CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-858

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/Serial Number:	21-858/N-000
Drug Name:	BONIVA™ (ibandronate sodium) Injection
Indication(s):	Treatment of postmenopausal osteoporosis
Applicant:	Hoffmann-La Roche, Inc.
Date(s):	Received 12/06/04; user fee (10 months) 10/07/05; extended user fee 01/07/2006
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II (HFD-715)
Statistical Reviewer:	Cynthia Liu, MA
Concurring Reviewer(s):	Todd Sahlroot, Ph.D., Statistical Team Leader
	S. Edward Nevius, Ph.D., Division Director
Medical Division:	Div. of Metabolic and Endocrine Drug Products (HFD-510)
Clinical Team:	Theresa Kehoe, M.D., Medical Reviewer
	Eric Colman, M.D., Medical Team Leader
Project manager:	Durand Hedin, R.Ph.
Keywords:	NDA review, clinical study, non-inferiority trial, minimization

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

After 12 months of treatment with ibandronate in postmenopausal women with osteoporosis, the changes in lumbar spine bone mineral density (BMD) in the 2 intermittent intravenous (IV) dosing groups were not worse than that in the daily oral treatment group. In other words, the study objective of non-inferiority of the 2 mg every 2 months (q 2 mo) IV and 3 mg every 3 months (q 3 mo) IV regimens to the approved 2.5 mg daily oral tablet was met. In addition, both IV doses also showed superiority to the 2.5 mg daily oral one in increasing BMD of lumbar spine, total hip, and trochanter. However, only the 3 mg q 3 mo IV dose showed superiority to the 2.5 mg in improving femoral neck BMD. The serum CTX (a biochemical marker of bone resorption) in each study group had a rapid reduction during the first 3 months, and was further decreased by 6 months, then was maintained throughout the rest of the 12-month treatment period. The decrease in serum CTX in the 2 mg q 2 mo IV group was numerically larger, but not statistically significant, than that in the 2.5 mg daily oral group. The 3 mg q 3 mo IV group exhibited the least reduction in serum CTX among all the 3 treatment groups over the course of the study.

In summary, both the 2 mg q 2 mo and 3 mg q 3 mo IV doses were shown to be equally efficacious in improving BMD while suppressing bone resorption. The cumulative annual systemic dose was 12 mg for both regimens. The sponsor is seeking approval of the 3 mg q 3 mo IV dose for the market based on patient and physician survey preference, health care utilization advantages (fewer office visits and less procedural costs), the desire to minimize risks associated with venipuncture, and the need to maximize the potential for patient adherence. However, although there were no statistical differences between the 2 regimens in general, the 2 mg q 2 mo IV dose was numerically more effective in increasing lumbar spine BMD, total hip BMD, trochanter BMD, and in decreasing serum CTX than the 3 mg q 3 mo IV dose. In addition, the lack of IV medication compliance in this single pivotal study was numerically greater in the 3 mg q 3 mo IV group than in the 2 mg q 2 mo IV group.

1.2 Brief Overview of Clinical Studies

Ibandronate has been studied by Hoffmann-La Roche Inc. for several years and has been approved for 2.5 mg once daily oral tablet on 5/16/2003 for the treatment and prevention of postmenopausal osteoporosis (PMO). On 3/24/2005, the 150 mg once monthly oral tablet was also approved. The current submission is seeking approval of pre-filled syringes of ibandronate injection containing 3 mg/mL to be administered once every three months for the treatment of PMO.

The submission contains one Phase III, 2-year, randomized, double-blind, double-dummy, active-controlled trial, conducted in postmenopausal women with osteoporosis from 58

centers around the world. Patients were randomized to treatment using an adaptive minimization procedure that incorporated a random biased-coin element. A total of 1386 subjects were treated with either 2.5 mg daily oral (468), 2 mg q 2 mo IV (449), or 3 mg q 3 mo IV (469) doses of ibandronate. The mean age at entry was 66 years and mean years since menopause was 18.66. Approximately 94% of the randomized subjects were Caucasian. More than 50% of the study subjects did not have any previous fractures at entry. The mean baseline lumbar spine BMD T-score was about -3.3. The single pivotal non-inferiority trial was to compare change in lumbar spine (L2-L4) BMD after 1 year of treatment with intermittent IV dosing regimens to that with the approved daily oral dosing regimen. Note that Month 12 was the primary time point for efficacy evaluation in this submission; the Year 2 data are intended to satisfy the requirements of the EU agencies, according to the sponsor.

1.3 Statistical Issues and Findings

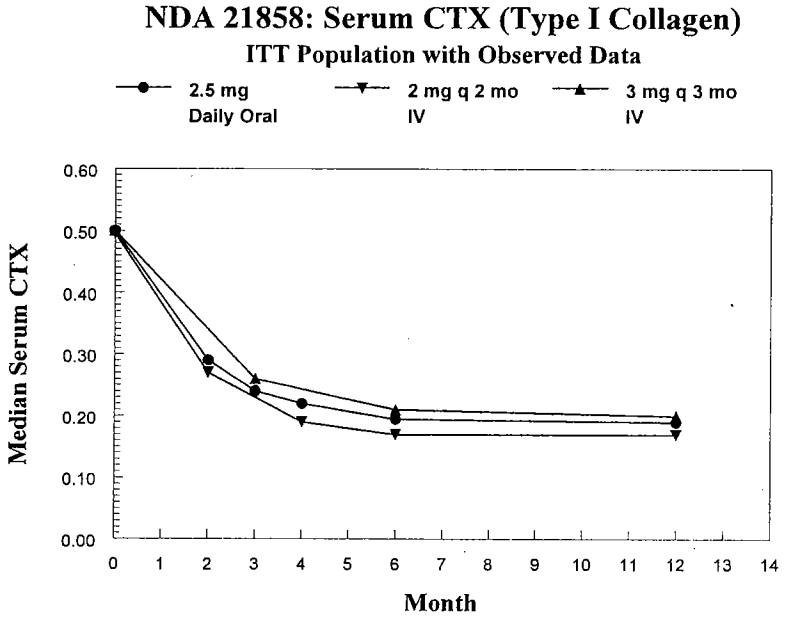
There were no serious statistical issues that may impact the overall conclusions. In general, this reviewer was able to confirm the sponsor's findings based on the per-protocol (PP) population and agreed with the sponsor's conclusions based on her own independent analyses on the intention-to-treat (ITT) population. The 5 efficacy parameters this reviewer reviewed in this study are briefly summarized below.

ITT	2.5 mg daily oral	2 mg q 2 mo IV	3 mg q 3 mo IV
Lumbar Spine	3.4521 ± 0.2873 (434)	4.6716 ± 0.2935 (412)	4.4991 ± 0.2897 (429)
Unadjusted p-value, 95% CI		<.0001, (**0.6929**, 1.7462)	<.0001, (**0.5259**, 1.5682)
Total Hip	1.4896 ± 0.2250 (430)	2.2693 ± 0.2302 (405)	2.0784 ± 0.2269 (425)
Adjusted p-value, 95% CI		0.0005, (0.3116, 1.2477)	0.0093, (0.1265, 1.0510)
Trochanter	2.8288 ± 0.3523 (430)	3.9505 ± 0.3605 (405)	3.6734 ± 0.3553 (425)
Adjusted p-value, 95% CI		0.0014, (0.3887, 1.8547)	0.0188, (0.1206, 1.5684)
Femoral Neck	1.2741 ± 0.2887 (430)	1.6225 ± 0.2954 (405)	1.8964 ± 0.2911 (425)
Adjusted p-value, 95% CI		0.333, (-0.2521, 0.9490)	0.0380, (0.0292, 1.2154)
Serum CTX	-62.5000 (413)	-64.2857 (383)	-57.5758 (399)
Non-parametric p-value		0.6207	0.0084

- For skeletal sites: least-squares mean % change from baseline at Month 12 ± standard error (sample size)
- For serum CTX: median % change from baseline at Month 12 (sample size)
- The p-values and 95% confidence intervals for lumbar spine were unadjusted for sequential testing techniques used.
- The p-values and 95% confidence intervals for other skeletal sites were adjusted based on Dunnett's t-test.

