

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER for: 020560, S015

MEDICAL REVIEW(S)

MEDICAL OFFICER'S REVIEW sNDA # 20-560-018

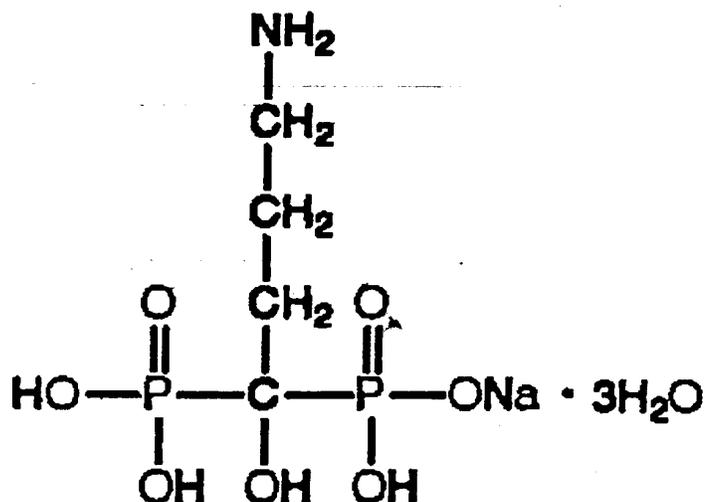
November 5, 1999

DRUG NAME: Fosamax®

GENERIC NAME: Alendronate Sodium Tablets

PROPOSED TRADE NAME: Fosamax®

CHEMICAL STRUCTURE:



Alendronate sodium

1.3 SPONSOR: Merck & Co., Inc., West Point, PA 19486

1.4 PHARMACOLOGICAL CATEGORY: Alendronate sodium (4- amino- 1- hydroxybutylidene bisphosphonic acid monosodium salt trihydrate, $\text{C}_4\text{H}_{12}\text{NNaO}_7\text{P}_2 \cdot 3\text{H}_2\text{O}$, f.w. 325.12) is an aminobisphosphonate. Bisphosphonates, synthetic analogs of pyrophosphate, bind to hydroxyapatite in bone. Alendronate specifically inhibits osteoclast- mediated bone resorption.

1.5 INDICATION: Prevention and treatment of postmenopausal osteoporosis. In this sNDA, the sponsor proposes revisions to the current labeling. The revisions are based on controlled clinical studies that document the safety and efficacy of

alendronate taken in combination with hormone replacement therapy (HRT; estrogen with or without progestin). Efficacy is defined as changes in bone mineral density and biochemical markers of bone turnover.

1.6 DOSAGE FORM AND ROUTE OF ADMINISTRATION: Tablets, oral.

1.7 NDA DRUG CLASSIFICATION: Bisphosphonate, oral

1.8 IMPORTANT RELATED DRUGS: etidronate, pamidronate, clodronate, risedronate

1.9 RELATED REVIEWS:

Statistics review

2 TABLE OF CONTENTS

**APPEARS THIS WAY
ON ORIGINAL**

3 MATERIAL REVIEWED: All clinical data in the 14-volume submission. The data were reviewed both from an electronic submission and from paper sources.¹

4 CHEMISTRY/MANUFACTURING CONTROLS: The sponsor has applied for categorical exclusion from environmental assessment.

5 PRE-CLINICAL PHARMACOLOGY/TOXICOLOGY: Per masterfile. The pre-clinical pharmacology/toxicology data have been reviewed as part of the original NDA.

6 CLINICAL BACKGROUND

Postmenopausal osteoporosis is a common disorder that is characterized by low bone mass and microscopic deterioration in bone architecture. In this condition, the quantity of bone is diminished, but the quality of the remaining skeletal tissue remains histologically normal, with no evidence of osteomalacia. The loss of bone mass and deterioration of bone microarchitecture results in increased bone fragility and susceptibility to fracture. In the postmenopausal period, bone loss results from an imbalance in bone resorption, relative to formation. The major cause of the loss of bone after menopause is estrogen deficiency, although other factors play a role, particularly with advancing age. During the first few years after menopause, estrogen deficiency is presumably the predominant factor in producing the accelerated rate of bone loss.

