are considered, there were statistically significant Treatment by Weight (low and high, excluding medium group) and Treatment by Years Since Menopause (medium and high, excluding low group) interactions (2-25-03 and 3-24-03 submissions). However, the analysis by including each interaction term in the model separately, provided statistically significant p-values for the 2.5mg vs placebo comparisons,

The distribution of fractures across the three weight levels is not consistent between the treatment groups. For placebo, there is a slightly increasing trend in the fracture incidence as weight increases, whereas for the 2.5mg group, a slight decreasing trend is observed:

Lifetable Analysis for the First New Incident Vertebral Fracture and Estimate of Relative Risk Reduction through Year 3 by Weight (ITT)

	Fracture Incidence			Relative Risk Reduction			
	Placebo	2.5mg	20mg	2.5mg vs. Placebo	p-value	20mg vs. Placebo	p-value
Weight							
Low weight	8.78% (n=328)	6.02% (n=333)	5.74% (n=316)	31.75%	0.2585	28.51%	0.3208
Medium weight	9.22% (n=330)	4.60% (n=320)	4.15% (n=332)	57.66%	0.0224	58.24%	0.0165
High weight	10.35% (n=315)	3.44% (n=324)	4.84% (n=329)	86.43%	0.0002	56.86%	0.0167

Note: 1) The Cox regression model also contained baseline lumbar spine t- score (≤ -2.0 SD, >- 2.0 SD) as a covariate and the interaction between baseline lumbar spine t- score and treatment. 2) Weight has been split into 3 categories using tertiles based on the following rules: Low Weight: <= 61. 2 Kg, Medium Weight: 61. 2 Kg < Weight <= 70 Kg, High Weight: > 70 Kg

With respect to Years Since Menopause, in the 2.5mg group, the relative Risk Reduction was 70% (much higher) in the upper tertile (>24) of the Years Since Menopause, compared with 33% in the medium tertile (18-24):

Lifetable Analysis for the First New Incident Vertebral Fracture and Estimate of Relative Risk Reduction through Year 3 by Years Since Menopause (ITT)

	Fracture Incidence			Relative Risk Reduction			
	Placebo	2.5mg	20mg	2.5mg vs. Placebo	p-value	20mg vs. Placebo	p-value
Years Since Menopause							
Low level	10.40% (n=323)	2.16% (n=334)	3.78% (n=331)	79.23%	0.0006	66.79%	0.0031
Medium level	8.21% (n=341)	8.20% (n=333)	4.77% (n=336)	32.67%	0.2287	42.67%	0.1117
High level	10.28% (n=308)	3.62% (n=310)	6.48% (n=309)	70.05%	0.0052	35.51%	0.1863

Note: 1) The Cox regression model also contained baseline lumbar spine t- score (≤ -2.0 SD, >- 2. 0 SD) as a covariate and the interaction between baseline lumbar spine t- score and treatment. 2) Years since Menopause has been split into 3 categories using tertiles based on the following rules: Low Meno: <= 17 yrs, Medium Meno: 17 yrs< Meno <= 24 yrs, High Meno: > 24 yrs These ranges were then used to create binary dummy.covariates.

There was a difference in the distribution of fractures amongst the low and high Vitamin D tertile levels and the treatment groups (interaction p-value = 0.038). For the placebo group, the incidence of fractures decreased in the high vitamin D level compared to the low and medium vitamin D levels, whereas for the 2.5mg group, the incidence of fractures increased in the high vitamin D level. The treatment effect between the 2.5mg group and placebo was nominally significant for the low and medium levels of vitamin D. Although the treatment effect between 2. 5 mg and placebo was not significant at the 5% level in the high level group, a risk reduction of 25% was observed.

Lifetable Analysis for the First New Incident Vertebral Fracture and Estimate of Relative Risk Reduction through Year 3 by Vitamin D Status at Baseline (ITT)

	Fracture Incidence			Relative Risk Reduction			
	Placebo	2.5mg	20mg	2.5mg vs. Placebo	p-value	20mg vs. Placebo	p-value
Vitamin D Status							
Low level	10.41% (n=314)	3.58% (n=346)	5.61% (n=323)	65.61%	0.0603	49.76%	0.0379
Medium level	10.26% (n=335)	5.81% (n=307)	4.51% (n=299)	43.13%	0.1647	56.48%	0.0287
High level	8.21% (n=318)	6.74% (n=317)	4.65% (n=346)	25.25%	0.3944	41.51%	0.1362

Note: 1) The Cox regression model also contained baseline lumbar spine t- score (-2. 0SD, >- 2. 0SD) as a covariate and the interaction between baseline lumbar spine t- score and treatment. 2) Baseline Vitamin D Status has been split into 3 categories using tertiles based on the following rules: Low Vitamin D: <= 33ng/ ml, Medium Vitamin D: 33ng/ ml < Vitamin D <= 46ng/ ml, High Vitamin D: > 46ng/ ml

The sponsor has provided a "Consolidated Discussion of Subgroup Analyses of New Vertebral Fractures" in the NDA Module V, Section 2.2.2.3.

§ Five variables were found to have a significant imbalance (without multiple comparison adjustments) between at least one of the active treatment groups versus

placebo at baseline. Three of those variables (body height, clinical fractures in last 5 years, and serum bone-specific alkaline phosphatase) were for differences between the 2.5mg group versus placebo.

All five parameters, body height, history of oophorectomy, number of previous clinical fractures in the last 5 years, serum bone-specific alkaline phosphatase and urinary calcium were included separately into the primary efficacy model. The following table shows the significance of each parameter in predicting the primary efficacy endpoint (based on the ITT population).

Test of the Individual Covariates in the Cox Regression

Covariate in the Model	2.5mg vs. placebo P-value	20mg vs. placebo P-value
Body height	0.1853	0.1503
Treatment	<0.0001	0.0006
History of oophorectomy	0.8378	0.1543
Treatment	<0.0001	0.0007
No. of prev. fractures in last 5 years	0.0971	0.3470
Treatment	<0.0001	0.0006
Serum bone-specific alkaline phosphatase	0.0225	0.0236
Treatment	0.8051	0.0095
Urinary calcium	0.7606	0.7514
Treatment	0.0072	0.0110

Note: Model also included terms for treatment, BMD lumbar spine (L2- L4) T-score and their interaction.

Serum bone-specific alkaline phosphatase was found to be a significant predictor of new vertebral fractures at 3 years for all treatment groups. A higher baseline serum bone-specific alkaline phosphatase value was associated with a higher fracture risk.

History of oophorectomy was also a significant predictor for placebo and the 2. 5mg group. A higher risk of fracture was associated with no history of oophorectomy.

For each Cox regression model fitted above, the treatment group parameter was also found to be a significant predictor of the primary efficacy endpoint for both doses.

In addition to including the significant baseline variables separately, all five variables were entered together, and the least significant was removed from the model (one at a time), using a backward selection procedure (using a selection criterion of 7.5%).

Test of Covariates in the Cox Regression Model using a Backward Selection Procedure (2.5mg vs. placebo)

	P-value				
	Step 1	Step 2	Step 3	Step 4	Step 5
Body height	0.4615	0.4603*			
History of oophorectomy	0.4269	0.4432	0.4199*		
Prev. Clinical Fractures in last 5 yrs	0.3306	0.3209	0.2770	0.2493*	
Serum bone-specific alk. Phos.	0.0180	0.0149	0.0157	0.0206	0.0225
Urinary Calcium	0.7965*				

Note: Group, BMD T- score and the interaction term were kept in the model.
Only patients with non- missing baseline parameter values were included.
* Variable to be dropped from the model

Test of Covariates in the Cox Regression Model using a Backward Selection Procedure (20mg vs. placebo)

	P-value				
	Step 1	Step 2	Step 3	Step 4	Step 5
Body height	0.8577*				
History of oophorectomy	0.8396	0.8397*			
Prev. Clinical Fractures in last 5 yrs	0.1448	0.1472	0.1402	0.1146*	
Serum bone-specific alk. Phos.	0.0206	0.0203	0.0211	0.0213	0.0236
Urinary Calcium	0.6574	0.6628	0.6599*		

Note: Group, BMD T- score and the interaction term were kept in the model.
Only patients with non- missing baseline parameter values were included.
*Variable to be dropped from the model.

