

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020560/S013**

**STATISTICAL REVIEW(S)**

## STATISTICAL REVIEW AND EVALUATION

MAY 5 1999

sNDA#: 20-560 SE8-013  
Applicant: Merck Research Laboratories  
Name of Drug: Fosamax (alendronate sodium) Tablets  
Indication: Treatment of postmenopausal osteoporosis and Paget's disease of bone  
Documents Reviewed: Vol.1, vol.5, vol.6 dated June 5, 1998; SAS Database dated July 31, 1998  
Medical Officer: Bruce Schneider, M.D. and Gloria Troendle, M.D. (HFD-510)  
Statistical Reviewer: Sue-Jane Wang, Ph.D. (HFD-715)  
Date of Review: March 24, 1999

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This review has been discussed with the medical review team.

## I Background

Fosamax (alendronate sodium) tablet was approved for treatment of postmenopausal osteoporosis and paget's disease of bone effective on September 29, 1995. The approved application provided results from a clinical development program with Fosamax that included clinical efficacy and safety documentation from Protocols 035 and 037, which were 3-year double-blind studies. This supplemental application provides longer-term clinical efficacy and safety documentation from 2-year extensions (years 4 and 5) of Protocols 035 and 037.

This review pertains to an aggregate of the original 3-year and the 2-year extension clinical study in which results on effect on bone mineral density, adverse experience profile for treatment of osteoporosis, etc. are added to the labelling. For a detailed review of the original 3-year study, please see Statistical Review and Evaluation written by Mr. Daniel N. Marticello dated 06/20/95.

*Keywords:* Percent change from baseline, ANOVA, ITT, Pooling of study, Bone mineral density (BMD),

## II Brief summary of original protocols 035 and 037

**Design:** These were multicenter, double-blind, randomized, placebo-controlled studies. Eligible patients were randomized to receive placebo, 5mg, 10mg, or 20 mg of alendronate (Aln) for 2-years double-blind treatment period. Later, an amendment allowed double-blind treatment to continue for an additional year for all patients who so consented to participate, which was necessary to meet certain regulatory requirements for approval in some countries including the U.S. Among consenting patients, those who were randomized to receive alendronate 20mg were blindly switched to receive alendronate 5 mg during the third year, all others remained on their original treatment. Study 035 was conducted in 18 US centers, Study 037 was a 19 center international study.

**Objective:** The study objective was to evaluate the safety, tolerability, and effect on bone density and bone and calcium biochemistry, of daily oral alendronate for up to 3 years. Primary efficacy endpoint was the percent change from baseline in lumbar spine bone mineral density (BMD) subsequent to three years of double-blind treatment.

**Drug administration:** patients self-administered their randomized medication once daily each morning. All patients also received a daily (evening meal) dietary calcium supplement of 500 mg elemental calcium throughout the study.

**Statistical Plan:** Intent-to-treat analysis was to include patients who had a baseline and at least one post-treatment lumbar spine BMD measurement. The last observation carried forward (LOCF) procedure was utilized for patients who withdrew from the study. A prospective data analysis plan called for pooling across all active treatment doses, and both studies, for analyses of the 3 fracture endpoints, viz., vertebral fracture, vertebral deformity, and stature loss.

Results on the primary efficacy endpoint (extracted from p.13 and p.17 of Mr. Marticello's review) were summarized, see Table 1.

Table 1. Lumbar Spine BMD Means ( $g/cm^2$ ) and its mean percent change from baseline

	placebo	Aln 5mg	Aln 10mg	Aln 20mg/5mg
<b>Study-035</b>				
N (total=449)	186	89	88	86
baseline	.75	.73	.73	.75
month-36	.74	.77	.80	.80
mean % change (adjusted mean)	-0.64(-0.74)	5.60 (5.57)*	9.58 (9.54)*++	7.88 (7.79)*+
<b>Study-037</b>				
N (total=461)	188	89	92	92
Baseline	.75	.76	.75	.75
Month-36	.75	.80	.80	.81
Mean % change (adjusted mean)	-0.31(-0.05)	4.87 (5.15)*	6.84 (7.16)*+	7.77(8.12)*++

\* p<.001 in favor of alendronate over placebo.