Strategies for the prevention of postmenopausal osteoporosis include adequate daily intake of calcium and vitamin D, maintenance of reasonable body weight and level of exercise, cessation of smoking, and avoidance of excessive intake of caffeine. In principle, pharmacological intervention can be directed at decreasing bone resorption (anti-resorptive agents), or increasing bone formation (anabolic agents). Approved classes of anti-resorptive agents include hormone (estrogen) replacement therapy, calcitonin, selective estrogen receptor modulators, and bisphosphonates. Each class of drug has advantages and disadvantages. At the time of this review, there are no FDA-approved effective anabolic agents for bone.

Alendronate is a potent bisphosphonate that was approved in 1995 for the treatment of postmenopausal osteoporosis. The drug is selectively concentrated in bone and interferes with osteoclastic bone resorption via mechanisms that have not been completely elucidated. Alendronate binds tightly to bone mineral hydroxyapatite; however, there are abundant data which suggest that alendronate also exerts intracellular actions on osteoclasts themselves and that

¹ Several tables and figures were reproduced from the electronic submission. Unless otherwise indicated, tables and figures are the sponsor's.

the primary mechanism of action is inhibition of osteoclast function. In addition, alendronate does not appear to inhibit bone mineralization directly. There is no evidence that alendronate causes osteomalacia.²

By inhibiting bone resorption, alendronate reverses the loss of bone mineral that accompanies estrogen-deficient states, such as menopause. Consequently, bone mineral density increases at several skeletal sites, particularly those areas that are rich in trabecular bone. The preferential effect of alendronate on trabecular bone is due to the relatively high mineral turnover in this type of bone after menopause. Alendronate resides in bone for many years. The terminal elimination half-life of the drug is 10 years. Nonetheless, the drug has to be administered continuously in order to maintain inhibition of bone resorption. Once initiated, postmenopausal osteoporosis is a condition that is present for the remainder of the lifespan; thus, currently available anti-resorptive therapy must be continued for many years, if not indefinitely.

Alendronate has consistently demonstrated efficacy, in terms of increases in BMD at the spine and hip. In addition, fracture efficacy (particularly at the spine) has been demonstrated in several clinical trials. The absolute numbers of fractures that are prevented by alendronate treatment vary with the severity of osteoporosis that is present in the trial population (see earlier review of the 4-year FIT trial and Combined Fracture Analysis submission)³. Nonetheless, important issues regarding the relationship between changes in BMD and fracture rates remain, for it is certain that factors other than BMD or BMC play a role in determination of bone fragility. In the reviews alluded to above (supplemental NDAs 20560-013 and 20560-15), questions were raised regarding the lack of strict correlation between spinal BMD changes and ongoing loss of stature in postmenopausal women treated with alendronate. On theoretical grounds, an anti-resorptive agent-induced gain in BMD would not be expected to reverse the loss of bone strength that is due to severed trabecular connections. On the other hand partial protection from loss of bone strength may be afforded by anti-resorptive therapy.

² The complete array of intracellular actions of bisphosphonates has not been determined. Furthermore, the intracellular actions differ among the bisphosphonates. Some, those that resemble PPI, may be incorporated into ATP analogs, whereas the nitrogen-containing bisphosphonates may interfere with the mevalonate pathway and post-translational protein prenylation. The latter may affect intracellular protein "trafficking" processes in which nascent proteins are directed to specific intracellular locations. Such actions may increase the rate of cellular apoptosis. Bisphosphonates may also affect the activities of enzymes that are involved in matrix resorption, as well as proton pump activities that are required for acidification of resorption cavities.

³ During this past year, labeling was approved for extended use of alendronate for up to 5 years, based on BMD efficacy and overall safety profile. In addition, the Division approved a labeling supplement for prevention of corticosteroid-induced osteoporosis. At the time of this review, the Division has also approved labeling changes based on data from the four-year arm of the Fracture Intervention Trial.

