CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER for: 020560, S018

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA #: 20-560/ SE8-018 NOV 1 1999

Applicant: Merck & Co., Inc.

Name of the Drug: Fosamax™ (alendronate sodium) tablets

Documents Reviewed: Vols. 1, 2, and 9 to 12, SAS programs and datasets dated January 28,1999. New datafiles and SAS programs dated October 1, 1999.

Clinical Reviewer: Bruce Schneider, M.D.(HFD-510)

The issues in this review have been discussed with the reviewing medical officer, Bruce Schneider, M.D. (HFD-510).

I. Background/Introduction

This supplemental NDA (20-560) provides clinical efficacy and safety documentation (2 studies) for Fosamax when taken in combination with estrogen/hormone replacement therapy (i.e. estrogen with or without progestin). Conjugated estrogen will be denoted by CE throughout this review. Alendronate and placebo will be denoted by ALN and PBO in this review. Hormone replacement therapy will be denoted by HRT. Bone mineral density (BMD) was determined by dual-energy X-ray absorpiometry (DXA).

This review will mainly focus on the effects of treatments on the BMD of the lumbar spine (protocol specified primary analysis) and femoral neck, because these were used to determine whether the patient was eligible to enter the study. Although BMD of other locations were presented in the study reports, the sponsor was not consistent in the two studies nor was any explanation given why the other locations were given for that particular study.

This reviewer noted that the sponsor's programs for Study 097 produced analysis results for the analysis of lumbar spine BMD that did not agree with the study report. (The analysis results for the other BMD density analyses agreed with the sponsor study report.) The sponsor provided a corrected program that generated the results for lumbar spine BMD in the study report in their October 1, 1999 submission. (The baseline value of one patient was corrected.)

II. Clinical Studies

All analyses referred to in this report are the sponsor's.

1. Study 097

A. Study Description and Method of Analysis

The study under Protocol 097 was a double-blind, randomized, placebo-controlled study that enrolled 428 postmenopausal (at least 5 years), osteoporotic women who were on ongoing HRT for at least 1 year, and were randomized to receive either placebo (N=214) or alendronate 10mg/day (N=214) for 1 year. Patients continued on their HRT for the duration of the study.

The patient had to have osteoporosis defined as a BMD ≥2 standard deviations (SD) below peak bone mass for either the posterior/anterior lumbar spine (L1 to L4) or femoral neck based on normative values provided by [redacted] and ≥1.5 SD below peak bone mass for the other site.

There were two different densitometers used: Hologic and Lunar. All subjects within a center used the same densitometer. Since the densitometers do not give identical measurements, comparable calibration values were given for -1.5 and -2 SD units for Lumbar Spine BMD and Femoral Neck BMD.

The dosage of estrogen taken had to be at least equivalent to the lowest effective dose for the management of osteoporosis (0.625 mg of conjugated equine estrogen). Randomization within a center was stratified based on duration of HRT therapy to ensure an equal distribution of long-term HRT users in each treatment group. The two strata were: (1) less than 2 years of HRT and (2) 2 or more years of HRT.

Patients with an intact uterus were required to take either medroxyprogesterone acetate or micronized progestin on either a cyclical or low-dose continuous schedule. The estimated average daily intake of calcium was assessed using a dietary calcium questionaire administered to each patient at screening and baseline. If daily dietary calcium intake was 500 to 999 mg/day, 500 mg of open-label elemental calcium (as carbonate) was administered. If daily calcium intake was <500 mg/day calcium, supplementation with 1000 mg/day was administered. Study medication was also supplemented with 400 IU/day of open-label vitamin D in all patients.

All patients were instructed in lifestyle changes to reduce bone loss consistent with the standard of care of the medical community including recommendations for exercise, smoking cessation, and avoidance of excessive alcohol use.