+ p<.001 in favor of alendronate 10mg, 20mg/5mg over alendronate 5mg (Study-035);

+ p=.01 in favor of alendronate 10mg over alendronate 5mg (Study-037)

# p<.01 in favor of alendronate 10mg over alendronate 20mg/5mg

++ p<.001 in favor of alendronate 20mg/5mg over alendronate 5mg

### III Two-year Extension MK-217 Protocols 035 (US) and 037 (International)

**Protocol "A 2-year, double-blind, multicenter extension study to evaluate the safety and effect on bone density of daily oral alendronate in osteoporotic postmenopausal women"**

#### Study Design

Protocols 035 and 037 were multi-center, double-blind, two-year extension studies. To be eligible for entry into the study, each patient must have participated in the original MK-217 Protocol 035/037 and must have completed the study (through 36-month visit). All eligible patients in the extension study received either 5 or 10 mg daily oral alendronate (Aln) for two years. Patients who did not consent to continued blinded treatment were offered alendronate 10 mg open-label. Alendronate were not available to patients who did not agree to continued safety and efficacy monitoring. Patients visited the clinic every six months.

#### Study Objective

The primary objective of these trials was to assess the relative effects of alendronate, 5 and 10 mg daily for five years, to increase bone mineral density (BMD) of the spine, hip, forearm, and total body and to obtain safety and tolerability data in postmenopausal women treated continuously with alendronate for up to five years. The sponsor hypothesized that alendronate 10 mg will result in a greater increase in

lumbar spine BMD from the original pretreatment baseline than that achieved with alendronate 5 mg continuously for five years. The primary efficacy endpoint for the primary objective stated above was the Month-60 percent change from baseline in lumbar spine BMD (BMD of the posterior-anterior lumbar spine (L1 to L4) determined by DXA, see Appendix I of p.17). Baseline and Month-60, for BMD parameters, were defined in the sponsor ground rules section for relative day ranges, see Appendix II of p.17.

The secondary objective was to evaluate and compare the changes in BMD of the spine, hip, forearm, and total body between Months 24 and 60 in the groups receiving either 5 or 10 mg continuously for five years or 20 mg for two years followed by 5 mg in the last three years; to determine the effects of alendronate on biochemical markers of bone turnover and calcium and phosphate metabolism; and to assess whether the Vitamin D receptor allele have utility in predicting the baseline (Month 0) BMD and/or the rate of bone loss in placebo-treated patients.

**Data Analysis Plan (DAP)**

ANOVA was used. For data pooled across the studies, the two-way ANOVA model included treatment, protocol, center nested within protocol, and treatment-by-protocol interaction as factors. The assumptions of variance homogeneity and normality were to be tested by Levene's test and the Kolmogorov D statistic, respectively. If the p-value associated with F-statistic for overall treatment effect is  $\leq 0.05$ , then the p-values from pairwise comparisons based on the least squares means will be reported. Otherwise, the p-values of pairwise comparisons will be reported. The sponsor stated that "this procedure is a modification of the least significant difference (LSD) test and should provide greater protection against false-positive results." All within-group tests were performed using a paired t-test. LSMEANS procedure of SAS were used for all between-group pairwise comparisons. Final data analysis plan (DAP) was dated February 11, 1997. In particular, DAP was "revised to indicate the most inferential statistical analysis will be performed using the combined Protocol 035 and 037 database", and "definition of ITT was revised to exclude patients who either chose open-label therapy rather than blinded treatment or continued on the open-label therapy from the 3<sup>rd</sup> year onward", *to be commented in the Reviewer Evaluation and Comments Section.*

Blinded and open-label assignments of treatment during the five-year period were summarized in the following two Tables.

Blinded patients		Treatment (5-year study period)		
Group	Years1-2	Year 3	Extension (years 4-5)	
A	Placebo	Placebo	Aln 10 mg	
B	Aln 5 mg	Aln 5 mg	Aln 5 mg	
C	Aln 10 mg	Aln 10 mg	Aln 10 mg	
D	Aln 20 mg	Aln 5 mg	Aln 5 mg	

Open-label patients in years 3 to 5		Treatment (5-year study period)		
Group	Years1-2	Year 3	Extension (years 4-5)	
A	Placebo	Aln 5 mg	Aln 10 mg	
B	Aln 5 mg	Aln 5 mg	Aln 10 mg	
C	Aln 10 mg	Aln 5 mg	Aln 10 mg	
D	Aln 20 mg	Aln 5 mg	Aln 10 mg	

According to the sponsor, approximately 350 patients were anticipated to continue until Month-60 in each study. The anticipated sample size per group was n=80. Based on the standard deviation in lumbar spine BMD seen at the two-year interim analysis (s= 4.37), the detectable difference between treatment groups at Month-60 is assumed to be 1.59%. The power calculations were based on a 2-sided  $\alpha = 0.05$  with 90% power from the pooled studies.