As noted above, estrogen deficiency is probably the most important cause of bone loss and osteoporotic fractures in postmenopausal women. In most women, hormone replacement therapy (HRT) with estrogen or estrogen/progestin prevents the rapid loss of bone mineral that occurs immediately following menopause. In addition, HRT prevents bone loss and increases bone mass if administered several years after menopause. This positive effect on bone is dependent on continuous treatment; bone loss resumes upon cessation of HRT.

Despite these positive effects on BMD, the overall effects of HRT on fracture incidence are still uncertain. A few studies have demonstrated statistically significant reductions in fracture rates at the hip, spine, and wrist. However, there have not been large prospective randomized trials designed to investigate this issue, and it has been argued that the better health status of women who elect to take HRT enhances the apparent efficacy of estrogen in observational studies. In the randomized, placebo-controlled HERS study of 2763 postmenopausal women (mean age 67 years) followed for an average of 4.1 years, HRT provided no beneficial effect on fracture incidence.

It is possible that beneficial effects of HRT on fracture incidence may be apparent in subsets (e.g., related to specific genetic, nutritional, behavioral characteristics) of osteoporotic women. It should also be emphasized that drug-associated increases in BMD may not accurately predict fracture reduction across all drugs. A 2% increase in BMD that is afforded by treatment with one agent may offer the fracture efficacy equivalent of a 4% increase seen with another agent. Thus the efficacy of HRT in fracture risk reduction has not been established with certainty.

In a preclinical study in intact (estrogen-replete) rats, chronic alendronate treatment resulted in increased bone mass and strength (e.g., Guy et al, *Calcif. Tissue Int.* 53:283-288). However, in another study of ovariectomized rats, there was no demonstrable synergy between alendronate and estradiol in the tibia, measured by several parameters, including histomorphometry. In vertebra, combined treatment increased BMD over either treatment alone, (all were increased over ovariectomized controls), but the increase was not statistically significant. Similar results were found for vertebral bone strength. In this estrogen-depleted model, either E2 alone or alendronate alone reduced the elevated levels of biochemical markers of bone turnover; however, combined E2 and alendronate treatment showed no further effect over either treatment alone (Seedor et al, Dec. 1994, submitted as an unpublished ms. with the NDA). In intact male and female dogs, long-term treatment with alendronate caused no measurable bone toxicity; however, there were no significant changes in bone strength or morphology in intact male or female animals, compared to controls.

Thus the results of long-term preclinical studies have suggested that there is no obvious toxicity of alendronate when given in the presence of endogenous or exogenous estrogen. However, on the basis of these data, it is difficult to predict that, in postmenopausal women, combined therapy with alendronate and

estrogen will increase bone mass and strength beyond that which is achieved with either drug alone. Clearly, appropriate clinical trials are required to answer this question.

Since all previous clinical trials of alendronate excluded patients taking HRT, there is a dearth of data on the effects of combined alendronate-HRT therapy. Thus, the sponsor has conducted two separate clinical trials to determine the safety and efficacy of alendronate combined with HRT in the treatment of postmenopausal osteoporosis. In addition, a clinical pharmacology study, using biochemical bone metabolism markers as endpoints, was designed to examine the effects of the addition a progestin to estrogen replacement. The results of all three studies were submitted in this sNDA and are the subjects of this review.

Protocol 072 was a two-year, randomized, double-blind, placebo-controlled trial that compared the bone-sparing effects of four treatment regimens: placebo, HRT alone, alendronate alone, and alendronate+HRT. The primary endpoint was spinal bone mineral density. Because HRT patients received continuous estrogen without a progestin, the study enrolled only hysterectomized postmenopausal women. Four hundred twenty-five women with "osteoporosis," defined by the sponsor as a lumbar spine BMD T-score ≤ -2.0 , were randomized into this protocol. The prior hysterectomy allowed treatment with unopposed estrogen. In addition, by eliminating uterine bleeding, the hysterectomy improved compliance with estrogen therapy, and abolished a source of unblinding to the administration of estrogen.