Across the 4 skeletal sites, the mean % increases from baseline in BMD at Month 12 in the 2 mg q 2 mo and 3 mg q 3 mo IV treatment groups were all numerically larger than that in the 2.5 mg daily oral treatment group. The 2 intermittent IV dosing regimens were shown to be not only non-inferior (the 95% lower confidence limits ≥ the pre-defined non-inferiority margin, -1%) but also superior to the daily dosing regimen in increasing lumbar spine BMD (the 95% lower confidence limits > 0). Both IV dosing groups were also superior to the 2.5 mg daily oral one in improving BMD of total hip and trochanter, but not femoral neck. The analyses based on the per-protocol population and completers revealed similar findings to the ones based on the intention-to-treat population. Treatment effects on % change from baseline in lumbar spine BMD at Month 12 were consistent across the subgroups of age, race, baseline lumbar spine BMD T-score, region, any previous fractures since age of 45, and calcium compliance.

Over the course of the 1-year study, the 2 mg q 2 mo IV group showed the most reduction in serum CTX, while the 3 mg q 3 mo IV group showed the least. The 2 mg q 2 mo IV group, but not the 3 mg q 3 mo IV group, was actually statistically comparable to the 2.5 mg daily in median % decrease from baseline at Month 12. In all treatment groups, the most rapid reductions in serum CTX occurred during the first 3 months, where at least 40% of the decreases from baseline were seen; then the levels were further reduced by Month 6 and were sustained throughout the rest of the 12-month treatment period.



2. INTRODUCTION

2.1 Overview

On 5/16/2003, BONIVA™ (ibandronate sodium) 2.5 mg daily oral tablets was approved for the treatment and prevention of postmenopausal osteoporosis (PMO) (NDA 21-455, Study MF4411). On 3/24/2005, the 150 mg once monthly oral tablets were also approved (NDA 21-455/SE2-001, Study BM16549). The current submission (NDA 21-858) is seeking approval of pre-filled syringes of BONIVA intravenous (IV) injection containing 3 mg/mL to be administered once every three months for the treatment of PMO.

The sponsor has submitted the results of 1 Phase III active-controlled clinical trial conducted in postmenopausal women between age 54 and 80 years old with osteoporosis (Study BM16550, see the table below). Patients were randomized to treatment using an adaptive minimization procedure that incorporated a random biased-coin element (see Appendix I). Note that the study was designed for 2 years, but Month 12 was the primary time point for efficacy evaluation in this submission. According to the sponsor, the study is continuing blinded for a second year to comply with the European Guideline (CPMP/EWP/552/95 rev 1) and a confirmatory analysis after 24 months of treatment will be performed as required by the European Medicines Agency (EMEA).

Protocol No. Locations	Study Design Start Date – Completion Date	Dose (N)	Age/Gender/ Race	Primary Endpoint
BM16550 16 countries USA sites: 18% Foreign sites: 82% 58 centers	Phase III, 2-year, randomized, double-blind, double-dummy, active-controlled, multicenter, international study to evaluate change in bone mineral density in postmenopausal women with osteoporosis (a non-inferiority study) June 2002 - ongoing	2.5 mg daily oral (468) 2 mg every 2 months IV (449) 3 mg every 3 months IV (469)	54 – 80 years (Mean = 65.99) F: 1386 (100%) White: 1298 (93.7%) Hispanic: 77 (5.6%) Oriental: 4 (0.3%) Black: 0 (0%) Others: 7 (0.5%)	% Change from baseline in lumbar spine bone mineral density at Month 12

N = Number of subjects randomized and received medication
Others include Asian Indian, Inhabitants of Greenland, Mixed Race, and Native American.

2.2 Data Sources

The study report is located in \\Cdsesub1\n21858\N_000\2004-12-06\clinstat\pmo\bm16550.pdf. The electronic data files this reviewer used are located in \\Cdsesub1\n21858\N_000\2004-12-06\crt\datasets\bm16550. In general, those data files (efficacy.xpt, demo.xpt, excl.xpt, and exit.xpt) were not difficult to work with and information was sufficient, except that no last-observation-carried-forward (LOCF) indicator was given for serum CTX parameter.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Protocol BM16550 was a Phase III, 2-year, randomized, double-blind, double-dummy, 4-parallel-group, active-controlled, multicenter, international study, conducted in women aged 54 to 80 years with postmenopausal osteoporosis. Patients were stratified by center and baseline lumbar spine BMD T-score (consisting of 3 strata defined as <-2.5 and ≥-3.0, <-3.0 and ≥-3.5, and <-3.5 and ≥-5.0), and then were randomized into one of the following 4 treatment groups in a 2:1:2:1 ratio using an adaptive minimization method (see Appendix I for details). For centers performing bone biopsies, patients were also stratified by consent for bone biopsy. All patients were required to take calcium 500 mg and vitamin D 400 IU per day as supplements.

Group A: 2 mg every 2 months (2 mg q 2 mo) IV ibandronate + daily oral placebo
Group B: 2.5 mg daily oral ibandronate + every 2 months IV placebo
Group C: 3 mg every 3 months (3 mg q 3 mo) IV ibandronate + daily oral placebo
Group D: 2.5 mg daily oral ibandronate + every 3 months IV placebo

To avoid patients receiving injections every two and every three months, the study was unblinded as to the injection schedule, but not the treatment allocation.

The primary objective was to demonstrate non-inferiority of lumbar spine bone mineral density (BMD) changes of two IV dosing regimens (2 mg q 2 mo, 3 mg q 3 mo) to that of the approved daily oral 2.5 mg tablet. The associated primary efficacy variable was percentage change from baseline in lumbar spine BMD at Month 12. There were at least 22 secondary efficacy parameters listed in the protocol, including ones from the Month 24 data. The secondary efficacy variables this review focused on were percentage change from baseline in BMD of proximal femur (total hip, trochanter, and femoral neck) at Month 12, percentage of BMD responders, and percentage change from baseline in serum CTX (a biochemical marker of bone resorption). Dual energy X-ray absorptiometry (DXA) scans on lumbar spine and proximal femur were performed at screening/baseline and Months 12 and 24. Serum CTX was collected at baseline, Months 2, 3, 4, 6, 12, and 24 depending on the injection schedule.

The margin of clinical equivalence the sponsor defined for the primary efficacy endpoint was 1%, about 30% of the minimum treatment difference between placebo and the 2.5 mg daily oral dose at 12 months (= 3.321%) from 3 prior studies (MF4348, MF4433, and MF4411) conducted in postmenopausal women with osteoporosis, as stated in the protocol synopsis. Accounting for a 20% rate for dropouts and non-compliance and using the 1% non-inferiority margin with SD = 4.5% for a 1-sided 2.5% significance level test, 1194 randomized subjects

(318, 159, 318, and 159 evaluable subjects for Groups A, B, C, and D, respectively) was expected to provide 80% power for the study.