**Overview of Sponsor Results**

A total of 994 patients were randomized to receive double-blind treatment: 397 placebo, 202 Aln5mg, 196 Aln10mg, and 199 Aln20mg in the original 2-year study in which Aln20mg was changed to Aln5mg in the third year extension study. Individually, protocol-035 consisted of 478 patients: 192 placebo, 98 Aln5mg, 94 Aln10mg, and 94 Aln20mg, and protocol-037 516 patients: 205 placebo, 104 Aln5mg, 102 Aln10mg, and 105 Aln20mg. Numbers of patients were about 2:1 ratio between placebo and each individual alendronate arm. Patient accountability was summarized in Table 2. Of note, a total of 715 patients (72% of all randomized patients or 91% of patients entering the extension study) completed years 4 and 5 of treatment.

Table 2. Patient accountability for the entire five-year study period from pooled studies (035 & 037)

Originally randomized population with at least one dose of treatment	total	Pbo/Aln10	Aln5	Aln10	Aln20/5
	994	397	202	196	199
Entered Extension phase (yrs 4-5)					
Total	788	316	156	161	155
Entered - double blind(%)*	727(73%)	288 (73%)	145 (72%)	151(77%)	143(72%)
Entered - open label	61	28	11	10	12
Intent-to-treat (ITT) used**	644(82%)	257 (81%)	123 (79%)	142(88%)	122^(79%)
Excluded from ITT#	143	59	33	19	32
Discontinued – total (%)**	73 (10%)	33 (11%)	16 (11%)	9 (6%)	15 (10%)
Clinical adverse experience	23	12	4	4	3
Patient withdrew consent	36	14	10	4	8
Protocol deviation	6	4	1	0	1
Lost to follow-up	8	3	1	1	3
Completed: 60 months (%)~	715(72%)	283(71%)	140(69%)	152(78%)	140(70%)

\* percent of originally randomized population with at least one dose of treatment.

^ one patient (AN 2624) was not counted as she continued only to follow-up and accounted for no data in analysis

# patients with no efficacy data at baseline, no efficacy data at both Months 48 and 60, and/or on open-label therapy

\*\* percent of those patients entered double-blind extension

~ includes 61 patients who elected open-label treatment during extension period (years 4-5) only, or continued on open label from year 3 to years 4-5 and percent of originally randomized population

Patients who entered the extension study (years 4 and 5) were compared with patients who did not enter, or were not eligible for, the extension study. Percent change in lumbar spine BMD over the first 3 years was generally smaller in patients not eligible for extension (n=138) as compared to those who either did not enter (n=85), or entered the extension (n=683) studies for all treatment groups except placebo/10mg group [REDACTED]. All other characteristics were comparable in response for patients among the not eligible, did not enter, and entered extension studies. Among patients who entered the extension study, there were no significant differences among treatment groups at baseline

other than body mass index (nominal p=0.033). There were no significant difference between treatment groups in patients who entered the extension study on demographics at baseline, including ethanol intake, family history of osteoporosis, oophorectomy status, race, renal status, except percent of cigarette smoking (p=0.011) and percent of patients with prevalent vertebral fracture (p=0.030), Table 3.

Table 3. Summary of significant baseline characteristics among treatment groups (035 & 037)\*

	Pbo/Aln10mg		Aln5mg		Aln10mg		Aln20mg		p-val*
	N	%	N	%	N	%	N	%	
Cigarette smoking (N=726)	288	6.6	145	16.6	151	11.9	142	9.2	0.011
Vertebral fracture prevalence (n=698)	276	28.3	142	21.1	143	16.1	137	27.0	0.030
	N	mean	N	mean	N	mean	N	mean	
Body Mass Index (kg/m <sup>2</sup> ) (n=684)	271	24.3	136	24.8	143	23.6	134	24.4	0.033

\* extracted from sponsor Table 8 of the submission.

\* overall comparisons for the four treatment groups

Summaries of baseline and month-36 values by treatment group for clinical efficacy parameters, including lumbar spine, femoral neck, trochanter, total body, Ward's triangle, total hip, ultra-distal forearm, and one-third distal forearm (radius+ulna) BMD, can be found in Sponsor Tables 11 and 12, see Appendix III in p.18 to p.20.