Protocol 097, was a one-year, double-blind, randomized, placebo-controlled study of 428 postmenopausal (at least 5 years), osteoporotic women (defined as having either a lumbar spine or femoral neck BMD T-score ≤ -2.0 and a BMD T-score ≤ -1.5 at the other site) who had been taking hormone replacement therapy for at least 1 year. All subjects continued their HRT and in addition received either placebo (N=214) or alendronate (N=214) for the duration of the study. Hysterectomy was not required for entry into this study, and patients' HRT consisted of either continuous estrogen (hysterectomized women) or estrogen plus progestin. Efficacy endpoints were BMD and bone turnover markers. The format of this study replicated a not uncommon clinical situation in which a postmenopausal woman has been taking HRT for prevention of bone loss, and for other indications not related to osteoporosis. In individuals with sub-optimal BMD responses to estrogens, it is important to determine whether the addition of another anti-resorptive agent is beneficial.

Protocol 080 was designed to compare effects of estrogen+progestin to those of estrogen alone on biochemical markers of bone turnover. This was 4-month placebo-controlled, randomized study in which 41 postmenopausal women were randomized to receive either 0.625mg of CE or CE+ 10mg cyclic MPA. This was a small study that essentially reconfirmed earlier data, which failed to

demonstrate deleterious mineral effects due to addition of MPA to estrogen replacement therapy.

In the submitted trials that studied alendronate, the dose of the drug was 10 mg/day. This dose was selected on the basis of extensive prior work on efficacy, safety, and tolerability of doses of alendronate in the range, 1-20 mg/day, administered for up to 2 years. In Protocol 072, conjugated equine estrogens (CEE) were selected because they are the most extensively used and studied estrogen preparation for osteoporosis and cardiovascular prevention. The dose of CEE, 0.625 mg/day, is recommended for osteoporosis and cardiovascular indications.

7 DESCRIPTION OF CLINICAL DATA SOURCES

Clinical data were obtained only from the women who participated in the three studies. Further details are provided below.

8 CLINICAL STUDIES

8.1 Reviewer's trial #1, Sponsor's Protocol # 080

"A Placebo-Controlled, Randomized, Parallel-Group Study of the Effects of Addition of Progestin to Estrogen Replacement Therapy on Biochemical Markers of Bone Turnover in Postmenopausal Women"

8.1.1.1 Objectives

The objective of this four-month study was to determine the mineral homeostatic effects of monthly addition of a progestin (medroxyprogesterone acetate [MPA] 10 mg, on Days 1 through 12) to continuous estrogen replacement therapy. Efficacy endpoints were biochemical markers of bone resorption and bone formation, as well as serum calcium and phosphorus.

The stated hypothesis was: *"Addition of cyclic progestin (MPA on Days 1 through 12) to continuous estrogen replacement therapy (CEE daily) for 4 months will not produce a clinically meaningful change in the excretion of NTx (i.e., the difference in mean percent change from baseline will be less than \pm 30% at the completion of the fourth cycle in the treatment groups)."*

8.1.1.2 Study Design

This was a randomized, placebo-controlled, parallel group design, in which 40 women were randomized (1:1) to receive either MPA or placebo on Days 1-12 of

each month for 4 months. Women who had been taking CEE were continued on their estrogen, but were randomized to receive MPA, 10 mg/day, for Days 1-12 of each month. The sponsor assessed biochemical markers of bone turnover and mineral metabolism 3 times during a pretreatment period when subjects were receiving estrogen only and then on Day 13 of each month during the 4-month period in which they had received both estrogen and progestin. Additionally, during the last 2 months of the study, markers were measured on Day 30.

COMMENTS: This study did not include a control group that was not receiving HRT. Thus the study compares CEE to CEE/MPA in a group of patients whose bone marker excretion patterns had already been modified by CEE. The lack of a control group precludes determination of efficacy of the CEE itself. Further comments on endpoints are provided below. This was a small study, of short duration, that could provide a limited body of information on the effects of progestin/CEE.

8.1.1.3 Protocol

8.1.1.3.1 Population, Procedures, Concurrent Treatment

Population: The subjects were hysterectomized postmenopausal women aged 40-75 years, who had received continuous estrogen replacement (CEE) with (PREMARIN™, Wyeth-Ayerst), for at least the previous year. Subjects were generally in good health and within 25% of ideal body weight (Metropolitan Life Insurance Co.)