3.1.2 Statistical Methods

For the purpose of efficacy analyses, the sponsor combined Groups B and D (the two 2.5 mg groups) as a single group. To ensure the validity of the combination, the data (demographic parameters, BMD of lumbar spine and proximal femur, and serum CTX) of the 2 groups were first compared. According to the sponsor, no significant differences were found, meaning that the effect of the injection schedule was negligible and pooling of data was justified for efficacy evaluation. The comparisons were verified randomly by this reviewer. The descriptive statistics of the primary and secondary efficacy variables of interest of the 2 study groups are shown in Appendix II.

Percentage change from baseline at Month 12 in lumbar spine BMD was analyzed by ANOVA techniques using treatment as the main factor and baseline lumbar spine BMD T-score and region as the stratifying factors (the sponsor's model). The non-inferiority of an IV dose to the daily one was determined if the lower bound of the 95% confidence interval of the treatment difference (IV – oral) was $\geq -1\%$. To maintain an overall Type I error rate, the sponsor used a sequential hypothesis testing procedure for the primary efficacy parameter. That is, 3 mg q 3 mo IV dose was tested only if 2 mg q 2 mo IV dose was not inferior to the 2.5 mg daily oral one. If non-inferiority was demonstrated, then the ANOVA model was used to test for superiority. If both the IV doses were found to be superior to the 2.5 mg oral one, a test for superiority between the 2 IV doses was also performed using the same ANOVA model.

The sponsor defined the intention-to-treat (ITT) population as all randomized subjects who received at least 1 dose of the trial medication and had at least 1 efficacy follow-up data point, and defined the per-protocol (PP) population as all ITT subjects who had no major violations of the protocol. Last-observation-carried-forward (LOCF) approach was used for subjects who withdrew early. The sponsor chose to use the per-protocol population as their primary analysis set for evaluating the efficacy data since the study is an international trial in which PP is the accepted primary by other health authorities. Based on our past experience with no consistent evidence of ITT analyses showing less conservative results than PP analyses, the ITT population (which best preserves the randomization) was, however, chosen to be the primary analysis population in this review. Note that there were 6 patients in this study receiving medications that did not correspond to their randomized treatment groups. For the ITT analysis, patients were analyzed as randomized. For the PP analysis, patients were analyzed with the actual treatment received most frequently.

Percentage change from baseline at Month 12 in BMD of proximal femur was also analyzed by this reviewer using the same ANOVA model as mentioned above. Dunnett's t-test for comparing the IV doses with the oral one was performed so that the overall Type I error rate for each of the secondary skeletal sites could be preserved. Note that the 95% confidence intervals in the sponsor's clinical study report for those cases were unadjusted.

The sponsor's planned analysis for serum CTX was repeated measures ANOVA. However, since neither raw serum CTX nor log-transformed data were normally distributed, the analysis method was deemed inappropriate (page 2373 of clinical study report). This reviewer used Wilcoxon-Mann-Whitney test (a non-parametric test, no controlling for geographic location and baseline lumbar spine BMD T-score) to analyze the observed data of percentage change from baseline in serum CTX at Months 6 and 12.

3.1.3 Subject Disposition

A total of 1395 subjects were randomized and 1386 of them received at least 1 dose of trial medication: 468, 449, and 469 subjects for 2.5 mg daily oral, 2 mg q 2 mo IV, and 3 mg q 3 mo IV ibandronate, respectively. The overall withdrawal rate by Month 12 was 15.1% (= 210/1395) with no group having a withdrawal rate greater than 20%, a factor accounted for during the sample size calculation. In other words, the number of completers in each group was more than the sample size that the trial was powered on (318 per group for 80% power). The reasons for withdrawal were similar across the three treatment groups (Fisher-Freeman-Halton asymptotic test p = 0.3928). Adverse events were the most common recorded reason for withdrawal in this trial (Table 1).

Table 1 – Subject Disposition

	2.5 mg daily oral	2 mg q 2 mo IV	3 mg q 3 mo IV
Number of randomized subjects	470	454	471
Number of completers at Month 12	409 (87.0%)	382 (84.1%)	394 (83.7%)
Number of withdrawals by Month 12	61 (13.0%)	72 (15.9%)	77 (16.3%)
No medication taken	2	5	2
No follow-up assessment	3	1	0
Adverse event	30	30	39
Death	1	1	2
Other protocol violation	1	3	0
Refused treatment	22	23	27
Failure to return	0	5	4
Other	2	4	3

Information above was compiled from the sponsor's Figure 1 and Table 5 in the clinical study report

Thirty-seven subjects were excluded from the ITT population due to either no trial medication received and/or no efficacy follow-up information. The 1358 ITT subjects (including withdrawn patients who had BMD collected at the end-of-study visit) came from

58 centers in various countries around the world and most of them had a small number of patients in each group. To avoid sparseness problem and ensure similarity to a previous trial where the approved 2.5 mg daily oral tablets were studied (MF4411), the sponsor grouped the centers into the following 4 regions and the numbers of ITT subjects in each region were similar across the treatment groups (Table 2).

US/Canada:	USA and Canada
Western Europe:	Belgium, Denmark, Spain, France, UK, Germany, Italy, and Norway
Eastern Europe:	Czech Republic, Hungary, and Poland
Rest of the World:	Australia, Mexico, and South Africa

Table 2 – Number of ITT Subjects in Each Region

	US/Canada	W. Europe	E. Europe	Rest of World	Total
2.5 mg daily oral	63	210	104	81	458
2 mg q 2 mo IV	54	202	103	83	442
3 mg q 3 mo IV	68	204	108	78	458
Total Subjects	185	616	315	242	1358

3.1.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics of all randomized subjects, such as weight, height, BMI, age at menarche, age at last natural menstruation, BMD of lumbar spine, hip, neck, and trochanter, T-score of lumbar spine BMD, and serum CTX, were similar among the 3 treatment groups (Table 3). Subject distributions in race, center, country, continent, region, number of previous fractures, and stratum of lumbar spine BMD T-score were also balanced across the treatment groups. However, there was a statistically significant difference in mean age at entry among the 3 study groups ($p = 0.0387$).

Note that the inclusion criterion for lumbar spine BMD T-score was from -5.0 to, but not including, -2.5. Due to applying the cross-calibrated and longitudinal correction factors, the baseline lumbar spine BMD values for 64 patients were changed (page 2331 of the clinical study report), which resulted in 18 subjects having the T-score $\geq$-2.5. As a consequence, 4 strata of the baseline lumbar spine BMD T-score (as opposed to 3 strata used originally for randomization) were employed in the sponsor's statistical analyses as well as in this review. Although the inclusion criterion for age was from 55 to 80 years, there were 2 subjects enrolled at 54 years old. The overall mean age was 66 years with more than half of the patients in each group $\geq$65 years old (considered as geriatric population) at entry. There were 6 subjects having <5 years of menopause prior to entry, even though the inclusion criterion required at least 5 years after menopause. The overall mean years since menopause at entry

was 18.66. All patients were female in this study and about 94% of them were Caucasian. Approximately 68% of the patients were recruited from the European centers and 18% from North America. More than 50% of the subjects in each group did not have any previous fractures at entry.