Only serum bone-specific alkaline phosphatase was found to be a statistically significant predictor of new vertebral fractures at year 3 for all treatment groups.

For each Cox regression model fitted above, the treatment group parameter was also found to be a significant predictor of the primary efficacy endpoint overall ($p < 0.02$).

§ **Sponsor's Sensitivity Analyses** (Various Analyses of the Primary Efficacy Parameter)

Treatment Comparison	Analysis	P-value	Population	Relative Risk Reduction	95% CI for reduction
2.5mg versus placebo	Life table	0.0002	ITT		
2.5mg versus placebo	Sensitivity Life table	0.0002	ITT		
2.5mg versus placebo	Cox regression (exc. baseline BMD)	0.0003	ITT	51.81%	28.43% - 67.56%
2.5mg versus placebo	Cox regression (inc. baseline BMD)	0.0003	ITT	52.11%	28.88% - 67.76%
2.5mg versus placebo	Cox regression (inc. baseline BMD and interaction)	0.0001	ITT	61.62%	40.89% - 75.08%
2.5mg versus placebo	Sensitivity Cox regression (exc. baseline BMD)	0.0002	ITT	48.55%	26.63% - 63.92%
2.5mg versus placebo	Sensitivity Cox regression (inc. baseline BMD)	0.0002	ITT	48.73%	26.90% - 64.05%
2.5mg versus placebo	Sensitivity Cox regression (inc. baseline BMD and interaction)	<0.0001	ITT	58.58%	38.71% - 72.01%
2.5mg versus placebo	Cox regression (exc. baseline BMD)	0.0023	PP	48.21%	20.90% - 66.10%
2.5mg versus placebo	Cox regression (inc. baseline BMD)	0.0021	PP	48.64%	21.54% - 66.37%
2.5mg versus placebo	Cox regression (inc. baseline BMD and interaction)	0.0001	PP	59.11%	35.22% - 74.20%
20mg versus placebo	Life table	0.0006	ITT		
20mg versus placebo	Sensitivity Life table	0.0007	ITT		
20mg versus placebo	Cox regression (exc. baseline BMD)	0.0007	ITT	48.96%	24.71% - 65.40%
20mg versus placebo	Cox regression (inc. baseline BMD)	0.0005	ITT	49.82%	25.98% - 65.99%
20mg versus placebo	Cox regression (inc. baseline BMD and interaction)	0.0006	ITT	49.87%	25.66% - 66.20%
20mg versus placebo	Sensitivity Cox regression (exc. baseline BMD)	0.0009	ITT	44.32%	21.32% - 60.59%
20mg versus placebo	Sensitivity Cox regression (inc. baseline BMD)	0.0007	ITT	45.01%	22.30% - 61.08%
20mg versus placebo	Sensitivity Cox regression (inc. baseline BMD and interaction)	0.0012	ITT	44.19%	20.49% - 60.83%
20mg versus placebo	Cox regression (exc. baseline BMD)	0.0028	PP	47.62%	20.00% - 65.71%
20mg versus placebo	Cox regression (inc. baseline BMD)	0.0019	PP	48.96%	22.04% - 66.58%
20mg versus placebo	Cox regression (inc. baseline BMD and interaction)	0.0016	PP	49.84%	22.96% - 67.34%

Sponsor's Comment: Therefore, the primary efficacy results from MF4411 are consistent using the various defined populations, and different survival analysis techniques.

2.3.3.1.6 Reviewer's Comments and Conclusions on Study MF 4411

This study has provided statistical evidence of efficacy for both the ibandronate doses studied, especially the 2.5 mg dose. Various analyses by the sponsor (sensitivity analyses above) and by the reviewer (SAS PROC LIFETEST and PHREG) as well as a crude analysis (Fisher's exact test by the reviewer) were performed.

If statistical significance is not mentioned, then the comparison is only numerical. BMD was the only covariate pre-specified in the Data Analysis Plan, for inclusion in the Cox regression model of the primary analysis. The distribution of the small number of new fractures in the low risk group of patients with a BMD T- score > –2.0 was different to the new fractures found in the majority of patients with a T- score ≤-2.0. As a consequence, the interaction test between treatment and BMD T- score was significant for the 2.5 mg daily ibandronate treatment group (p= 0.0043), but not for the intermittent 20 mg treatment group (p= 0.9765). There was a greater treatment effect between 2.5mg versus placebo and 20mg versus placebo in the high-risk patients (i.e. BMD T- score <= -2.0 SD) than in the low risk patient subgroup. In fact, in the low risk patient subgroup, the 2.5mg group was numerically far inferior to placebo and statistically nearly significantly inferior to placebo. That is, the interaction was qualitative.

The following subgroup analyses were exploratory:

There was a statistically significant Age [<70 (Age 0) or ≥70 (Age 1)] by Treatment interaction (p= 0.0747) for the 2.5mg vs placebo comparison. The treatment benefit was more in the age group <70.

When Region was included in the model, 20mg result was non-significant. The relative risk reductions observed for the 2.5mg daily group versus placebo were a reduction of 54.8% in Norway, a reduction of 59.8% in Other European, a reduction of 81.9% in Canada/ Montana/ Seattle and 66.8% in Other North American.

When only the 2.5mg and placebo arms are considered, there were statistically significant Treatment by Weight (low and high, excluding medium group) and Treatment by Years Since Menopause (medium and high, excluding low group) interactions (2-25-03 and 3-24-03 submissions). However, the analysis by including each interaction term in the model separately, provided statistically significant p-values for the 2.5mg vs placebo comparisons.

The distribution of fractures across the three weight levels was not consistent between the treatment groups. For placebo, there was a slightly increasing trend in the fracture

incidence as weight increases, whereas for the 2.5mg group, a slight decreasing trend was observed.

With respect to Years Since Menopause, in the 2.5mg group, the relative Risk Reduction was 70% (much higher) in the upper tertile (>24) of the Years Since Menopause, compared with 33% in the medium tertile (18-24).

There was a difference in the distribution of fractures amongst the low and high Vitamin D tertile levels and the treatment groups (interaction p-value = 0.038). For the placebo group, the incidence of fractures decreased in the high vitamin D level compared to the low and medium vitamin D levels, whereas for the 2.5mg group, the incidence of fractures increased in the high vitamin D level. The treatment effect between the 2.5mg group and placebo was nominally significant for the low and medium levels of vitamin D. Although the treatment effect between 2. 5 mg and placebo was not significant at the 5% level in the high level group, a risk reduction of 25% was observed.

In summary, all the treatment by factor interaction occurred for the 2.5mg vs placebo comparisons and the factors were: Baseline lumbar spine T-score, age, weight, years since menopause, vitamin D status.

§ For all subgroup levels based on Age, Continent, and Region, the risk of the first new vertebral fracture is over 47% and over 39% less compared to placebo in the 2.5mg and the 20mg groups respectively. The relative risk reduction is higher for the 2.5mg group compared to the 20mg group.

§ The overall incidence of new vertebral fractures varied more or less depending on the subgroup (continent, BMI at baseline, age at baseline, time since menopause, number of prevalent fractures, lumbar spine BMD at baseline). Nevertheless, all subgroup analyses showed a robust trend to a reduction in fracture risk in both ibandronate treatment groups. These trends often reached statistical significance despite the fact that the study was not powered to show this for these sub-populations.

§ Graphs and numerical results for subgroups based on Baseline Height, History of Oopherectomy, Clinical Fractures in Last Five Years, Serum Bone Specific Alkaline Phosphatase (U/L), Urinary Calcium/Creatinine (mmol/mmol) are provided in the previous Section. For both active treatment groups, the reduction in the relative risk of the first new vertebral fracture for all subgroup levels is greater than 35%, except for "History of Oopherectomy= Yes" for the 20mg group. The risk of a new vertebral fracture in the "History of Oopherectomy= Yes" subgroup level is higher in the 20mg group compared to placebo. The risk of the first new vertebral fracture in the 2.5mg group is over 54% less compared to placebo for all subgroup levels.