The sponsor provides a list of 14 exclusionary criteria. Because many of these are relevant to a bone turnover study, the list is included below:

- *1) Subject had significant abnormalities on prestudy screening, clinical, or laboratory examinations (both were carried out within 6 weeks of the start of treatment).*
- 2) Subject had a history of, or evidence for, significant end-organ disease, e.g., genitourinary, gastrointestinal, cardiovascular, hepatic, psychiatric, renal, or pulmonary disease, which could have posed additional risk to her participation in the study.*
- 3) Subject had a history of, or evidence for any metabolic bone disease (other than postmenopausal bone loss) including, but not limited to, hyper- or hypoparathyroidism, Paget's disease of bone, osteomalacia, and osteogenesis imperfecta.*
- 4) Subject was using or had used drugs that might have affected calcium and/or bone metabolism including:*
 - a) Bisphosphonate or fluoride (>1 mg/day) treatment for any reason*
 - b) Calcitonin or corticosteroids (>5 mg/day prednisone or equivalent for >1 month) treatment within a year prior to the study, or*
 - c) Estrogens or progestins other than PREMARIN™ within 12 months prior to the study, or*
 - d) Vitamin A supplements exceeding twice the recommended daily allowance 6 months prior to the study, or*
 - e) Vitamin D supplements exceeding 3 times the recommended daily*

BEST POSSIBLE COPY

- allowance (1200 IU) within 6 months prior to the study, or
- f) Diuretics within 6 months prior to the study, or
- g) Anticonvulsants within 6 months prior to the study.
- 5) Subject had an ultrasensitive thyroid stimulating hormone (TSH) outside the normal range or a history of hyper- or hypothyroidism unless she was asymptomatic without any change in thyroid hormone replacement dose for at least 1 year prior to the study. Hypothyroidism may not have been treated with any medication other than thyroid hormone.
- 6) Subject had a history of glucocorticoid excess (either exogenous [>5 mg/day prednisone, inhaled glucocorticoid, or equivalent for more than 2 weeks] or endogenous) within 1 year of entry into the study. Subjects who had received therapeutic glucocorticoids before that time must have been considered very unlikely to require retreatment during the course of the study.
- 7) Subject had uncontrolled hypertension, had untreated angina, or had had a myocardial infarction within 1 year prior to entry into the study.
- 8) Subject had evidence for significantly impaired renal function, defined as serum creatinine >1.5 mg/dL.
- 9) Subject had any degree of active rheumatoid arthritis.
- 10) Subject was a current user (including "recreational use") of any illicit drugs or had a history of drug or alcohol abuse.
- 11) Subject habitually drank excessive amounts of coffee (greater than 6 cups/day) or drank more than 2 alcohol-containing beverages (more than 2 cans of beer, glasses of wine, or standard mixed drinks), on average per day.
- 12) Subject was mentally or legally incapacitated or otherwise unable to give informed consent.
- 13) Subject had participated in another clinical trial within 4 weeks of the screening examinations.
- 14) Subject had a history of any illness that, in the opinion of the investigator, might have confounded the results of the study or posed additional risk to the subject."

Procedures: The sponsor provides the following table, which displays the schedule of clinical and laboratory studies:

	Prestudy	Run-In		Study Day of the Month ¹												Poststudy ²	
		Month 1		Month 1	Month 2	Month 3		Month 4									
		Day 13	Days 25 to 31	Days 1 to 12	Day 13	Days 1 to 12	Day 13	Days 1 to 12	Day 13	Day 30	Days 1 to 12	Day 13	Day 30				
Medical history	X																
Physical examination	X																X
Pap smear	X																
Lumbar spine BMD	X																
Twelve-lead ECG	X																
Mammogram	X																
Laboratory safety	X																X
Plasma lipids ³	X																X
MPA/PBO				X		X		X		X		X		X		X	
Bone/mineral biochemistry		X ⁴	X ⁴		X		X		X		X		X		X		X

¹ Although the study was designed based on calendar months, Day 1 of the study was not necessarily the first day of a calendar month.