The primary efficacy endpoint was the percent change in BMD of the PA lumbar spine at 1 year as determined by DXA. An ANOVA

model including terms for treatment, centers, strata and all two-way interactions with treatments was fit. If the interaction terms were not significant at the 0.10 level, they were dropped from the model. The p-value presented for treatments came from a model with only treatment and center effects in the model. (Interaction terms were not significant and, for unknown reasons, the sponsor also dropped the strata effect from the model.) Centers of small size were combined with other small centers to create as much balance in the design among centers as possible. Care was taken to combine centers with the same DXA machines so that variation due to machine remained completely confounded with site effects.

The protocol stated that 300 patients (150 per group) would have 90% power to detect a 1.5 % difference in bone mineral density in the lumbar spine (assuming a SD of 4% and a 0.05 significance level). Four hundred patients were chosen to ensure at least 300 evaluable patients.

B. Results

There were 428 patients (214 in each treatment group) randomized into the study at 38 centers. The treatment groups were comparable at baseline in demographic and medical history variables except that the placebo + HRT group had less of a family history of osteoporosis and less history of cigarette smoking.

The groups were comparable in their baseline bone mineral density measurements. There were 200 patients measured by a Hologic densitometer and 227 measured by a Lunar densitometer. The groups were, also, comparable at baseline in their biochemical efficacy parameters (NTx,BSAP).

Of the 428 patients entered, 394 (92.1%) completed 12 months of treatment. There were 23 (10.7%) patients in the PBO + HRT group who discontinued compared to only 11 (5.1%) in the ALN + HRT group. One of the PBO + HRT patients withdrew without returning for a subsequent visit. It is not known whether this patient took study drug.

The intent-to-treat analysis includes 408 patients (202 PBO + HRT, 206 ALN + HRT). This includes all patients who had baseline and some on-treatment BMD determinations. If a patient did not have a 12-month determination, the 6-month determination was carried forward.

The table below provides the mean percent improvements in BMD at 12 months for the intent-to-treat population for lumbar spine and femoral neck with the p-values comparing treatment groups.

Mean Percent Improvement (S.D.) and P-values Comparing Treatments at 12 months - Intent-to-treat population

	PBO + HRT	ALN + HRT	P-Value
Lumbar Spine BMD	1.1 (3.5)	3.7 (3.9)	<0.001
Femoral Neck BMD	0.8 (4.9)	1.6 (5.1)	0.072

A significant difference favoring ALN + HRT over PBO + HRT was seen for percent changes from baseline in the lumbar spine BMD but not in femoral neck BMD.

The table below provides the number of patients having non-vertebral fractures in the treatment groups and the total number of non-vertebral fractures. Some patients in the ALN + HRT therapy group had multiple fractures. There were no vertebral fractures.

Number (% of Patients with Specific Non-vertebral Fracture Adverse Experiences By Body System and Treatment Group (Incidence ≥ 1 Patient in One or More Treatment Groups)

	PBO + HRT (N=214)	ALN+HRT (N=214)
	n (%)	n (%)
Patients with one or more nonvertebral fracture clinical adverse experiences	9 (4.2)	15 (7.0)
Fracture, ankle left	0 (0.0)	1 (0.5)
Fracture, arm	1 (0.5)	0 (0.0)
Fracture, ankle right	1 (0.5)	0 (0.0)
Fracture, foot	1 (0.5)	0 (0.0)
Fracture, foot phalanx left	0 (0.0)	3 (1.4)
Fracture, foot, left	0 (0.0)	1 (0.5)
Fracture, foot, right	1 (1.5)	2 (0.9)
Fracture, Hand, Phalanx, left	0 (0.0)	1 (0.5)
Fracture, metatarsal, left	1 (0.5)	0 (0.0)
Fracture, metatarsal, right	1 (0.5)	1 (0.5)
Fracture, patella, right	0 (0.0)	1 (0.5)
Fracture, radius, left	1 (0.5)	0 (0.0)
Fracture, rib	1 (0.5)	1 (0.5)
Fracture, rib, 10^{th} right	0 (0.0)	1 (0.5)
Fracture, rib, 11^{th} right	0 (0.0)	1 (0.5)
Fracture, rib, 4^{th} left	0 (0.0)	1 (0.5)
Fracture, rib, 5^{th} left	0 (0.0)	1 (0.5)
Fracture, rib, 6^{th} right	0 (0.0)	1 (0.5)
Fracture, rib, 7^{th} right	0 (0.0)	1 (0.5)
Fracture, rib, 8^{th} right	0 (0.0)	1 (0.5)
Fracture, rib, 9^{th} right	0 (0.0)	1 (0.5)