The relative risk reduction is higher for the 2.5mg group compared to the 20mg group for all subgroup levels except, Fracture 2 (≥2 clinical fractures), Serum Bone 3 (serum bone-

specific alkaline phosphatase > 48 U/ L) and Urinary Calcium 2 (urinary calcium between 0.255 and 0.424 mmol/ mmol).

§ Five variables (body height, history of oophorectomy, number of previous clinical fractures in the last 5 years, serum bone-specific alkaline phosphatase and urinary calcium) were found to have a significant imbalance (without multiple comparison adjustments) between at least one of the active treatment groups versus placebo at baseline.

Serum bone-specific alkaline phosphatase was found to be a significant predictor of new vertebral fractures at 3 years for all treatment groups. A higher baseline serum bone-specific alkaline phosphatase value was associated with a higher fracture risk.

History of oophorectomy was also a significant predictor for placebo and the 2. 5mg group. A higher risk of fracture was associated with no history of oophorectomy.

For each Cox regression model fitted, the treatment group parameter was also found to be a significant predictor of the primary efficacy endpoint ($p < 0.02$).

2.3.3.2 Study MF 4499

Synopsis of the Study follows:

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT Clinical Study Report – Protocol MF 4499: Dose- finding study on 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). Research Report 1004114 / May 8, 2002.

INVESTIGATORS / CENTERS AND COUNTRIES: Twelve investigators at 11 study centers in the United States and Canada.

PERIOD OF TRIAL: August 4, 1998 to March 21, 2001 CLINICAL PHASE: III

OBJECTIVES: The objective of study MF 4499 was to investigate the dose-response, efficacy, and safety of continuous oral ibandronate administration for the prevention of bone loss in postmenopausal women, and to define the optimum dose to prevent bone loss.

STUDY DESIGN: MF 4499 was a randomized, double- blind, placebo- controlled, dose-finding study. Patients were allocated into 1 of 4 strata according to the length of time

since menopause and the baseline BMD T- score of the lumbar spine (L1- L4), then randomized into 1 of 4 dose groups [placebo or ibandronate (0.5, 1.0, or 2.5 mg)].

NUMBER OF SUBJECTS: A total of 653 patients were randomized into the trial - 162 in placebo, 162 in 0.5 mg, 165 in 1.0 mg, and 163 in 2.5 mg groups.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: A patient was included in the study if she was a woman at least 1 year post- menopause and provided written informed consent.

DOSE / ROUTE / REGIMEN / DURATION: Patients received one tablet of oral study medication daily for two years. Patients took medication with at least 100 ml (4 oz.) of plain water after waking up in the morning; and were not to recline after intake. No food or liquid except water was to be ingested for at least 6 hours prior to and at least 30 minutes following intake of medication.

EFFICACY: The primary variable was the relative change from baseline in BMD of the lumbar spine (L1- L4) after 2 years of treatment. Secondary variables were: absolute and relative change (from placebo) in BMD of lumbar spine, forearm, and proximal femur, absolute and relative change in total body bone mass, and change from baseline and placebo in rate of bone turnover (assessed by serum CTX, parathyroid hormone and osteocalcin concentrations, and urinary CTX excretion).

STATISTICAL METHODS:

A closed test procedure was adopted for the primary efficacy variable. The statistical hypotheses were ordered to investigate the difference between the treatment groups for relative change in BMD of the lumbar spine after 2 years of treatment, at the same alpha level. This ordering of hypotheses allowed for a test at the level of alpha = 5% for each of the individual hypotheses, unless the previous hypothesis could not be rejected. The primary model was an ANOVA which took treatment and allocated stratum into account as independent factors. The primary analysis group was the ITT population. Subgroup analyses for the primary efficacy variable were conducted for stratum, weight, calcium compliance, baseline vitamin D status, and time since menopause. A one- way ANOVA model which contained only the treatment factor was used.

The methods for the secondary variables for the comparison between treatment groups of relative change in BMD were the same as those used for the analysis of the primary variable. The Wilcoxon Rank- Sum test was used for the comparison between treatment groups for relative change from baseline in markers of bone turnover and PTH.

2.3.3.2.1 Objective

The objective is to investigate the efficacy, dose- response and safety of ibandronate in daily oral administration for the prevention of bone loss in ostmenopausal women, and to determine the optimum dose that prevents such bone loss.

2.3.3.2.2 Disposition of Patients

A total of 653 patients (of 1484 screened) at 11 study centers in the United States and Canada were assigned to one of four strata (Table below), 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 (Appendix t- pops Summary of Analysis Populations page 89 of Report). Five patients did not receive study medication (three in placebo and one each in the 0.5 mg and 1.0 mg groups). Of the 648 patients who received at least one dose of study medication, 547 (84.4%) completed the full two years of treatment.

Distribution of Randomized Patients by Stratum and Treatment Group:

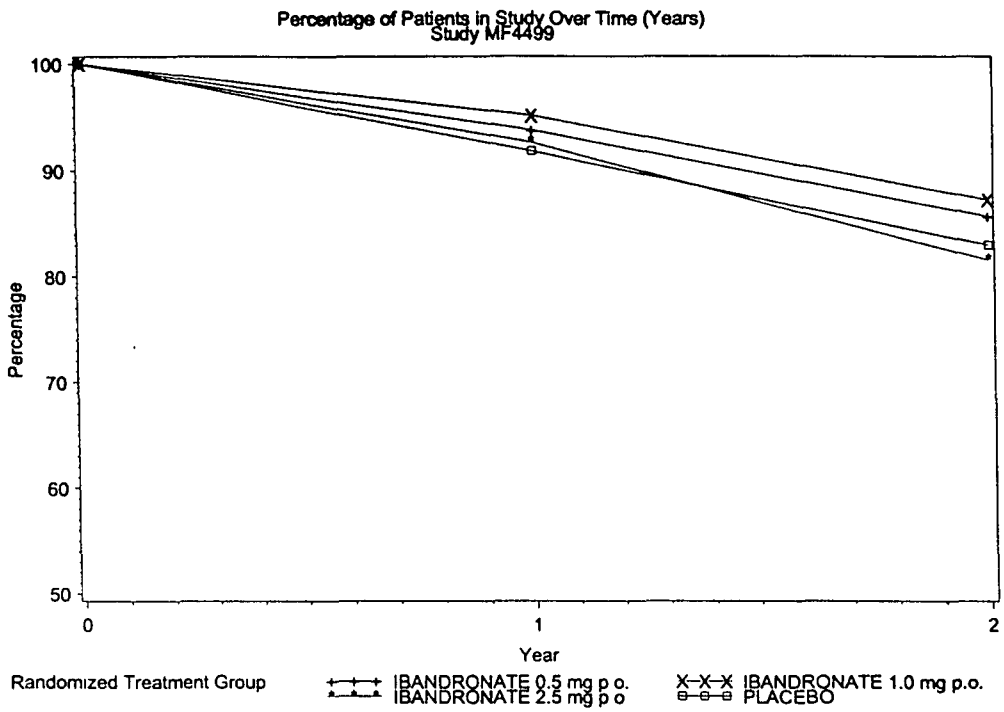
Stratum (T-score, TSM)	Daily Placebo N	Oral Daily Ibandronate 0.5mg N	1.0 mg N	2.5 mg N
A (> -1 SD, 1-3 yrs)	29	27	28	28
B (-1 to -2.5 SD, 1-3 yrs)	48*	50	53*	48
C (> -1 SD, > 3 yrs)	29*	29	29	29
D (-1 to -2.5 SD, > 3 yrs)	56*	56*	56	58
Total	162	162	166	163

*One patient did not receive study medication.
Source: \PROD\cdp10131\nda\reports\t_demo_ran.rtf 19NOV2001 15:31

Summary of Patients Prematurely Withdrawn from Treatment (Safety):