Similar findings were also observed for the ITT population, except that mean age became comparable among the study groups ($p = 0.0841$, 65.7, 66.5, and 65.7 for the 2.5 mg daily oral, 2 mg q 2 mo, and 3 mg q 3 mo groups, respectively).

According to the sponsor (page 34 of the clinical study report), the study is being conducted in a population similar to the one studied in MF4411 in terms of time since menopause, racial distribution, and age. Pre-existing (prevalent) vertebral fractures at entry, however, were not required in this study.

Table 3 – Demographic and Baseline Characteristics of All Randomized Subjects

Characteristic	2.5 mg daily oral	2 mg q 2 mo IV	3 mg q 3 mo IV
Age (year): Mean ± SD	65.7 ± 6.08 (470)	66.6 ± 6.26 (454)	65.7 ± 6.29 (471)
Range	54 – 79	55 – 80	54 – 79
<65 (%)	207 (44.04)	185 (40.75)	201 (42.68)
≥65 (%)	263 (55.96)	269 (59.25)	270 (57.32)
Race: Caucasian (%)	443 (94.26)	422 (92.95)	441 (93.63)
Hispanic (%)	26 (5.53)	26 (5.73)	25 (5.31)
Oriental (%)	0	3 (0.66)	1 (0.21)
Black (%)	0	0	1 (0.21)
Other (%)	1 (0.21)	3 (0.66)	3 (0.64)
Weight (kg): Mean ± SD	63.6 ± 11.0 (469)	64.3 ± 10.8 (451)	64.1 ± 10.8 (469)
Height (cm): Mean ± SD	158.2 ± 6.50 (469)	158.1 ± 6.52 (451)	158.1 ± 6.84 (469)
BMI (kg/m^2): Mean ± SD	25.4 ± 4.25 (469)	25.8 ± 4.16 (451)	25.7 ± 4.35 (469)
Age at menarche (year): Mean ± SD	13.8 ± 1.68 (469)	14.0 ± 1.82 (454)	13.8 ± 1.66 (470)
Age at last natural menstruation (year):			
Mean ± SD	47.5 ± 5.49 (470)	47.3 ± 5.66 (454)	47.2 ± 5.71 (470)
Range	24 – 59	26 – 60	23 – 60
Years since menopause: Mean ± SD	18.2 ± 7.98 (470)	19.3 ± 8.22 (454)	18.5 ± 8.04 (470)
Range	1 – 51	4 – 48	3 – 44
Lumbar spine BMD: Mean ± SD	0.75 ± 0.07 (470)	0.75 ± 0.07 (454)	0.75 ± 0.08 (471)
Lumbar spine BMD T-score:			
Mean ± SD	-3.25 ± 0.55 (470)	-3.27 ± 0.57 (454)	-3.27 ± 0.59 (471)
≥-2.5 (%)	7 (1.49)	5 (1.10)	6 (1.27)
≥-3.0 and <-2.5 (%)	177 (37.66)	173 (38.11)	184 (39.07)
≥-3.5 and <-3.0 (%)	139 (29.57)	133 (29.30)	140 (29.72)
≥-5.0 and <-3.5 (%)	147 (31.28)	143 (31.50)	141 (29.94)
Hip BMD: Mean ± SD	0.73 ± 0.10 (468)	0.74 ± 0.10 (450)	0.74 ± 0.10 (467)
Neck BMD: Mean ± SD	0.64 ± 0.10 (468)	0.65 ± 0.10 (450)	0.65 ± 0.10 (467)
Trochanter BMD: Mean ± SD	0.57 ± 0.09 (468)	0.58 ± 0.09 (450)	0.57 ± 0.09 (467)
Serum CTX: Mean ± SD	0.55 ± 0.25 (468)	0.52 ± 0.24 (450)	0.53 ± 0.25 (466)
Number of previous fractures:			
0 (%)	265 (56.38)	260 (57.27)	265 (56.26)
1 (%)	126 (26.81)	126 (27.75)	132 (28.03)
2 (%)	41 (8.72)	38 (8.37)	47 (9.98)
3 (%)	20 (4.26)	16 (3.52)	17 (3.61)
≥4 (%)	18 (3.83)	14 (3.08)	10 (2.12)

3.1.5 Efficacy Results and Discussion

Following are the sponsor's efficacy findings based on the 12-month data of PP population.

- The mean % increase in lumbar spine BMD from baseline at 1 year in both IV treatment groups (5.1% and 4.8% for the 2 mg q 2 mo and 3 mg q 3 mo groups, respectively) was non-inferior to the 2.5 mg oral daily regimen (3.8%). The increases in both IV groups were also shown to be superior to that seen in the 2.5 mg treatment group. The differences between the two IV dose groups were marginal.

- In both IV treatment groups, the mean % increases from baseline in total hip (2.6% and 2.4% for the 2 mg q 2 mo and 3 mg q 3 mo groups, respectively) and trochanter (4.1% and 3.8% for the 2 mg q 2 mo and 3 mg q 3 mo groups, respectively) BMD at 1 year were significantly greater than that in the 2.5 mg oral daily treatment group (1.8% for total hip and 3.0% for trochanter). However, only the 3 mg q 3 mo group was shown to be superior to the 2.5 mg group for the case of femoral neck (2.0%, 2.3%, and 1.6% for the 2 mg q 2 mo IV, 3 mg q 3 mo IV, and 2.5 mg daily oral groups, respectively).

- All dosing regimens of ibandronate significantly suppressed bone resorption as assessed by serum CTX. The median % decrease from baseline in serum CTX was 62.5%, 65.1%, and 58.4% at 6 months for the 2.5 mg daily oral, 2 mg q 2 mo IV, and 3 mg q 3 mo IV treatment groups, respectively, and 62.6%, 64.6%, and 58.6% at 12 months, respectively.

In general, this reviewer's results based on the ITT population (see below discussion) agree with the sponsor's conclusions based on the PP population.

BMD of Lumbar Spine (L2-L4). After 1 year of treatment with ibandronate, all the study groups showed an increased mean lumbar spine BMD over baseline using the ITT population with LOCF techniques (Table 4). The least-squares mean (adjusted for 4 regions and 4 strata of baseline lumbar spine BMD T-score) % changes from baseline for the 2.5 mg daily oral, 2 mg q 2 mo IV, and 3 mg q 3 mo IV treatment groups were 3.45%, 4.67%, and 4.50%, respectively. Note that between the 2 IV doses, the % increase was numerically larger in the 2 mg q 2 mo group than in the 3 mg q 3 mo group.

As shown in Table 5, the least-squares (LS) mean % changes in lumbar spine BMD after 1 year in the 2 IV dose groups were non-inferior to that in the 2.5 mg daily oral treatment group, according to the lower limits of 95% confidence intervals (both $\geq$ -1%, the non-inferiority margin defined by the sponsor). In fact, both IV treatment groups were also superior to the 2.5 mg daily oral group ($p < 0.0001$) in this case. There was no statistically

significant difference between the 2 IV groups (p = 0.5221) in mean % change from baseline in lumbar spine BMD at 1 year.