² Conducted on Day 30 of Month 4 or within 14 days thereafter.

³ Total and high-density lipoprotein (HDL) cholesterol, triglycerides.

⁴ Three urine collections: one on Day 13 (± 3 days) prior to menstrual/progestosterone accurate/placebo treatment and two within 5 days prior to MPA/PBO treatment.

On Day 13 of Months -1 through 4 and Day 30 of Months 3 and 4, the first morning urine was collected to determine excretion of NTx, calcium, phosphate,

and creatinine. Additionally, baseline urine samples were collected on two occasions in Month -1, prior to administration of MPA/PBO. At each of these time points, blood samples were obtained for the measurement of serum BSAP, calcium, phosphate, and creatinine.

For laboratory safety analysis, a full battery of blood chemistries, a hematology profile, and urinalysis were obtained pre- and post-study. The specific laboratory tests are provided in Table 2 of the NDA reference 1.

8.1.1.4 Endpoints

Efficacy

The primary efficacy endpoint was urinary excretion of NTx at study end (Month 4, Day 30), expressed as mean percent change from baseline. Methodologies for measurement of urinary NTx, serum BSAP, and other relevant analytes are provided in the NDA.

Comments: Efficacy was defined in terms of biochemical markers of bone turnover. A longer and much larger study would be required to provide adequate statistical power to detect treatment-related BMD differences. It is worth noting that biochemical markers provide a surrogate for, or predictor of, BMD changes, which in turn provide a variably reliable surrogate for fracture efficacy.

The primary efficacy outcome for the major clinical studies (072 and 097, reviewed below) was based on BMD changes (and not fracture efficacy); a biochemical endpoint for a small study 080 is not unreasonable in the context of the overall submission.

Safety

Safety analysis was conducted according to well-established procedures. Full details are provided in the NDA submission. The safety/tolerability analysis applies to patients taking CEE or CEE+MPA. No subject received alendronate during this study.

During visits, subjects were questioned regarding any adverse events. Investigators evaluated all AE's regarding intensity, seriousness, and possible relation to test medication. Safety data were also gathered from laboratory tests, ECG's and physical examinations.

8.1.1.5 Statistical Considerations

The primary efficacy endpoint was the mean per cent change from baseline in urinary NTx at Month 4, Day 30.

The 90% CI was used for the comparison of the between-treatment group differences in mean percent changes from baseline to study end. If this CI was within the range -30 to 30%, the hypothesis was to be rejected. An ANOVA model was used to calculate the between-treatments difference in least squares change in NTx from baseline ($p=0.05$). The sponsor used the same approach to determine the effect of addition of MPA to CEE on all the other markers of mineral metabolism.

8.1.2 Results

8.1.2.1 Populations enrolled/analyzed

A total of 41 subjects entered the study, with 38 completing. Two subjects discontinued due to an AE (hives and mood swings) and one subject withdrew consent. The race, mean age, height, and weight did not differ between the two treatment groups (Table 4 of the NDA). The average age was about 56 years; weight, 152 lbs.; height, 64 inches. Ninety-three per cent of the enrolled population was white, and the remaining subjects were black. Data from all 41 subjects were included in the safety analysis.

8.1.3 Efficacy endpoint outcomes

For the efficacy analysis the sponsor used a per-protocol approach. An ITT analysis is also provided in the NDA submission.