	PLACEBO (N=159)	IBANDRONATE 0.5 mg p.o (N=161)	IBANDRONATE 1.0 mg p.o (N=165)	IBANDRONATE 2.5 mg p.o (N=163)
Number of patients who withdrew from trial treatment	27 (17%)	23 (14%)	21 (13%)	30 (18%)
Primary reason for early withdrawal				
ADVERSE EVENT(S)	14 (9%)	8 (5%)	8 (5%)	12 (7%)
DEATH			1 (1%)	
LOST TO FOLLOW-UP	5 (3%)	7 (4%)	4 (2%)	10 (6%)
NON-COMPLIANCE WITH TRIAL PROTOCOL	1 (1%)		3 (2%)	2 (1%)
OTHER REASONS		1 (1%)		3 (2%)
PERSONAL REASONS	6 (4%)	7 (4%)	5 (3%)	3 (2%)

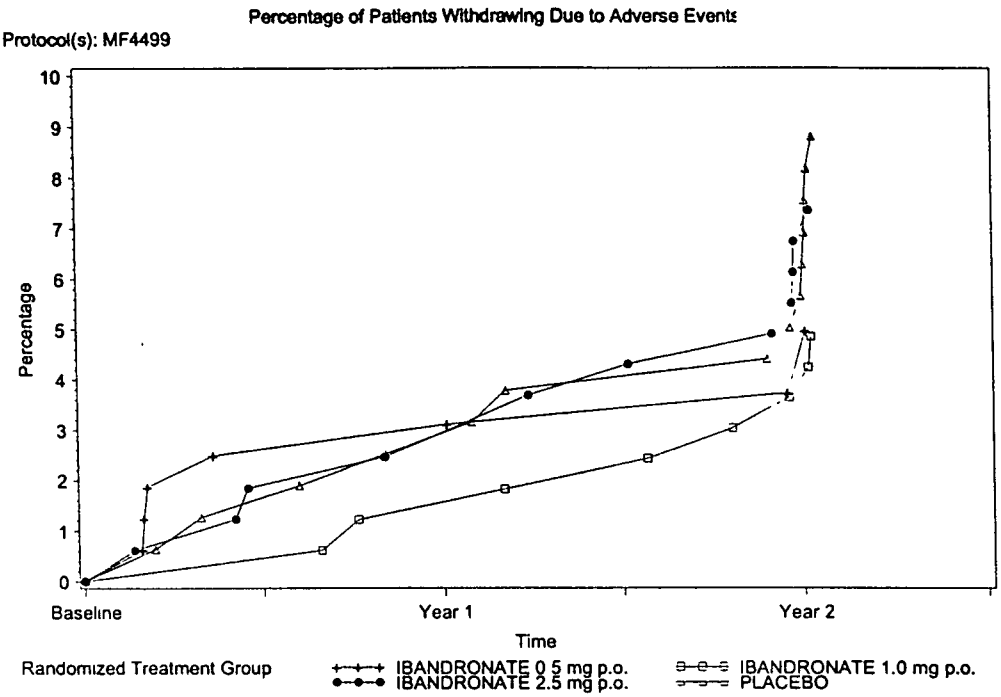
Figure for Distribution of Treatment Completion/Withdrawal by Year (Safety)



Program . $PROD/cdp10131/mf4499/prem_with.sas / Output : $PROD/cdp10131/mf4499/reports/prem_withall.cgm
13NOV2002 18 19

APPEARS THIS WAY
ON ORIGINAL

Figure for Distribution of Withdrawals (Cumulative) due to Adverse Events by Year (Safety)



Program . $PROD/cdp10131/mf4499/prem_with2.sas / Output : $PROD/cdp10131/mf4499/reports/prem_with2ae.cgm
13NOV2002 18 44

Less than 10% of the patients in each treatment group withdrew during the first year. This percentage did increase during the second year to less than 20%. In addition, the number of patients that withdrew due to an adverse event was highest in the placebo group (8.81%).

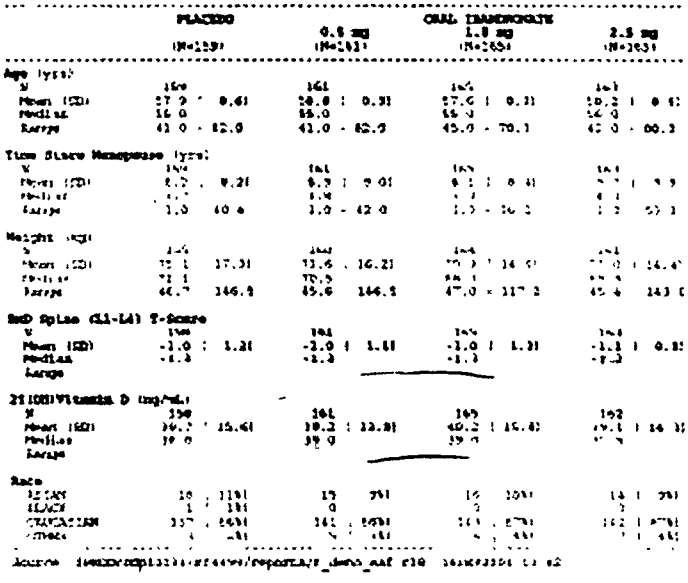
Overview of Analysis Populations

The demographic and safety analyses include data for all patients who were administered study medication and had at least one follow-up visit. Two analyses were performed for the efficacy parameters, ITT and PP. Efficacy data presented in this report express results from the ITT population; the corresponding analyses for the PP population have been included as appendices.

ANALYSIS POPULATION	PLACEBO (N=162)	ORAL IBANDRONATE 0.5 mg (N=162)	1.0 mg (N=166)	2.5 mg (N=163)
ITT				
Included	150	157	160	153
Excluded	12 (100.0%)	5 (100.0%)	6 (100.0%)	10 (100.0%)
Primary reason for exclusion				
NO TRIAL MEDICATION TAKEN	3 (25.0%)	1 (20.0%)	1 (16.7%)	0 (0.0%)
NO BASELINE END ASSESSMENT	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
NO FOLLOW-UP END ASSESSMENT	8 (66.7%)	4 (80.0%)	5 (83.3%)	10 (100.0%)

2.3.3.2.3 Demographic and Other Baseline Characteristics

Summary of Baseline Demographic Characteristics (Safety):

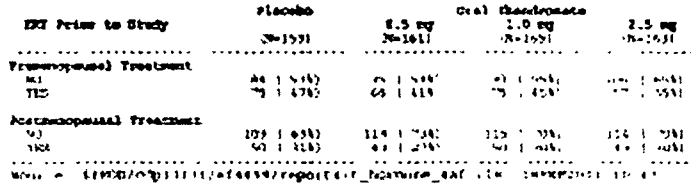


	PLACEBO (N=159)	ORAL IBANDRONATE 0.5 mg (N=161)	1.0 mg (N=165)	2.5 mg (N=163)
Age (yrs)				
N	159	161	165	163
Mean (SD)	57.9 (8.61)	58.8 (8.31)	57.6 (8.31)	58.2 (8.61)
Median	56.0	55.0	55.0	56.0
Range	41.0 - 82.0	41.0 - 82.0	45.0 - 70.1	41.0 - 80.3
Time Since Menopause (yrs)				
N	159	161	165	163
Mean (SD)	8.0 (8.28)	8.9 (9.01)	8.1 (8.41)	9.1 (9.9
Median	5.0	5.0	5.0	6.1
Range	1.0 - 40.6	1.0 - 42.0	1.0 - 36.2	1.0 - 55.3
Weight (kg)				
N	159	161	165	163
Mean (SD)	72.1 (17.31)	73.6 (16.21)	77.3 (16.0)	74.0 (16.4)
Median	71.1	70.5	76.1	73.5
Range	46.7 - 146.5	45.0 - 146.5	47.0 - 117.2	45.6 - 143.0
BMD Spine (L1-L4) T-Score				
N	159	161	165	163
Mean (SD)	-1.9 (1.21)	-2.0 (1.11)	-1.9 (1.31)	-1.9 (0.81)
Median	-1.8	-1.8	-1.8	-1.8
Range				
25(OH)Vitamin D (ng/mL)				
N	158	161	165	162
Mean (SD)	30.2 (15.61)	30.2 (13.81)	29.2 (15.61)	29.1 (14.3)
Median	28.0	28.0	28.0	27.5
Range				
Race				
[illegible]	16 (10%)	15 (9%)	15 (10%)	14 (9%)
[illegible]	1 (1%)	0	2	2
[illegible]	137 (86%)	141 (88%)	143 (87%)	142 (87%)
[illegible]	5 (3%)	5 (3%)	5 (3%)	5 (3%)

Source: [illegible]/reports/r_demo_saf.rtf 21Oct2003 11:40

There was a baseline imbalance in weight between ibandronate 1.0mg and placebo (p-value = 0.0195, Dec. 11, 2002 submission).