Table 4 – Descriptive Statistics for Lumbar Spine BMD Using ITT Population with LOCF Approach

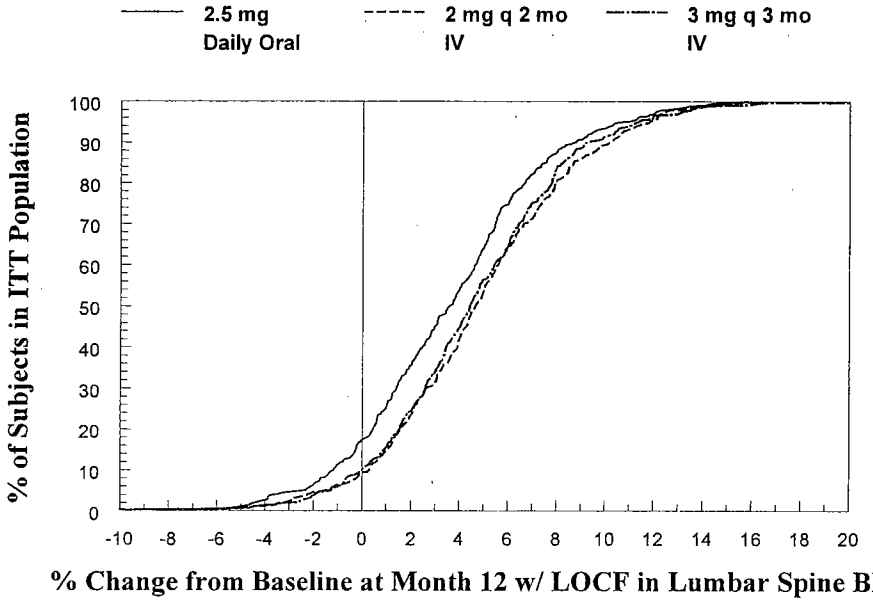
ITT	2.5 mg daily oral	2 mg q 2 mo IV	3 mg q 3 mo IV
Raw mean lumbar spine BMD ± standard deviation (sample size)			
Baseline	0.7470 ± 0.0712 (434)	0.7481 ± 0.0735 (412)	0.7454 ± 0.0753 (429)
Month 12	0.7738 ± 0.0766 (434)	0.7837 ± 0.0765 (412)	0.7796 ± 0.0799 (429)
Raw mean % change from baseline ± standard deviation (sample size)			
Month 12	3.6292 ± 3.9783 (434)	4.8407 ± 3.9076 (412)	4.6436 ± 3.9119 (429)
Least-squares mean % change from baseline ± standard error (sample size)			
Month 12	3.4521 ± 0.2873 (434)	4.6716 ± 0.2935 (412)	4.4991 ± 0.2897 (429)

Table 5 – Statistical Results for LS Mean % Change from Baseline in Lumbar Spine BMD at Month 12

ITT Population Comparison	Treatment Difference	95% (LCL, UCL)	Non-inferior to 2.5 mg?	Unadjusted p-value	Superior to 2.5 mg?
2 mg q 2 mo vs. 2.5 mg	1.2195	(**0.6929**, 1.7462)	Yes	<0.0001	Yes
3 mg q 3 mo vs. 2.5 mg	1.0471	(**0.5259**, 1.5682)	Yes	<0.0001	Yes

Figure 1: NDA 21858: Cumulative Distribution Function

% of subjects having at most % change in Lumbar Spine BMD



As depicted in Figure 1, the 2.5 mg daily ibandronate group had more subjects (17.3%) showing decreased lumbar spine BMD from baseline at Month 12 (non-responders defined by CPMP) compared to either of the 2 IV ibandronate groups (9.2% and 10.0% for 2 mg q 2 mo and 3 mg q 3 mo groups, respectively). Also, for almost any percentage of subjects, the 2.5 mg curve exhibited the least efficacy, while the 2 mg q 2 mo one showed the most, even though the 2 mg q 2 mo and 3 mg q 3 mo curves had similar profiles. Note that one can easily obtain the % of subjects achieving a given level of response for any definition of responders from Figure 1.

BMD of Proximal Femur. After 1 year of treatment with ibandronate, all the study groups showed an increased mean BMD of proximal femur (total hip, trochanter, and femoral neck) over baseline using the ITT population with LOCF techniques. For both total hip and trochanter, the mean % increases from baseline in both IV treatment groups were significantly larger than those in the 2.5 mg daily oral group (Table 6). However, for femoral neck, only the 3 mg q 3 mo IV group showed a significant mean % increase from baseline when compared with the daily oral one. The two IV groups were comparable in increasing BMD of total hip, trochanter, and femoral neck.

Table 6 – Results for BMD of Proximal Femur (Least-squares Mean % Change from Baseline ± SE (N))

ITT (LOCF)	2.5 mg daily oral	2 mg q 2 mo IV	3 mg q 3 mo IV
Total Hip	1.4896 ± 0.2250 (430)	2.2693 ± 0.2302 (405)	2.0784 ± 0.2269 (425)
Dunnett's Adjusted p-value		0.0005	0.0093
Dunnett's Adjusted 95% CI		(0.3116, 1.2477)	(0.1265, 1.0510)
Trochanter	2.8288 ± 0.3523 (430)	3.9505 ± 0.3605 (405)	3.6734 ± 0.3553 (425)
Dunnett's Adjusted p-value		0.0014	0.0188
Dunnett's Adjusted 95% CI		(0.3887, 1.8547)	(0.1206, 1.5684)
Femoral Neck	1.2741 ± 0.2887 (430)	1.6225 ± 0.2954 (405)	1.8964 ± 0.2911 (425)
Dunnett's Adjusted p-value		0.3330	0.0380
Dunnett's Adjusted 95% CI		(-0.2521, 0.9490)	(0.0292, 1.2154)

Serum CTX (Type I Collagen). As shown in Table 7, the means and medians of serum CTX in all study groups were decreasing over the first year of treatment period. Since the raw data showed skewed distributions (see box-plots in Appendix III), medians of the 3 study groups, as opposed to means, were compared. As Figure 2 shows, the most rapid reduction occurred during the first 3 months, where at least 40% of decrease from baseline was seen in each

treatment group. The serum CTX levels in all the study groups were further reduced by Month 6 and then were sustained throughout the rest of the 12-month treatment period.

Table 7 – Results of Serum CTX

ITT (observed)	2.5 mg daily oral	2 mg q 2 mo IV	3 mg q 3 mo IV
Raw mean serum CTX ± standard deviation (sample size)			
Baseline	0.5506 ± 0.2490 (457) Median = 0.50	0.5270 ± 0.2444 (442) Median = 0.495	0.5233 ± 0.2463 (456) Median = 0.50
Month 2	0.3299 ± 0.2224 (219) Median = 0.29	0.3070 ± 0.2009 (434) Median = 0.27	
Month 3	0.2933 ± 0.1946 (235) Median = 0.24		0.3110 ± 0.1954 (448) Median = 0.26
Month 4	0.2609 ± 0.2055 (213) Median = 0.22	0.2345 ± 0.1633 (419) Median = 0.19	
Month 6	0.2423 ± 0.1756 (428) Median = 0.195	0.2026 ± 0.1436 (407) Median = 0.17	0.2524 ± 0.1756 (418) Median = 0.21
Month 12	0.2383 ± 0.1774 (413) Median = 0.19	0.2102 ± 0.1447 (383) Median = 0.17	0.2396 ± 0.1462 (399) Median = 0.20
Median % change from baseline (Wilcoxon-Mann-Whitney test asymptotic p-value)			
Month 2	-45.0000	-46.6667 (p = 0.8034)	
Month 3	-51.7549		-42.2650 (p = 0.0042)
Month 4	-57.5221	-60.7143 (p = 0.9776)	
Month 6	-62.3975	-65.3846 (p = 0.0681)	-56.7117 (p = 0.0106)
Month 12	-62.5000	-64.2857 (p = 0.6207)	-57.5758 (p = 0.0084)