**Primary efficacy variable - % change from baseline at Month-60 in lumbar spine BMD**

Table 4. Summary of Primary Efficacy Endpoint Analysis by study and from pooled comparisons

Lumbar spine BMD mean (g/cm <sup>2</sup> )	Pbo/10mg	Aln5mg	Aln10mg	Aln20/5mg
<b>Study 035</b>				
N	127	63	68	57
Baseline	0.75	0.73	0.75	0.74
Month-60	0.79	0.78	0.82	0.81
Mean (adjusted)* %change	5.45 (5.16)	6.67 (6.45)	10.01 (9.88)	9.11 (8.85)
LSD** interval	4.50, 5.82	5.55, 7.36	9.01, 10.75	7.90, 9.80
<b>Pairwise comparison</b>				
Aln5mg	.	.	<0.001	0.011
Aln10mg	.	.	.	0.264
<b>Study 037</b>				
N	130	60	74	65
Baseline	0.76	0.76	0.75	0.75
Month-60	0.81	0.80	0.81	0.81
Mean (adjusted)* %change	6.55 (6.74)	6.03 (6.15)	8.82 (8.91)	9.12 (9.07)
LSD interval	5.92, 7.56	4.96, 7.34	7.84, 9.98	7.93, 10.20
<b>Pairwise comparison</b>				
Aln5mg	.	.	0.016	0.013
Aln10mg	.	.	.	0.885
<b>Pooled</b>				
N	257	123	142	122
Baseline	0.75	0.74	0.75	0.75
Month-60	0.80	0.79	0.82	0.81
Mean (adjusted)* %change	6.00 (5.97)	6.36 (6.31)	9.39 (9.37)	9.12 (8.96)
LSD interval	5.44, 6.50	5.57, 7.06	8.67, 10.06	8.21, 9.71
<b>Pairwise comparison</b>				
Aln5mg	.	.	<0.001	<0.001
Aln10mg	.	.	.	0.576

\*  $p \leq 0.001$   
 \*\* Least Significant Difference

The sponsor excluded patients with (1) no efficacy data at baseline, (2) no efficacy data at both Months 48 and 60, and/or (3) the patient was on open-label therapy from the intent-to-treat analysis, to be commented in the Reviewer Evaluation and Comments Section.

A significant mean percent increase from baseline at month-60 of 6.0%, 6.4%, 9.4%, and 9.1% were seen in the placebo/10, 5, 10, 20/5mg arms from the pooled result (Table 4), respectively. There was no significant treatment-by-protocol interaction, see Figures 1 (pooled), 2 (study-035), and 3 (study-037). The mean percent increase in lumbar spine BMD in the Aln5mg arm was significantly smaller than that in both the Aln10mg arm ( $p < 0.001$  for Study-035,  $p < 0.016$  for Study-037,  $p < 0.001$  for pooled analysis) and the Aln20/5mg arm ( $p = 0.011$  for Study-035,  $p = 0.013$  for Study-037,  $p < 0.001$  for pooled analysis).

Figure 1

Mean Percent Change ( $\pm$ SE) in Lumbar Spine BMD  
 (Intention-to-Treat Approach)  
 (Pooled 035/037)