History of Hormone Replacement Therapy (Safety):



ERT Prior to Study	Placebo (N=159)	Oral Ibandronate 0.5 mg (N=161)	1.0 mg (N=165)	2.5 mg (N=163)
Premenopausal Treatment				
NO	44 (28%)	45 (28%)	47 (28%)	44 (27%)
YES	75 (47%)	68 (42%)	75 (45%)	77 (47%)
Postmenopausal Treatment				
NO	109 (69%)	114 (71%)	113 (68%)	114 (70%)
YES	50 (31%)	47 (29%)	52 (32%)	49 (30%)

Source: [illegible]/reports/r_hormone_saf.rtf 21Oct2003 11:40

There was a baseline imbalance in Pre-menopausal Treatment between ibandronate 2.5mg and placebo (p-value = 0.0260, Dec. 11, 2002 submission).

Patients 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.

Summary of Baseline BMD (g/cm^2) (ITT):

MEASURED SITE (g/cm^2)	PLACEBO (N=150)	ORAL IBANDRONATE 0.5 mg (N=157)	ORAL IBANDRONATE 1.0 mg (N=160)	ORAL IBANDRONATE 2.5 mg (N=153)
Total Lumbar Spine (L1-L4)				
N	150	157	160	153
Mean	1.01	1.00	1.00	1.00
SD	0.14	0.13	0.13	0.13
Median	0.97	0.97	0.97	0.98
Range				
Total Hip				
N	150	157	159	153
Mean	0.87	0.87	0.86	0.88
SD	0.11	0.11	0.11	0.11
Median	0.87	0.86	0.86	0.87
Range				
Trochanter				
N	150	157	159	153
Mean	0.64	0.64	0.65	0.67
SD	0.11	0.10	0.10	0.10
Median	0.65	0.65	0.65	0.66
Range				
Femoral Neck				
N	150	157	159	153
Mean	0.74	0.74	0.74	0.75
SD	0.11	0.11	0.10	0.09
Median	0.72	0.73	0.73	0.73
Range				
Wards Triangle				
N	150	157	159	153
Mean	0.60	0.59	0.60	0.60
SD	0.14	0.14	0.13	0.12
Median	0.58	0.58	0.59	0.60
Range				
Total Body				
N	150	157	159	153
Mean	1.04	1.03	1.03	1.03
SD	0.10	0.09	0.09	0.09
Median	1.04	1.03	1.04	1.02
Range				
Radius 1/3				
N	150	156	159	153
Mean	0.66	0.65	0.66	0.65
SD	0.08	0.09	0.07	0.08
Median	0.67	0.65	0.66	0.65
Range				
Radius Ultra Distal				
N	150	156	159	153
Mean	0.42	0.41	0.42	0.42
SD	0.06	0.06	0.06	0.06
Median	0.43	0.42	0.42	0.42
Range				

There was a baseline imbalance in PTH between each ibandronate group and placebo (Dec. 11, 2002 submission):

PTH (pmol/l)				
N	149	156	140	154
Mean	42.84	37.62	37.46	38.63
SD	19.55	14.49	15.77	17.49
Median	38.30	36.95	34.22	36.12
Range				
P Value, Treatment vs Placebo:		0.0083	0.0080	0.0493

The baseline PTH was found to be significantly lower in each active group compared to placebo. Patients in the 1.0mg group were found to weigh significantly less than the

patients in the placebo group, and fewer patients in the 2.5mg group were using pre-menopausal treatments than in placebo.

Exploratory efficacy analyses adjusting for these imbalances were performed (see the subsection "Covariation, Interaction, and Subgroup Results" after the discussion of the main results in the Section 2.3.3.2.5 Efficacy Results).

2.3.3.2.4 Measurements of Treatment Compliance and Other Factors That Could Affect Response

Calcium Supplement Intake and Concomitant Calcium

The large majority of patients in the study (463, 71.5%) took the calcium supplement for a minimum of 721 days (Table 13). The mean duration of intake was fairly balanced across the four groups, ranging from a minimum average of 650 days (1.8 years) for the placebo group to 676 days (1.9 years) for the 1.0 mg group.

	PLACEBO (N=159)	ORAL IBANDRONATE 0.5 mg (N=161)	1.0 mg (N=165)	2.5 mg (N=162)
Calcium Intake Prior to Study				
NO	108 (67.9%)	103 (64.0%)	111 (67.3%)	109 (66.3%)
YES	51 (32.1%)	58 (36.0%)	54 (32.7%)	54 (33.1%)
Days on Study Calcium Supplement				
1 - 180 days	12 (7.5%)	9 (5.6%)	8 (4.8%)	11 (6.8%)
181 - 360 days	7 (4.4%)	4 (2.5%)	4 (2.4%)	7 (4.3%)
361 - 540 days	3 (1.9%)	5 (3.1%)	4 (2.4%)	7 (4.3%)
541 - 720 days	28 (17.6%)	30 (18.6%)	21 (12.7%)	23 (14.2%)
721+ days	109 (68.6%)	112 (70.0%)	128 (77.6%)	114 (70.4%)
N	159	160	165	162
Mean (SD)	650.0 (194.02)	664.8 (176.89)	675.9 (163.72)	654.8 (179.93)
Median	727	728	729	728
Q1 - Q3	717 - 733	719 - 733	721 - 734	720 - 734
Range				

APPEARS THIS WAY
ON ORIGINAL

Summary of Concomitant Treatments by Superclass (Safety):

Treatment or Procedure	Placebo N = 159 No. (%)	Oral Ibandronate 0.5 mg N = 161 No. (%)	1.0 mg N = 165 No. (%)	2.5 mg N = 163 No. (%)
ALL CLASSES	156 (98)	157 (98)	156 (95)	155 (95)
CENTRAL NERVOUS SYSTEM	119 (75)	122 (76)	115 (70)	116 (71)
GENERAL ANTIINFECTIVES,SYSTEMIC	78 (49)	85 (53)	87 (53)	90 (55)
RESPIRATORY SYSTEM	85 (53)	78 (48)	84 (51)	86 (53)
ALIMENTARY TRACT AND METABOLISM	73 (46)	88 (55)	76 (46)	87 (53)
MUSCULO-SKELETAL SYSTEM	75 (47)	83 (52)	88 (53)	77 (47)
BLOOD AND BLOOD FORMING ORGANS	71 (45)	90 (56)	79 (48)	76 (47)
CARDIOVASCULAR SYSTEM	45 (28)	52 (32)	53 (32)	42 (26)
SYSTEMIC HORMONAL PREP.,EXCL SEX HORMONES	48 (30)	43 (27)	39 (24)	56 (34)
DERMATOLOGICALS	43 (27)	44 (27)	48 (29)	44 (27)
SENSORY ORGANS	33 (21)	35 (22)	37 (22)	33 (20)
GENITO URINARY SYSTEM AND SEX HORMONES	29 (18)	35 (22)	37 (22)	31 (19)
VARIOUS	19 (12)	28 (17)	22 (13)	24 (15)
ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE DRUGS	8 (5)	11 (7)	10 (6)	11 (7)
NOT YET SPECIFIED	3 (2)	-	4 (2)	3 (2)
PARASITOLOGY	-	-	3 (2)	2 (1)

Percentages are based on N.
TR11 29AUG2001:15:32:41

Summary of Exposure to Trial Medication (Safety)