Figure 2

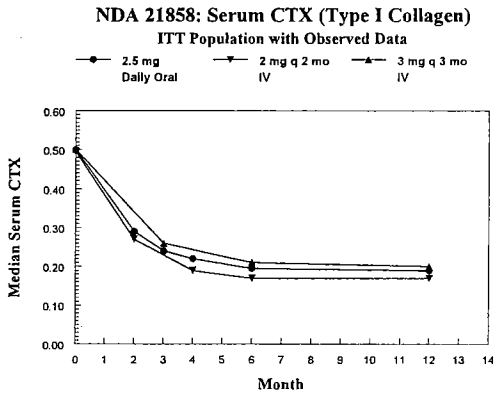
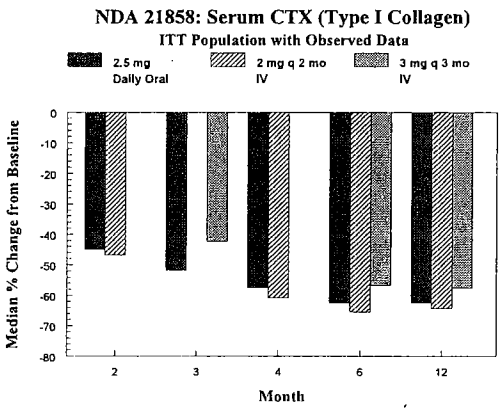


Figure 3



Based on the results from Wilcoxon-Mann-Whitney test (Table 7), there was no statistically significant difference between the 2.5 mg daily oral and 2 mg q 2 mo IV groups in median % reduction from baseline in serum CTX at every time point measured, although the latter group consistently showed a numerically greater decrease than the former one (Figure 3). No such comparable finding was observed for the 3 mg q 3 mo IV group. In fact, the median % decrease from baseline in the 3 mg q 3 mo IV group was significantly less than that in the 2.5 mg daily oral treatment group.

3.2 Evaluation of Safety

Safety is not the focus of this review. See Dr. Theresa Kehoe's review for safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

Treatment effects on % change from baseline in lumbar spine BMD at Month 12 were consistent across the subgroups of age (Table 8) and race, as no significant treatment-by-subgroup interactions were observed ($p > 0.10$ in both cases). Since all the study subjects were females, no subgroup analysis for gender was performed.

Table 8 – Raw Mean ± SD (N) for % Change from Baseline in Lumbar Spine BMD at Month 12 by Age

ITT	2.5 mg daily oral	2 mg q 2 mo IV	3 mg q 3 mo IV
Age < 65 years	3.3915 ± 4.0567 (190)	4.2370 ± 4.0481 (168)	4.6010 ± 3.7242 (182)
Age ≥ 65 years	3.8143 ± 3.9144 (244)	5.2563 ± 3.7602 (244)	4.6750 ± 4.0519 (247)
Age < 70 years	3.6135 ± 3.9311 (304)	4.4258 ± 3.9932 (271)	4.5088 ± 3.7335 (299)
Age ≥ 70 years	3.6659 ± 4.1016 (130)	5.6382 ± 3.6196 (141)	4.9536 ± 4.2935 (130)

4.2 Other Special/Subgroup Populations

Treatment effects on % change from baseline in lumbar spine BMD at Month 12 were also consistent across the subgroups defined by baseline lumbar spine BMD T-score, study center, country, continent, region, any previous fractures since age of 45, measurement device (Hologic vs. Lunar), calcium compliance, and smoking status (all interactions $p > 0.10$). However, the effects were not consistent across the subgroups of calcium cumulative dose and use of bone effective treatments that could potentially decrease or increase BMD (interaction $p = 0.0768$, 0.0302, and 0.0413, respectively).

As shown in Table 9, for the subgroup of patients with calcium cumulative dose between 182000 and 183700 mg, the mean % increase from baseline in lumbar spine BMD at Month 12 in the 3 mg q 3 mo IV group was smaller than that in the 2.5 mg daily oral group, which

was opposite to the main efficacy finding. There were only few patients using bone effective treatments during the study; therefore, the results may not be reliable. For the subgroup of patients with no use of bone effective treatments, their response patterns were similar to the ones observed in the whole ITT population.

Table 9 – Raw Mean ± SD (N) for % Change from Baseline in Lumbar Spine BMD at Month 12 by Calcium Cumulative Dose and Bone Effective Treatments

ITT	2.5 mg daily oral	2 mg q 2 mo IV	3 mg q 3 mo IV
Calcium Cumulative Dose			
≤ 182000 mg	3.3637 ± 3.8397 (191)	4.7993 ± 3.8191 (179)	4.3374 ± 3.8845 (190)
> 182000 mg to ≤ 183700 mg	5.2195 ± 3.7165 (74)	5.9604 ± 4.1338 (78)	4.8806 ± 3.7331 (86)
> 183700 mg	3.6193 ± 3.8404 (148)	4.5386 ± 3.6971 (134)	5.1405 ± 3.9941 (135)
Use of Bone Effective Treatments that Potentially Decrease BMD			
Yes	10.3767 ± 0.3085 (2)	3.3518 ± 3.2240 (4)	4.1417 ± 5.8587 (3)
No	3.5979 ± 3.9607 (432)	4.8553 ± 3.9142 (408)	4.6471 ± 3.9049 (426)
Use of Bone Effective Treatments that Potentially Increase BMD			
Yes	2.7540 ± 4.6875 (3)	-0.2328 ± 3.7469 (6)	4.0683 ± 4.6235 (12)
No	3.6353 ± 3.9786 (431)	4.9157 ± 3.8647 (406)	4.6601 ± 3.8948 (417)

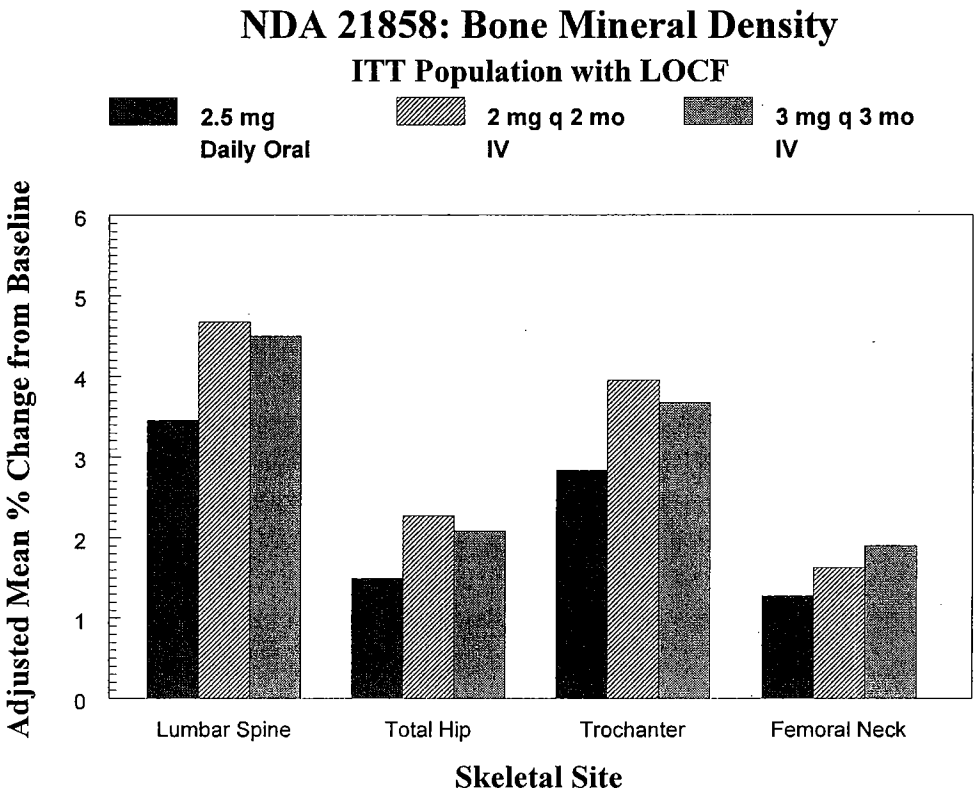
5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