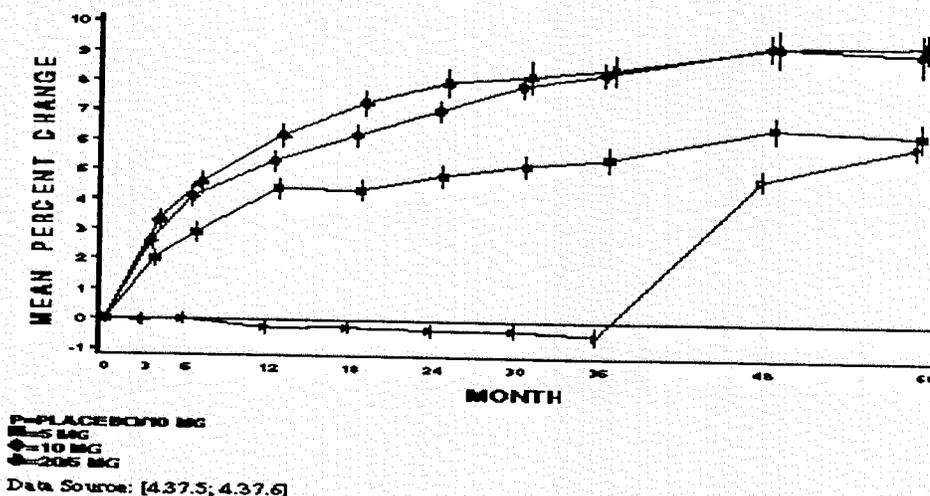


Figure 2

Mean Percent Change ( $\pm$ SE) in Lumbar Spine BMD  
 (Intention-to-Treat Approach)  
 (Protocol 035-10)

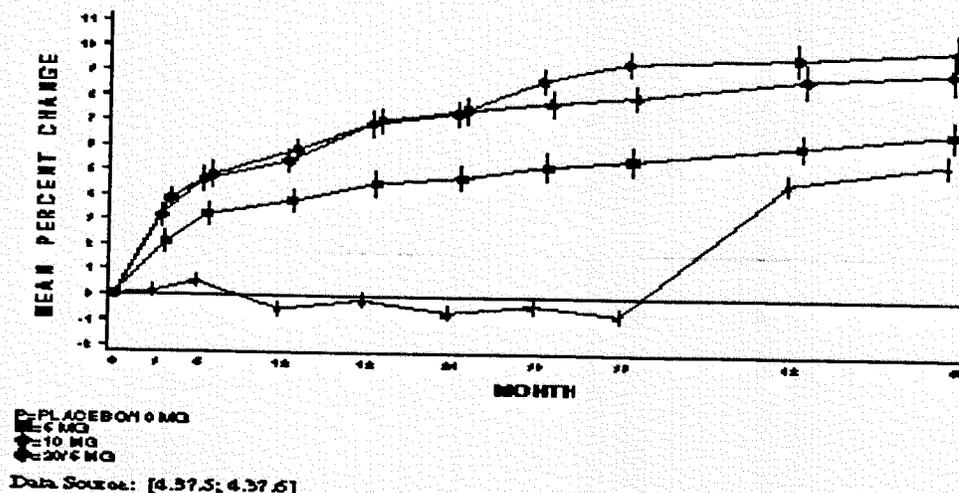
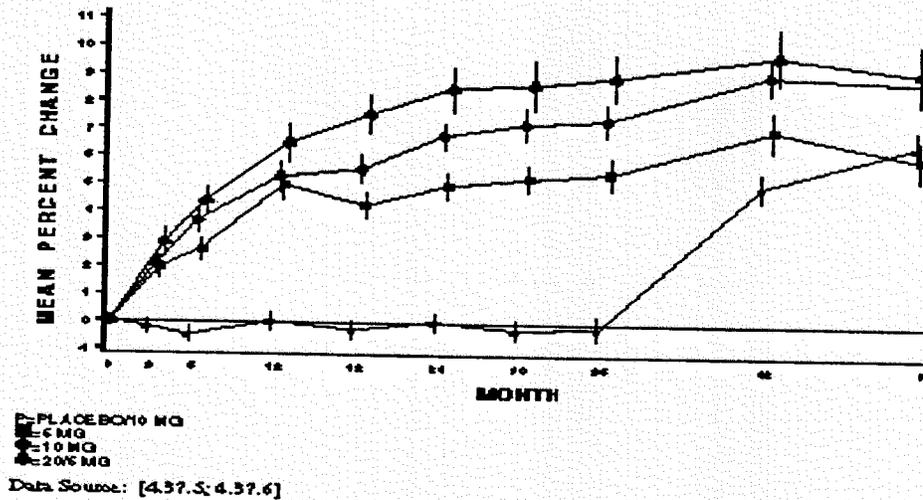


Figure 3

Mean Percent Change ( $\pm$ SE) in Lumbar Spine BMD  
(Intention-to-Treat Approach)  
(Protocol CB7-10)



Secondary efficacy variables and hypotheses:

Alendronate 10mg will result in a greater increase in hip, forearm, and total body BMD measured by % change from baseline at Month-60 than that of alendronate 5 mg in postmenopausal women

Table 5. Percent change from baseline at Month-60 for secondary Efficacy Endpoints from Pooled Comparisons