TOTAL NUMBER OF TABLETS TAKEN	PLACEBO (N=159)	ORAL IBANDRONATE 0.5 mg (N=161)	1.0 mg (N=165)	2.5 mg (N=163)
<= 90 tablets	13 (8.2%)	7 (4.3%)	5 (3.0%)	6 (3.7%)
91 - 180 tablets	5 (3.1%)	6 (3.7%)	5 (3.0%)	8 (4.9%)
181 - 270 tablets	3 (1.9%)	1 (0.6%)	4 (2.4%)	5 (3.1%)
271 - 360 tablets	4 (2.5%)	5 (3.1%)	3 (1.8%)	4 (2.5%)
361 - 450 tablets	1 (0.6%)	2 (1.2%)	2 (1.2%)	7 (4.3%)
451 - 540 tablets	2 (1.3%)	4 (2.5%)	4 (2.4%)	2 (1.2%)
541 - 630 tablets	9 (5.7%)	7 (4.3%)	7 (4.2%)	5 (3.1%)
631+ tablets	122 (76.7%)	129 (80.1%)	135 (81.8%)	126 (77.3%)
N	159	161	165	163
Mean (SD)	607.5 (221.43)	634.6 (189.77)	643.9 (177.82)	615.6 (205.66)
Median	708.0	717.0	716.0	714.0
Q1-Q3	640 - 726	664 - 727	689 - 725	651 - 728
Range				

Source: $PROD/cdp10131/mf4499/reports/t_dose_saf.rtf 18SEP2001 13:26

The mean total exposure to active drug was 317.3 mg for patients receiving 0.5 mg/ day (634.6 tablets x 0.5 mg), 643.9 mg for the 1.0 mg patients, and 1539 mg for patients taking the 2.5 mg daily dose (NDA Table 36; Listing of Patient Drug Administration, Module IV).

Summary of Patient Compliance with Dosing Regimen (ITT)

	Placebo (N=150)	Oral Ibandronate 0.5 mg (N=157)	Oral Ibandronate 1.0 mg (N=160)	Oral Ibandronate 2.5 mg (N=153)
Overall Compliance %				
< 25%	10 (6.7%)	10 (6.4%)	6 (3.8%)	7 (4.6%)
25% - < 50%	7 (4.7%)	5 (3.2%)	7 (4.4%)	7 (4.6%)
50% - < 75%	3 (2.0%)	7 (4.5%)	6 (3.8%)	9 (5.9%)
75% - < 85%	9 (6.0%)	5 (3.2%)	3 (1.9%)	4 (2.6%)
85% - < 95%	24 (16.0%)	18 (11.5%)	19 (11.9%)	17 (11.1%)
95% +	97 (64.7%)	112 (71.3%)	119 (74.4%)	109 (71.2%)
N	150	157	160	153
Mean (SD)	87.1% (25.57%)	88.9% (23.24%)	90.5% (20.78%)	88.6% (23.17%)
Median	97.5%	98.2%	98.2%	97.9%
Q1-Q3	90% - 100%	93% - 100%	95% - 99%	91% - 100%
Range				

Source: SPROD/cdp10131/mf4499/reports/t_comply_itt.rtf 18SEP2001 13:26

A large proportion of patients in each treatment group took at least 75% of study medication: 130 (86.7%) placebo, 135 (86.0%) 0.5 mg, 141 (88.2%) 1.0 mg, and 130 (84.9%) 2.5 mg patients. The mean and median compliance across all groups was approximately 88% and 98%, respectively.

2.3.3.2.5 Efficacy Results

(Sponsor's Analyses)

The Data Analysis Plan (DAP) replaces any statistical methods stated in the protocol with respect to statistical analyses.

Date of finalization of DAP: 26th April 2001

Date of Database Closure: 30th April 2001 (Oracle Clinical Database Closure)

Date of Randomization Code Release: 22nd May 2001

The Data Analysis Plan (DAP) stated:

Primary Variable

The primary efficacy variable is the relative change from baseline in BMD of the lumbar spine (L1 - L4) after 2 years of treatment.

Statistical Hypotheses

A closed test procedure will be adopted. The confirmatory efficacy analysis will follow a set of partial a priori defined and ordered hypotheses. The statistical hypotheses will be ordered to investigate the difference in the relative change in the lumbar spine BMD after 2 years of treatment between the treatment groups at the same alpha level. This ordering of hypotheses will allow for a test at the level of alpha = 5% for each of the individual hypotheses, unless the previous hypothesis could not be rejected.

The partial a priori ordering of hypotheses is formally defined as follows.

H01: "There is no difference between placebo and the ibandronate 2.5 mg group in the relative change of lumbar spine BMD after two years of treatment";
H02: "There is no difference between placebo and the ibandronate 1.0 mg group in the relative change of lumbar spine BMD after two years of treatment";
H03: "There is no difference between placebo and the ibandronate 0.5 mg group in the relative change of lumbar spine BMD after two years of treatment".

The test procedure will first investigate, at the level of α=5%, whether H01 can be rejected. In case H01 is rejected, the hypotheses H02 will be tested at α=5%. If H02 is rejected, H03 will be tested at α=5%. The hypotheses will be tested by means of an analysis of variance (ANOVA). For both studies, the primary ANOVA will take into account as independent factors: treatment group and stratum, as defined by baseline BMD (> or ≤-1 SD T- score) and time since menopause (> or ≤3 years).

6.1.2 Analysis of Primary Efficacy Variable All analyses described in this section will be performed for both the ITT and the PP populations.

Primary analysis

The primary criterion for the evaluation of relative change in BMD is the BMD of non- fractured vertebrae of the lumbar spine (L1 - L4). The change in BMD is defined as the relative difference between the 2-year measurement (either measured or carried forward) and baseline, using the following formula:

Relative change = (2-year value – baseline value) / (baseline value) x 100

In the ITT population, a missing BMD value at Month 24 will always be imputed using the LVCF method. In the PP population, this method will be applied only if the patient stopped treatment due to lack of efficacy. In that case the last on-treatment value will be carried forward (see Section 3.4).

The primary model is an ANOVA which will take treatment and allocated stratum into account as independent factors. The primary analysis is the analysis of ITT population.

Efficacy Results
Primary Variable - BMD of the Lumbar Spine

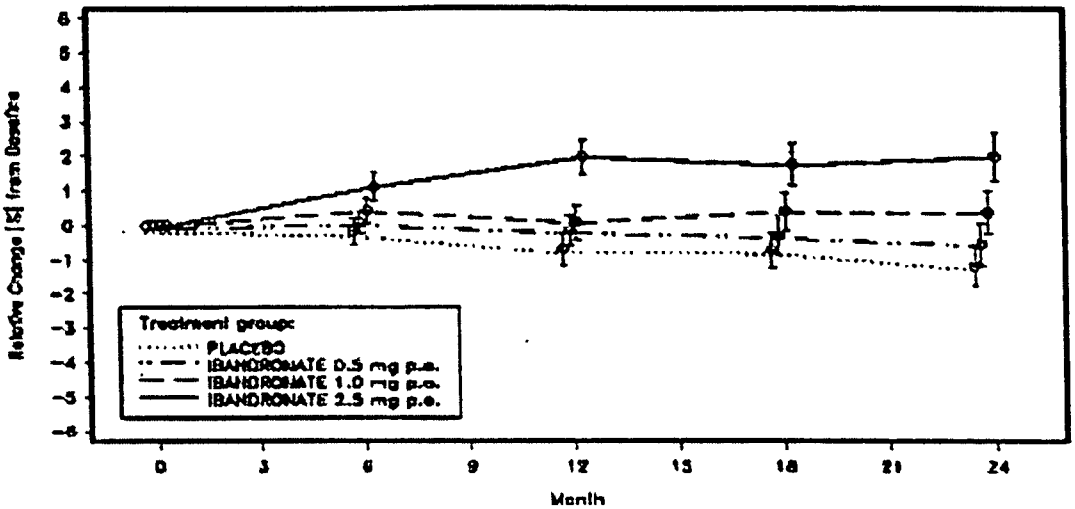
The ibandronate groups showed dose-dependent increases in lumbar spine (L1-L4) BMD, with greater increases seen with the 1.0 mg and 2.5 mg dose groups, as compared to placebo. The 0.5 mg dose group did not show any significant effect in lumbar spine BMD. (NDA Appendices t_bmds_av_itt page 267 and t_bmds_av_pp page 268). For the 2.5 mg group, the difference from placebo in mean relative change from baseline was statistically significant at all sampling time points (p < 0.001 at last value), beginning at Month 6 (Table below). While difference in relative change from baseline lumbar spine BMD was 1.9% greater for the 2.5 mg group after Month 24 LVCF, the BMD for the placebo group decreased by 1.2% during the same time period. Results for the PP population were similar to those observed for the ITT treatment groups. The difference in the mean relative change between the ibandronate 2.5 mg last value and placebo last value was calculated to be 3.1%.