In general, there were no serious statistical issues noted by this reviewer. Since there was only 1 study in this submission, no collective evidence was compiled here. The 5 efficacy parameters in this study this reviewer reviewed are briefly summarized below.

As shown in Figure 4, across the 4 skeletal sites, the mean % increases from baseline in BMD at Month 12 in the 2 IV treatment groups were all numerically larger than that in the daily oral treatment group. Clearly, the 2 intermittent IV dosing regimens were non-inferior to the daily oral one in increasing lumbar spine BMD based on the fact that both the 95% lower confidence limits were ≥ -1% (a pre-defined non-inferiority margin). Both the IV treatment groups also showed superiority to the 2.5 mg daily oral group in improving BMD of lumbar spine, total hip, and trochanter (see Tables 5 and 6). In the case of femoral neck, a significant positive finding relative to the 2.5 mg daily oral group was observed only in the 3 mg q 3 mo IV group. There were no statistically significant differences between the 2 IV dosing regimens in increasing BMD of lumbar spine, total hip, trochanter, and femoral neck. The analyses based on the per-protocol population and completers revealed similar findings to the ones based on the intention-to-treat population. Dropout cohorts also showed similar numerical results.

Figure 4



During the course of the study, the 2.5 mg daily oral and 2 mg q 2 mo IV groups were statistically comparable in suppressing bone resorption as assessed by serum CTX. No such finding was observed for the 3 mg q 3 mo IV group. In fact, significantly less reduction in serum CTX was observed in the 3 mg q 3 mo group when compared with the 2.5 mg group.

According to the sponsor, there was an inability to confirm the investigator blinding in study center 32408 (consisting of 29 ITT subjects) with respect to BMD measurements. This reviewer excluded the center from the analyses and found no major changes in the results.

5.2 Conclusions and Recommendations

After 12 months of treatment with ibandronate in postmenopausal women with osteoporosis, the changes in lumbar spine BMD in the 2 intermittent IV dosing groups were not worse than that in the daily oral treatment group. In other words, the study objective of non-inferiority of the 2 mg q 2 mo IV and 3 mg q 3 mo IV regimens to the approved 2.5 mg daily oral tablet was met. In addition, both IV doses also showed superiority to the 2.5 mg daily oral one in

increasing BMD of lumbar spine, total hip, and trochanter. However, only the 3 mg q 3 mo IV dose showed superiority to the 2.5 mg in improving femoral neck BMD. The serum CTX (a biochemical marker of bone resorption) in each study group had a rapid reduction during the first 3 months, and was further decreased by 6 months, then was maintained throughout the rest of the 12-month treatment period. The decrease in serum CTX in the 2 mg q 2 mo IV group was numerically larger, but not statistically significant, than that in the 2.5 mg daily oral group. The 3 mg q 3 mo IV group exhibited the least reduction in serum CTX among all the 3 treatment groups over the course of the study.

In summary, both the 2 mg q 2 mo and 3 mg q 3 mo IV doses were shown to be equally efficacious in improving BMD while suppressing bone resorption. The cumulative annual systemic dose was 12 mg for both regimens. The sponsor is seeking approval of the 3 mg q 3 mo IV dose for the market based on patient and physician survey preference, health care utilization advantages (fewer office visits and less procedural costs), the desire to minimize risks associated with venipuncture, and the need to maximize the potential for patient adherence (page 51 of the clinical overview). However, although there were no statistical differences between the 2 regimens in general, the 2 mg q 2 mo IV dose was numerically more effective in increasing lumbar spine BMD, total hip BMD, trochanter BMD, and in decreasing serum CTX than the 3 mg q 3 mo IV dose. In addition, the lack of IV medication compliance in this single pivotal study was numerically greater in the 3 mg q 3 mo IV group than in the 2 mg q 2 mo IV group (page 72 of the clinical study report).

Primary Statistical Reviewer: Cynthia Liu, MA

Concurring Reviewer: Todd Sahlroot, Ph.D., Statistical Team Leader
S. Edward Nevius, Ph.D., Division II Director

CC: HFD-510/RHedin, EColman, TKehoe
HFD-715/ENevius, SWilson, TSahlroot, CLiu
HFD-700/CAnello

6. APPENDIX I

FDA Question:

Please provide details regarding how patients were allocated to treatment. In other words, how the adaptive minimization method was implemented.

Roche Response:

It was estimated that 1194 subjects would be randomized into four treatment groups in the study BM16550, in a ratio of 2:1:2:1.

The four treatment groups were:

Treatment Group	Description
A	2 mg ibandronate IV every 2 months and daily oral placebo (n=398)
B	2 mg placebo IV every 2 months and 2.5 mg daily oral ibandronate (n=199)
C	3 mg ibandronate IV every 3 months and daily oral placebo (n=398)
D	3 mg placebo IV every 3 months and 2.5 mg daily oral ibandronate (n=199)

In order to ensure that across all treatment groups, the distribution of baseline BMD was comparable, the following three BMD strata were used in the randomization method:

1. BMD of lumbar spine (L2 – L4) with baseline T-score < -2.5 and ≥ -3.0
2. BMD of lumbar spine (L2 – L4) with baseline T-score < -3.0 and ≥ -3.5
3. BMD of lumbar spine (L2 – L4) with baseline T-score < -3.5 and ≥ -5.0

In addition, due to the large number of centers participating in the study, patients were also stratified by center. Patients were also stratified by consent for a bone biopsy for those sites participating in the bone biopsy sub-study.

The adaptive randomization method used was that proposed by Pocock and Simon [1] and it was performed by the central Interactive Voice Response (IVR) [redacted]

This method, as recommended in the ICH E9 guidance document, uses an element of randomization for each treatment allocation. Details of the method used are provided below using the same notation as that given in the reference.

1. 'The lack of balance' function 'D' was the 'standard deviation'.

2. The 'Total amount of imbalance' function G_k was the sum of the values d_{lk} of function D; Where next treatment assignment is k, d_{lk} was the 'lack of balance' among treatment assignments for patients with level r_l of factor l.

3. The probability p_k of assignment to the treatment with the lowest G value was defined as P = 0.80 for treatment groups A and C and 0.75 for treatment groups B and D. The alternative treatment was selected from the remaining available treatments with total probability 0.20 or 0.25 respectively which was divided between these remaining treatments according to the allocation ratio (2:1:2:1 for A:B:C:D).