Pooled results from Studies 035 and 037	Pbo/10mg	Aln5mg	Aln10mg	Aln20/5mg
<b>Femoral Neck BMD (n)</b>	227	113	122	119
Baseline	0.66	0.65	0.63	0.65
Month-60	0.67	0.67	0.66	0.68
Mean (SD) %change	1.92(5.92)	2.51(5.92)	4.77(6.27)	3.97(5.66)
Pairwise comparison to Aln10mg (pooled)	.	<b>0.004<sup>^</sup></b>	.	0.193
<b>Trochanter BMD (n)</b>	224	112	121	117
Baseline	0.57	0.56	0.55	0.55
Month-60	0.59	0.58	0.60	0.59
Mean (SD) %change	3.84(6.98)	5.01(8.38)	9.09(6.38)	7.19(7.09)
Pairwise comparison to Aln10mg (pooled)	.	<b>&lt;0.001</b>	.	0.017
<b>Total Body BMD (n)</b>	158	82	94	86
Baseline	0.95	0.93	0.94	0.93
Month-60	0.95	0.94	0.96	0.95
Mean (SD) %change	0.45(2.29)	1.02(2.82)	2.24(2.18)	2.32(2.90)
Pairwise comparison to Aln10mg (pooled)	.	<b>&lt;0.001</b>	.	0.735

<sup>^</sup> Bolded p-values were primary comparisons of interest

Patients treated with placebo/10, 5, 10, and 20/5mg of alendronate showed a significant ( $p < 0.05$ ) within treatment increase in femoral neck BMD, trochanter BMD, and total body BMD from baseline over 5 years on pooled analysis. The increase in the 10mg group was significantly greater ( $p = 0.004$  in femoral neck BMD,  $p < 0.001$  in trochanter BMD,  $p < 0.001$  in total body BMD from pooled analyses) than that observed in the 5mg group. Such increase in the 10mg group was not significantly different from that in the 20/5mg group in femoral neck BMD ( $p = 0.193$ ), and total body BMD ( $p = 0.735$ ), but was in trochanter BMD ( $p = 0.017$ ), Table 5.

**Alendronate 5 and/or 10 mg will preserve or increase spine, hip, forearm, and total body BMD from Months 36 to 60 measured by % change from Month-36 at Month-60 (original plan was % change from Month-24) in postmenopausal women with continuous use of alendronate for five years**

Table 6. Percent change from Month-36 at Month-60 for secondary efficacy Endpoints of pooled comparisons\*

Pooled results from Studies 035 and 037	Pbo/10mg	Aln5mg	Aln10mg	Aln20/5mg
Lumbar Spine BMD – n	269	130	147	131
Mean % change from Month-36 at Month-60	6.36	0.97	0.94	0.26
95% interval – pooled	(5.84, 6.97)	<b>(0.19, 1.76)</b>	<b>(0.31, 1.78)</b>	(-0.45, 1.12)
Femoral Neck BMD – n	253	128	142	128
Mean % change from Month-36 at Month-60	3.03	-0.45	0.45	0.32
95% interval – pooled	(2.49, 3.76)	<b>(-1.12, 0.61)</b>	<b>(-0.27, 1.36)</b>	(-0.37, 1.37)
Trochanter BMD – n	249	126	142	127
Mean % change from Month-36 at Month-60	4.28	-0.46	0.88	-0.56
95% interval – pooled	(3.99, 5.34)	<b>(-1.08, 0.74)</b>	<b>(0.26, 1.98)</b>	(-1.24, 0.58)
Total Body BMD – n	177	86	103	94
Mean % change from Month-36 at Month-60	1.50	-0.02	0.19	0.19
95% interval – pooled	(1.11, 1.68)	<b>(-0.42, 0.38)</b>	<b>(-0.20, 0.53)</b>	(-0.64, 0.12)

\* underline indicates percent change from Month-36 at Month-60 is significantly different from zero, bold indicates treatment groups of interest

From the pooled results of Table 6, a significant increase of 0.97% (95%CI: 0.19% to 1.76%) and 0.94% (95%CI: 0.31% to 1.78%) from Month-36 to Month-60 in the 5mg and 10mg groups in lumbar spine BMD was observed. There were no significant increase in femoral neck BMD from Month-36 to Month-60. For trochanter BMD, there was a significant increase of 0.88% in the 10mg ( $p < 0.05$ ) group, and a numerical decrease of -0.46% and -0.56% in the 5mg and 20/5mg groups, respectively, from Month-36 to Month-60. With total body BMD, nonsignificant changes of -0.02%, 0.19%, and -0.19% were observed in the 5mg, 10mg, and 20/5mg groups, respectively. Patients in pbo/10mg group were treated with placebo during the first three years, then blindly switched to Aln10mg for years 4 and 5. The improvement in BMD of lumbar spine, femoral neck, trochanter, and total body from Month-36 to Month-60 were all statistically significant. According to the sponsor, the per-protocol results differ from the ITT results in that there was a significant ( $p < 0.05$ ) decrease in mean percent change in femoral neck BMD (-0.82%) in the 5mg during years 4 and 5.