Summary of Spine BMD (L1-L4) Relative Change (%) Over 24 Months (ITT):

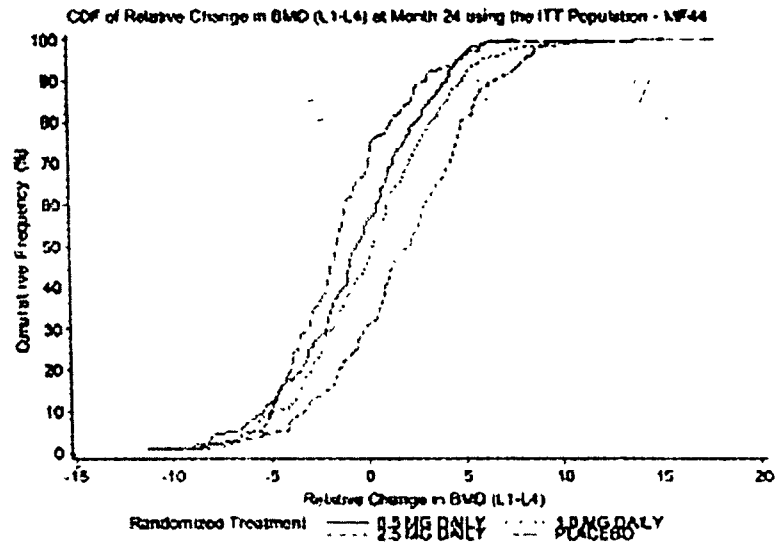
TREATMENT GROUP	BASELINE	MONTH 6	MONTH 12	MONTH 18	MONTH 24	LAST VALUE
Placebo						
N	150	148	141	140	141	150
MEAN	1.0070	-0.3584	-0.6828	-0.7260	-1.1957	-1.1878
SD	0.1425	2.1024	2.9439	3.1444	3.5497	3.4961
MEDIAN	0.9892	[illegible]	-0.8987	-0.6262	-1.3040	-1.5480
MIN						
MAX						
Ibandronate 0.5 mg						
N	157	157	150	142	143	157
MEAN	1.0032	[illegible]	-0.1228	-0.1076	[illegible]	-0.5474
SD	0.1263	2.7761	2.6995	3.2280	3.7116	3.6067
MEDIAN	0.9747	[illegible]	-0.1132	-0.2267	[illegible]	-0.4642
MIN						
MAX						
P-VALUE (a)	0.53978	[illegible]	0.11045	[illegible]	[illegible]	0.12371
Ibandronate 1.0 mg						
N	160	153	155	149	148	160
MEAN	1.0117	[illegible]	0.0971	0.6201	[illegible]	0.3011
SD	0.1313	3.1763	3.0682	[illegible]	3.7879	3.7238
MEDIAN	[illegible]	[illegible]	0.0905	0.5672	0.4741	0.3792
MIN						
MAX						
P-VALUE (a)	0.70419	[illegible]	0.02056*	[illegible]	[illegible]	[illegible]
Ibandronate 2.5 mg						
N	153	150	143	141	[illegible]	153
MEAN	0.9967	1.3316	1.9673	1.7548	[illegible]	1.9391
SD	0.1152	[illegible]	2.9461	[illegible]	[illegible]	4.0564
MEDIAN	0.9752	[illegible]	[illegible]	1.6559	[illegible]	2.3352
MIN						
MAX						
P-VALUE (a)	[illegible]	[illegible]	0.00000*	0.00000*	[illegible]	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).
Difference in the mean relative change between Ibandronate 2. 5 mg Last Value and Placebo Last Value = 3.1269%

Mean Relative Change (with 95% CI) from Baseline in BMD of Lumbar Spine (L1–L4) (ITT):



Following is the cumulative distribution graph for Percent Change from Baseline of Spine BMD (L1- L4) Over 24 Months (ITT):



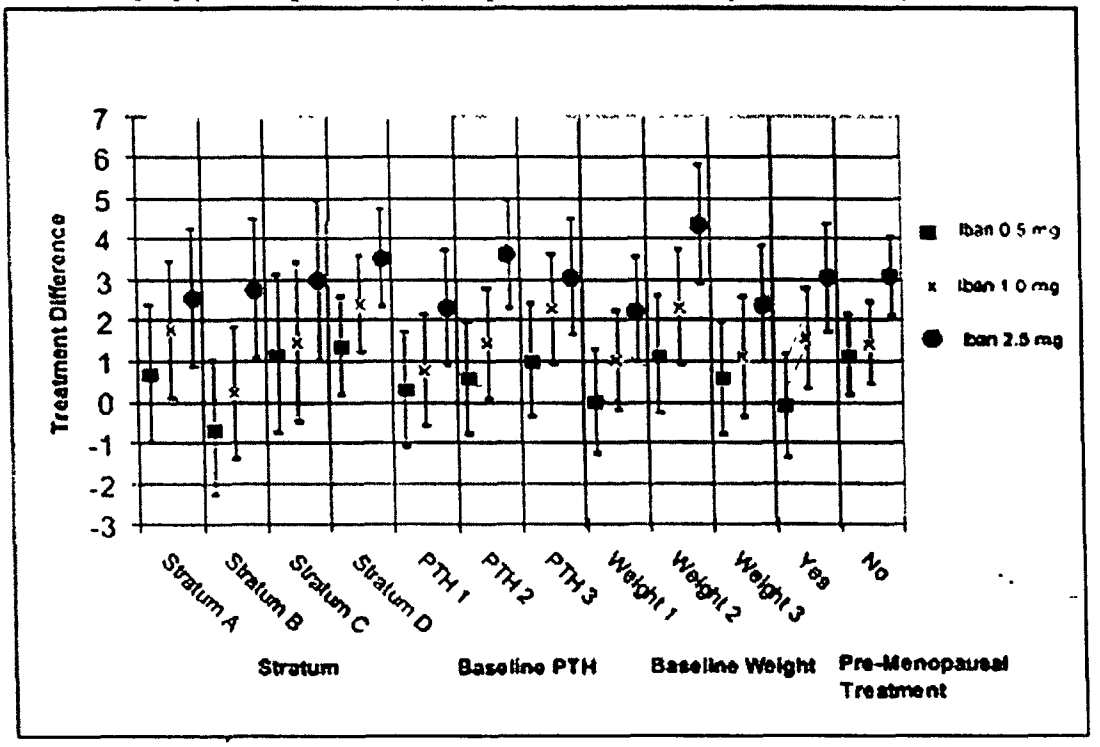
From this, percent of patients (y-axis value) with a value of Percent Change from Baseline, smaller than or equal to a value on the x-axis can be read. For example, nearly 70% (*Note: Only around 45% in Study 4411*) of the placebo patients had a ≤0% change from baseline (i.e., no improvement) compared with only around 44% of patients in the ibandronate 1.0mg group and around 30% in the ibandronate 2.5mg group.

§ Only 51 patients had their last value carried forward in the ITT LVCF population for the Month 24 assessment compared to 569 patient who had not. Even among the patients who withdrew before Month 24, placebo had the worst response. [12-20-02 submission]

§ Covariation, Interaction, and Subgroup Results

Note: The synopsis of this large subsection is provided in Section 2.3.3.2.6 Reviewer's Comments and Conclusions.