4. Where there was a tie, the treatment was determined by simple randomization with probabilities contained in the table below:

	A (2)	B (1)	C (2)	D (1)
2-way tie	0.667	0.333		
	0.500		0.500	
	0.667			0.333
		0.333	0.667	
		0.500		0.500
			0.667	0.333
3-way tie	0.400	0.200	0.400	
	0.500	0.250		0.250
	0.400		0.400	0.200
		0.250	0.500	0.250
4-way tie	0.333	0.167	0.333	0.167

When calculating imbalance, the procedure allowed different weightings to be applied to each factor, depending on their importance. The weightings applied were: 3 for Center, 2 for BMD Strata, and 2 for consent to a bone biopsy.

References:

1. S.J. Pocock and R. Simon, "Sequential Treatment Assignment With Balancing For Prognostic Factors in the Controlled Clinical Trial," *Biometrics*, 31, 103-115 (1975)

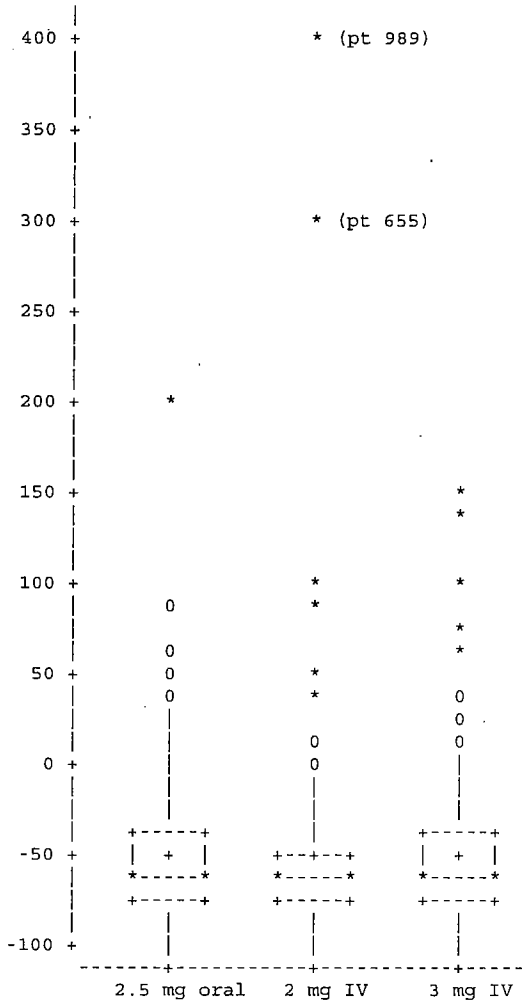
7. APPENDIX II

ITT	Group B 2.5 mg daily oral + 2 mg q 2 mo IV placebo	Group D 2.5 mg daily oral + 3 mg q 3 mo IV placebo
Lumbar Spine		
Baseline	0.7469 ± 0.0711 (212)	0.7472 ± 0.0714 (222)
Month 12	0.7741 ± 0.0756 (212)	0.7736 ± 0.0776 (222)
Mean % change from baseline at Month 12	3.6965 ± 3.8633 (212)	3.5649 ± 4.0927 (222)
Total Hip		
Baseline	0.7267 ± 0.1040 (210)	0.7461 ± 0.0944 (220)
Month 12	0.7401 ± 0.1040 (210)	0.7564 ± 0.0974 (220)
Mean % change from baseline at Month 12	1.9075 ± 2.7024 (210)	1.3970 ± 3.1153 (220)
Trochanter		
Baseline	0.5623 ± 0.0883 (210)	0.5785 ± 0.0875 (220)
Month 12	0.5795 ± 0.0885 (210)	0.5921 ± 0.0909 (220)
Mean % change from baseline at Month 12	3.2094 ± 4.1219 (210)	2.4019 ± 4.4391 (220)
Femoral Neck		
Baseline	0.6355 ± 0.1042 (210)	0.6473 ± 0.0972 (220)
Month 12	0.6461 ± 0.1044 (210)	0.6556 ± 0.0968 (220)
Mean % change from baseline at Month 12	1.7861 ± 4.2984 (210)	1.4010 ± 3.6573 (220)
Serum CTX		
Baseline	0.5557 ± 0.2729 (222)	0.5458 ± 0.2246 (235)
Month 6	0.2320 ± 0.1735 (206)	0.2518 ± 0.1773 (222)
Month 12	0.2292 ± 0.1685 (198)	0.2467 ± 0.1853 (215)
Median % change from baseline at Month 6	-64.7784	-59.8611
Median % change from baseline at Month 12	-61.5460	-62.6506

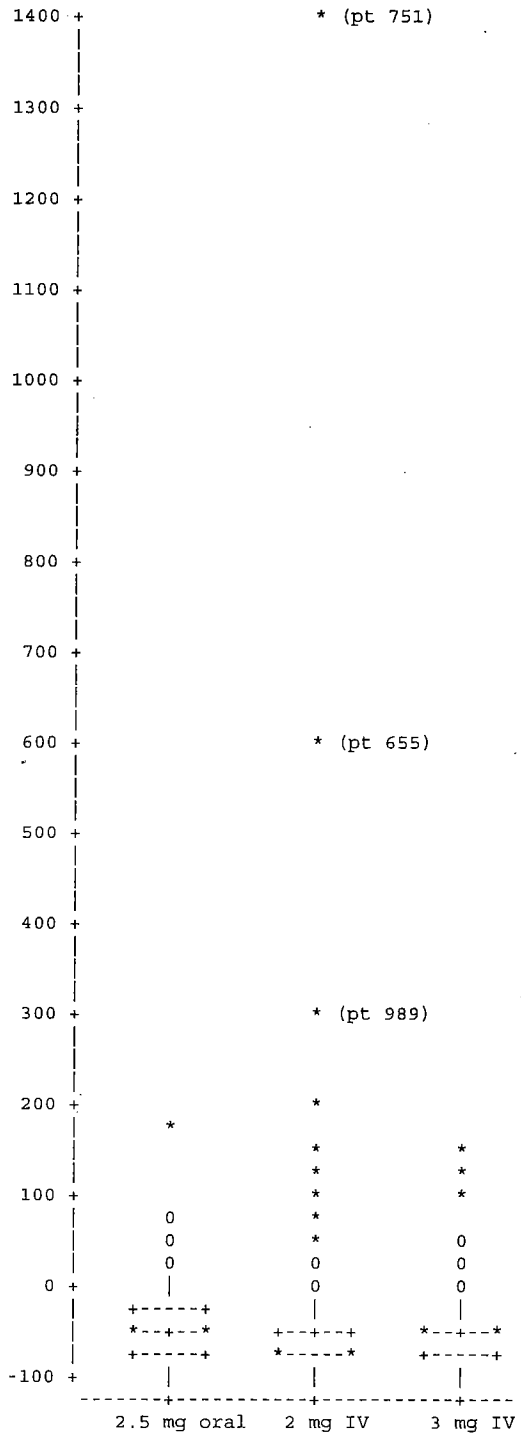
The only significant finding at $p \leq 0.05$ was mean % change from baseline in Trochanter, where $p = 0.0426$.

8. APPENDIX III

% change from baseline in s-CTX at Month 6



% change from baseline in s-CTX at Month 12



Note: The horizontal line inside the box shows the median and + sign shows the mean. Any value more than 1.5 interquartile range (= 75th - 25th percentiles) is marked with a 0.

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Cynthia Liu
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S. Edward Nevius
12/14/2005 09:31:38 AM
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Concur with review.