### Safety

The sponsor stated that ninety-eight patients (13.5%) of those entered extension phase had adverse experiences that were considered serious, including five deaths. The most frequently reported adverse experiences were upper respiratory infection and back pain. A significant positive difference was observed between the groups taking 5 and 10mg during years 4 and 5 for abdominal pain (2.8% in Aln5mg vs. 9.3% in Aln10mg, nominal  $p = 0.027$ ) and sinusitis (2.1% in Aln5mg vs. 7.3% in Aln10mg, nominal  $p = 0.052$ ). **The above p-values were confirmed by this reviewer from Fisher's Exact 2-sided test.** Details of safety evaluation can be found in the medical reviewer's evaluation report.

**REVIEWER EVALUATION AND COMMENTS**

Trial period for the first three years was from January, 1991 to July 1994, which was the basis for approval of Fosamax in 1995. The two-year extension was from August, 1994 to July 1996. According to the sponsor, the case report form cutoff dates were September 26, 1996 and November 07, 1996 for protocols 035 and 037, respectively. It appeared that the final DAP (dated February 11, 1997) was finalized three (for Study 037) to five (for Study 035) months after trials were completed. Two specific revisions, explanation of modification to ITT analysis and the combined Protocol 035 and 037 database would be the most inferential statistical analysis, will be carefully evaluated.

- Baseline imbalance

The primary hypothesis of interest was to compare Aln10mg to Aln5mg. Based on this reviewer's analysis, there was no statistical evidence that percent cigarette smoking at baseline differed [Aln5mg (16.6%), Aln10mg (11.9%)]. Percent vertebral fracture prevalence at baseline also appeared to be no difference [Aln5mg (21.1%), Aln10mg (16.1%)], Fisher's exact test. However, there was a statistically significant difference ( $p < 0.0001$ ) in body mass index (BMI) between Aln5mg ( $24.8 \text{ kg/m}^2$ ) and Aln10mg ( $23.6 \text{ kg/m}^2$ ). Thus, there was no conclusive baseline imbalance between Aln5mg and Aln10mg on percent cigarette smoking and percent vertebral fracture prevalence, but there was in BMI.

- ITT analysis on primary efficacy variable

Although this NDA focuses on the extension of years 4 and 5, evaluation of the primary efficacy variable, viz., percent change from baseline at Month-60 on lumbar spine BMD, should include all patients but those patients who went to open-label treatment.

According to the electronic database, the sponsor excluded 26 of 341 patients in Trial 035 and 54 of 383 patients in Trial 037 of those who entered the double-blind extension phase ( $n=727$ ) in the clinical ITT ( $n=644$ ) report, see Table 2. In addition, the sponsor ITT efficacy patients contained 81%, 79%, 88%, and 79% of those entered double-blind extension in placebo/10mg, Aln5mg, Aln10mg, and Aln20/5mg treatment arms, respectively. Approximately 10% more patients were included in the sponsor selected ITT patients in Aln10mg (88%) as compared to Aln5mg (79%). This difference could introduce some bias.

To assess the robustness of the sponsor results ( $n=644$ ) confirmed by this reviewer, traditional ITT patients were analyzed, that is, all patients who entered double-blind extension phase ( $n=724$  in electronic database). This reviewer performed a simple treatment comparison on the primary efficacy endpoint based on all patients who entered double-blind treatment period. Patients who entered the extension double-blind phase without completing 60 months of treatment, their last available observations were carried forward for percent change from baseline analysis. The mean percent changes from baseline at Month-60 in lumbar spine BMD were similar between Pbo/Aln10mg group vs. Aln5mg group (5.4% vs. 5.9%), and between Aln10mg vs. Aln20/5mg (9.0% vs. 8.2%), see Table 7. Results of global test and pairwise comparisons with LSD were displayed by study and by overall, see Table 8. Both studies, individually or combined, appeared to show that alendronate 10mg patients experienced a significantly greater mean percent lumbar spine BMD increase than did the alendronate 5mg patients, the primary hypothesis of the NDA. Statistical evidence is consistent between this reviewer's traditional ITT analysis results and the sponsor results shown in Table 4. The comparison of two means should be interpreted as a conditional comparison, i.e., conditional on the patient's choice of entering the double-blind extension phase in the study after Month-24 and/or Month-36, which is what was included in the electronic database. Note that patients who