Figure for Mean (& 95% CI) of Difference Between Ibandronate Groups vs. Placebo for Relative Change in BMD Lumbar Spine (L1- L4) from Baseline at Month 24 [%] (ITT Population) (Also provided numerically in the details):



Note. For PTH, Weight and Pre- menopausal Treatment, group and strata were included in the ANOVA model (only group was included for the strata subgroup). Where:
Stratum A = Time since menopause = 1- 3 years and baseline BMD (L1- L4) > -1 SD
Stratum B = Time since menopause = 1- 3 years and baseline BMD (L1- L4) ≤-1 SD and ≥-2.5SD
Stratum C = Time since menopause = >3 years and baseline BMD (L1- L4) > -1 SD
Stratum D = Time since menopause = >3 years and baseline BMD (L1- L4) ≤-1 SD and ≥-2.5SD

For all active groups, the highest treatment effect estimates were found in Strata D, the high risk patients.

For each active group versus placebo comparison, the highest mean difference in relative change in BMD (L1- L4) from baseline was found in patients weighing between 65.3kg to 76.8kg (Weight 2, middle group).

The difference in relative change in BMD between the 0.5mg and 1.0mg groups versus placebo increased as the baseline PTH increased. For the 2.5mg group versus placebo comparison, the highest mean difference in BMD was found for patients with a baseline PTH value between 29.7pmol/ l and 42.3pmol/ l (PTH 2, middle group).

Similar treatment differences between the 2.5mg group and placebo were found for patients taking pre- menopausal treatments to those not taking the treatments. This was also true for the comparison between the 1.0mg group and placebo.

Details:

§ **Stratum (T- score, TSM (*Time Since Menopause*))** (Section 3.2.2.1 of NDA Report)

Summary of Strata Results for Spine (L1- L4) BMD: Mean Relative Change from Baseline to Last Value (ITT) Placebo Oral Ibandronate:

BMD Subgroup	Placebo	Oral Ibandronate			
		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 (44)	-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 Last Value and Placebo Last Value
Source: Appendix t_bmds_pt_a_in page 271 and t_bmds_pt_b_in page 272

Across the strata, changes from baseline in lumbar spine BMD in both the ITT and PP analyses reflected the results of the overall study population, with one exception (Stratum B, 0.5 mg group). The 2.5 mg groups in all strata showed a significant difference from placebo by Month 12 (and as early as Month 6 for Stratum B and D) ($p \leq 0.0033$ at last value). Compared to the results of the main ITT population, greater increases in lumbar spine BMD were seen in all ibandronate groups of Strata C and D. Thus, the greatest treatment effect of ibandronate on lumbar spine BMD in this study was observed in osteopenic patients who were at least three years postmenopausal. The difference in mean relative change of spine BMD between ibandronate 2.5 mg and placebo was 3.5% (Table above).

More Details on These Strata Results

The table below summarizes the covariation and interaction p- values from the ANOVA model fitted to the primary efficacy parameter (based on the ITT population).

	P-value
Treatment	0.0901
Strata*	0.0001
Treatment*Strata	0.5173

* (1st * sign) where strata has 4 levels (A, B, C, D) defined before

No statistically significant interaction effect was found between treatment and strata, although both main effects were found to be highly significant.

The following table provides the treatment comparison p- values for the strata sub-group analysis performed on the primary ANOVA model (based on the ITT population).

	Treatment Comparison		
	0.5mg vs. placebo	1.0mg vs. placebo	2.5mg vs. placebo
Stratum A	0.4058	0.0383	0.0033
Stratum B	0.4643	0.7810	0.8015
Stratum C	0.2314	0.1193	0.0033
Stratum D	0.0278	0.0001	<0.0001

For each stratum level, the 2.5mg treatment group was found to be significantly different to placebo. All active treatment groups were significantly different to placebo for patients in Stratum D.

Mean (& 95% CI) of Difference Between Ibandronate Groups vs. Placebo for Relative Change in BMD Lumbar Spine (L1- L4) from Baseline at Month 24 (ITT Population):

Stratum A	0.717 (-0.956, 2.420)	1.802 (0.092, 3.504)	2.583 (0.880, 4.286)
Stratum B	-0.615 (-2.270, 1.040)	0.232 (-1.414, 1.879)	2.814 (1.095, 4.533)
Stratum C	1.192 (-0.771, 3.155)	1.487 (-0.492, 3.467)	3.007 (1.027, 4.986)
Stratum D	1.383 (0.152, 2.614)	2.418 (1.204, 3.632)	3.533 (2.328, 4.746)

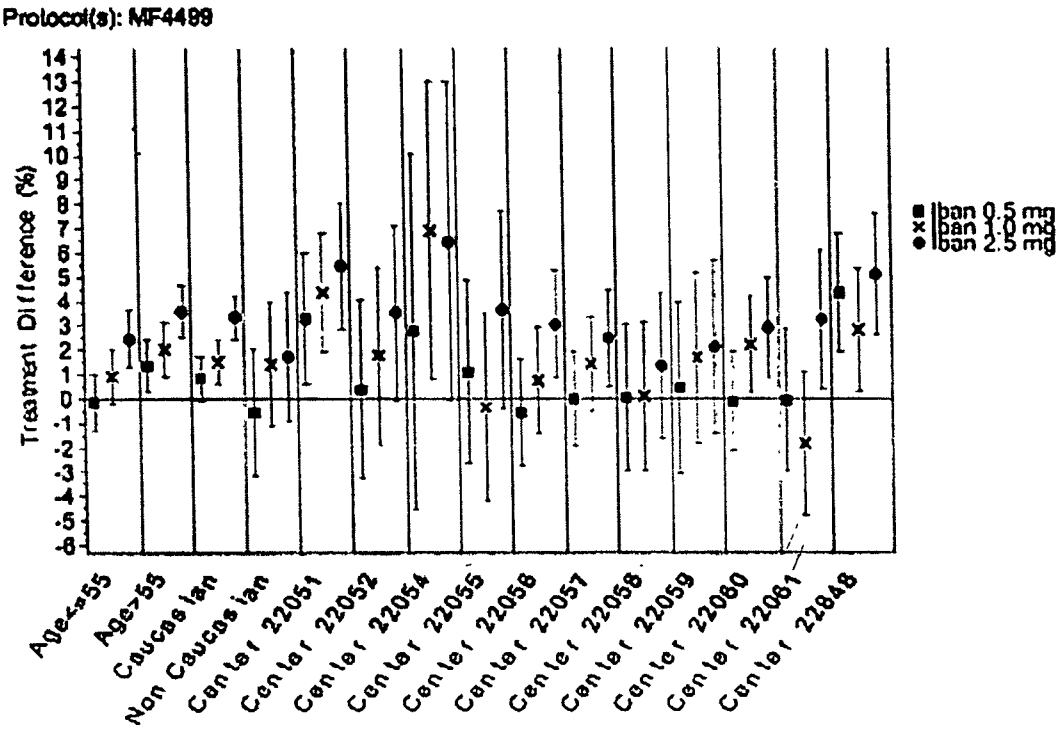
§ Gender, Age, Race, and Center Subgroups (Graph at the end of text)

All patients were female. Age (≤55 or >55) was a significant covariate. However, the interaction with treatment was not significant. For all active groups, the highest treatment effect estimates were found in patients aged > 55 years old.

There was no significant Race by Treatment interaction. Caucasians were found to have higher treatment effect estimates then non-Caucasians.

Center by Treatment interaction was significant only with respect to 1.0 mg ibandronate. Centers 22051, 22054 and 22848 were found to have the highest treatment effect estimates. However, these centers did not have excessive number of patients (had only 44, 12 and 46 patients (for all treatment arms) in each center respectively).

Mean (& 95% CI) of Difference Between Ibandronate Groups vs. Placebo for Relative Change in BMD Lumbar Spine (L1- L4) from Baseline at Month 24 [%] (ITT Population):



APPEARS THIS WAY
ON ORIGINAL