Fracture, stress, foot	0 (0.0)	3 (1.4)
Fracture, tibia, right	1 (0.5)	0 (0.0)
Fracture, wrist, left	0 (0.0)	1 (0.5)
This table does not include those adverse experiences that occurred during pretreatment. Patients with more than one non-vertebral fracture adverse experience were counted once in the total "Number (%) of patients with one or more non-vertebral fracture clinical adverse experience" and once for each specific non-vertebral fracture clinical adverse experience.		

In the above table one ALT+HRT patient had 6 fractures of different ribs due to coughing (3 ribs fractured on two different occasions). Three other patients had one fracture. There was one fracture of the foot (phalanx left) that the sponsor did not attribute to an individual patient. Irrespective of how that fracture is assigned, the difference seen between treatment groups would not be statistically significant using the Cochran-Mantel-Haenszel test.

Significant decreases from baseline levels were seen in the bone resorption marker (urine cross-linked N-telopeptides of type 1 collagen corrected for creatine) and in the bone formation marker (bone-specific alkaline phosphate) in the ALN + HRT group but not in the PBO + HRT group.

C. Reviewer's Comments

This study showed that Alendronate increased Lumbar Spine BMD more than placebo when each was added to hormone replacement therapy.

2. Study 072

A. Study Description and Method of Analysis

The study under Protocol 072 was a randomized, double-blind, placebo-controlled, multi-center study that enrolled 425 hysterectomized (at least 3 months prior to entry, with or without removal of the ovaries), postmenopausal (at least 3 years), osteoporotic (low lumbar spine bone density defined as <0.86 g/cm^2 by Hologic QDR measurement) women. Patients were randomized to 1 of 4 treatment groups: placebo (N=50), alendronate 10mg (N=92), CE 0.625 mg/day (N=143), or combined alendronate 10 mg and CE 0.625 mg/day (N=140). Treatment was for two years preceded by a 2-week placebo run-in period.

There were 19 investigators in 16 states in the U.S.

Randomization was stratified in each center using two strata:

prior use of estrogen or no prior use of estrogen. Randomization was unbalanced in the ratios 1:2:3:3 for the placebo, alendronate, CE, and ALN + CE groups.

The sponsor stated that 120 patients in the CE and ALN + CE groups should have 95% power to detect a 2% difference in lumbar spine BMD % changes from baseline between the ALN + CE and CE groups assuming a SD of 3.3% and a 40% dropout rate.

The analysis of BMD and biochemical parameters was identical to that of Study 097 with the exception that here the strata is prior use of estrogens (yes, no) and not duration of use of estrogens as in Study 097. Again the p-value for treatments came from an analysis that included only treatments and center. (The interaction terms of treatment-by-center and treatment-by-strata were not significant at the 0.10 level.)

There was an interim analysis for safety after approximately 80% of the active patients completed 1 year of treatment. The study was to be discontinued prematurely if the Month 12 spine BMD measurements indicated the percent change from baseline was significantly ($p<0.050$) lower for the ALN + CE group compared to the CE-only group. If the interim findings had suggested a statistically significant adverse trend ($p<0.100$) in the ALN only or ALN+CE groups compared to the CE-only or PBO groups for serious adverse experiences or clinical fractures, consideration would be given to stopping the study after a case-by-case review of the clinical relevance of the findings. (The study was not stopped.) The investigators were kept blinded to treatment assignment.

B. Results

Of 425 patients entered, 320 (75.3%) completed 24 months of treatment. The percentage of patients (relative to patients entered) completing the study was 34/50 (68%), 68/92 (74%), 108/143 (75.5%), and 110/140 (78.6%) respectively for the placebo, alendronate 10mg, CE 0.625mg and the combination of the two active arms.