continued extension phase had higher % change from baseline at Month-36 than those not eligible for extension (extracted from the sponsor report), indicating that treatment benefit was primarily attributed to patients completing the first three years of alendronate.

Table 7. Summary of mean % change from baseline at Month-60\*, its standard error by study & overall\*\*

Primary endpoint (lumbar spine BMD)	Pbo/Aln10mg		Aln 5mg		Aln 10mg		Aln 20/5mg	
	mean(se)	n	mean(se)	n	Mean(se)	n	mean(se)	n
Study -035 (n=341)	4.9 (0.5)	138	6.5(0.7)	68	9.8(0.6)	71	8.5(0.7)	64
Study -037 (n=383)	5.9(0.5)	149	5.5(0.8)	77	8.3(0.7)	80	8.0(0.8)	77
Pooled (n=724)	5.4(0.5)	287	5.9(0.5)	145	9.0(0.5)	151	8.2(0.5)	141

\* all % change from baseline at Month-60 were all significant (p<0.0001).

\*\* from electronic database

Table 8. P-values\* of treatment effect from global test, pairwise LSD on percent change from baseline at month-60\*\*

Primary endpoint (lumbar spine BMD)	Protocol -035			Protocol -037			Pooled		
	5	10	20/5	5	10	20/5	5	10	20/5
Pbo/Aln10mg	0.0462	0.0001	0.0001	0.6809	0.0085	0.0040	0.6666	0.0140	0.0054
Aln 5mg		<b>0.0002</b>	0.0156		<b>0.0085</b>	0.0043		<b>0.0122</b>	0.0052
Aln 10mg			0.2275			0.7652			0.7221
Global test		0.0001			0.0017			0.0030	

\* obtained using all patients entered double-blind treatment period of years 4 and 5 from electronic database.

\*\* one-way ANOVA

- Mean lumbar spine BMD from baseline up to Month-60

Table 9 summarizes simple average lumbar spine BMD by time point of baseline, year-2, year-3, and year-5. It appeared that when placebo patients were blindly switched to Aln10mg at years 4 and 5, increase in lumbar spine BMD during this two years were parallel with those in Aln5mg, 10mg, and 20mg at their corresponding years 1 and 2.

Table 9. Mean lumbar spine BMD at baseline, year-2, year-3, and year-5 from pooled Protocol 035/037^

Arm	Baseline	24-mon(year-2)	36-mon(year-3)	60-mon (year-5)
Pbo/Aln10mg*	0.75	0.75	0.75	0.80
Aln 5mg	0.74	0.78	0.79	0.79
Aln 10mg	0.75	0.80	0.81	0.82
Aln 20/5mg**	0.75	0.80	0.81	0.81

^ Extracted from sponsor Tables 21 (p.71), 22 (p.72), and 4.10.1 (p.791)

\* Aln10mg was administered at years-4 and 5

\*\* Aln5mg was administered from years 3 to 5.

Statistically significant increase in lumbar spine BMD from Month-24 at Month-60 for all treatment groups (6.33% in pbo/Aln10mg, 1.40% in Aln5mg, 2.20% in Aln10mg, 0.86% in Aln20/5mg, p<0.05) was observed. Such increase was not statistically different between Aln5mg vs. Aln10mg (p=0.120).

Statistically significant increase in lumbar spine BMD from Month-36 at Month-60 for three treatment groups (6.36% in pbo/Aln10mg, 0.97% in Aln5mg, 0.94% in Aln10mg, p<0.01) was observed, but not in Aln20/5mg (0.26%). Such increase was not statistically different between Aln5mg vs. Aln10mg (p=0.902).

From Mr. Marticello's Table 2 of Study-035 (p.14) and Table 6 of Study-037 (p.18), statistically significant increase in percent lumbar spine BMD was seen in all alendronate treatment groups from