Thirty patients were not included in the intent-to-treat group because they did not have at least one post-treatment measurement after baseline or did not have baseline values. The percentages of patients in each treatment group not included in the intent-to-treat analysis were comparable

The sponsor provided some descriptive statistics and stated, for categorical baseline patient characteristics, "There were no clinically meaningful differences between treatment groups at

baseline for these parameters although 56% of the PBO-treated patients reported prior estrogen use, versus only 41.3 to 43.6% in the other treatment groups. The statistical model used for analysis does include prior use of estrogen as a factor." For continuous baseline patient characteristics, including baseline BMD and baseline biochemical efficacy parameters, the sponsor stated, "There were no clinically meaningful differences between treatment groups at baseline for these parameters."

For the most common secondary diagnoses, the sponsor stated, "There were no clinically meaningful differences between the treatment groups, except for the greater incidence of endocrine disorders PBO versus ALN + CE (34.0 versus 15.0%), and the lower incidence of musculoskeletal disorders in CE (42.5%) versus PBO (82.0%), ALN (77.2%), and ALN + CE (74.3%)."

The table below provides the mean percent improvements and p-values comparing treatments at 24 months for the intent-to-treat population.

Mean Percent Improvement (S.D.) and P-values Comparing Treatments at 24 months - Intent-to-treat population

	Lumbar Spine		Femoral Neck	
	N	Mean (SD)	N	Mean (SD)
PBO	46	-0.60 (3.36)	46	-0.62 (4.11)
ALN	87	6.00 (4.3)	87	2.86 (4.72)
CE	136	5.99 (4.6)	130	2.62 (4.01)
ALN + CE	132	8.26 (4.4)	132	4.17 (3.99)

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Pairwise p-values for treatment comparisons.

	Lumbar Spine			Femoral Neck		
	ALN	CE	ALN+CE	ALN	CE	ALN+CE
PBO	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
ALN		0.995	<0.001		0.685	0.022
CE			<0.001			0.003

The combination was significantly better than placebo and both components for Lumbar Spine and Femoral Neck BMD.

The table below provides the number of patients having fractures in the treatment groups and the total number of fractures. Some patients had multiple fractures. There were 12 vertebral fractures: 2,1,5,4 in the PBO, ALN, CE, and CE+ALN groups, respectively. Numerically less fractures were seen in the ALN and ALN+CE groups.

Fractures	PBO (N=50)	ALN (N=92)	CE (N=143)	ALN + CE (N=140)
Patients (%)	4 (8.0)	4 (4.3)	8 (5.6)	5 (3.6)
No. of Fractures (%)	5 (10.0)	5 (5.4)	10 (7.0)	6 (4.3)

Significant differences in percent changes from baseline between the ALN + CE group and the other three groups were seen in the bone resorption marker (urine cross-linked N-telopeptides of type 1 collagen corrected for creatine) and in the bone formation marker (bone-specific alkaline phosphate).

C. Reviewer's Comments

The interim analysis that unblinded the sponsor to treatment assignment at 1 year should have little effect on the conduct of the study since most patients would have been enrolled at the time of the interim look. The study would not be stopped for an ALN or ALN + CE advantage. Thus no p-value adjustment is needed.

This reviewer found that the BMD data from patient 135 in site 17 might have been mishandled in the sponsor's analyses. [The visit 4 date was coded as 12/18/1997 and probably should have been coded as 12/18/1996. The sponsor used the 6 month BMD data as the 12 month data and had no 6 month data for this patient.] The effect on the p-values and treatment means due to this mistake were negligible.

III. Conclusion

Alendronate provided a significant increase in bone mineral density in the lumbar spine when added to HRT in Study 097 (an increase of 2.6%) or when added to conjugated estrogens in Study 072 (an increase of 2.3%). A significant difference of 1.5% favoring ALN + CE over CE was also seen in femoral neck BMD in study 072.

Although more fractures were seen in the ALN + HRT group than the placebo + HRT group in study 097, less fractures were seen in the ALN + CE group than the CE group in study 072. All the fractures

in Study 097 were non-vertebral.

/S/

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This review consists of 9 pages of text.

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