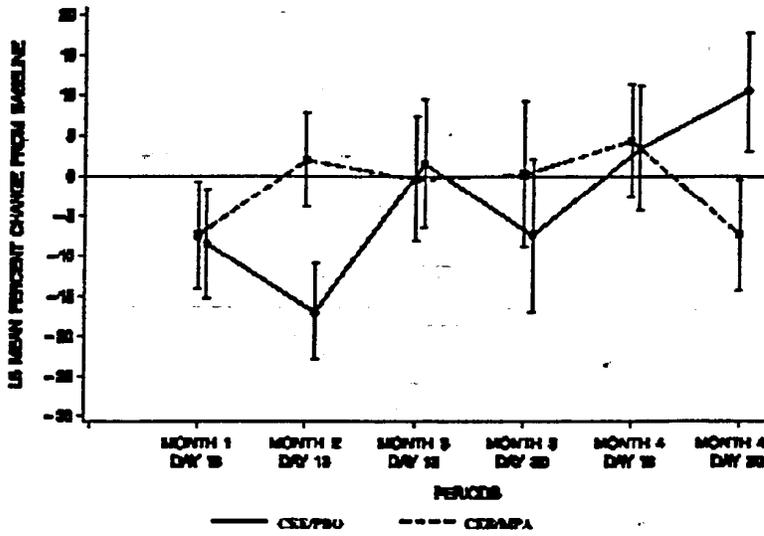
Urinary N-Telopeptide/Creatinine Excretion

Result: This was the primary efficacy outcome. At baseline the mean NTx did not differ between the two treatment groups. During the 4 months of the study, including study end, there was no consistent pattern of difference between treatment groups.

For NTx excretion, the LS mean % change (from baseline) showed a between-treatment difference that ranged from 18.93% at Month 2 to -17.80% at Month 4. At study end, the lower bound of the 90% CI was -33.9%, but the two treatment groups did not differ significantly. Averaged over the 4 months, the mean % change from baseline was -1.70% for the CEE/MPA group and -3.37% for

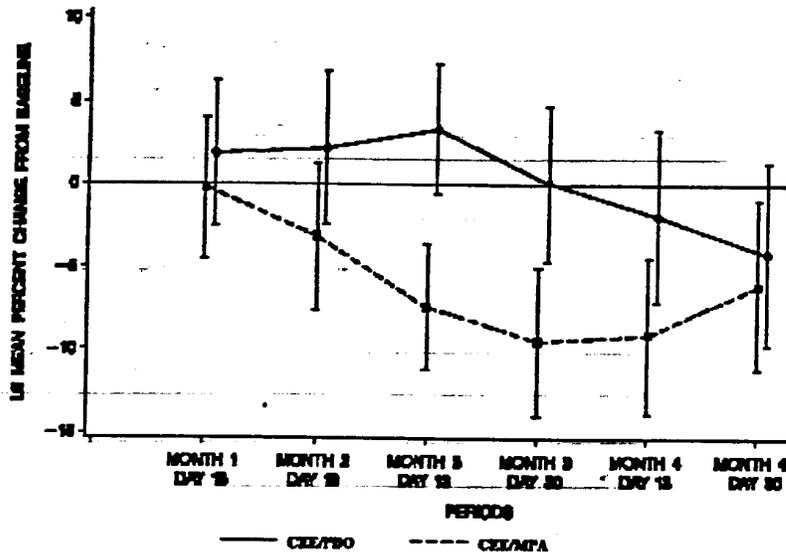
CEE/PBO. Averaged over 4 months, the between-group difference was 1.66% (90% CI -9.03%, 12.35%).

A complete data set is provided in the NDA submission. The results are displayed in the figure below:



APPEARS THIS WAY
ON ORIGINAL

Results for BSAP: Results for serum bone-specific alkaline phosphatase (BSAP), a marker of bone formation, also showed no consistent differences between the two treatment groups. The difference between groups attained statistical significance only at month 3. The data are displayed in the figure below:



APPEARS THIS WAY
ON ORIGINAL

Similarly, there were no between-group differences for changes in corrected serum calcium (pg. 22-23 of NDA and Table 8), or phosphorus (pg. 24, Table 9), or urinary calcium/creatinine (pg. 26, Table 10), or renal phosphate threshold (TmP/GFR, Table 11).

Additionally, there were no between-group differences in serum lipids (Total C, HDL C, LDL C, TG, or VLDL)

8.1.4 Safety outcomes

A complete tabulation of adverse events is provided in the NDA submission. As noted above, these were AE's that occurred in women taking CEE or CEE/MPA. No patient was receiving alendronate.

There was one serious AE, a fracture of the foot, in a woman in the CEE/MPA arm. There was one subject with a laboratory adverse event, a depression in WBC (from 4200 at baseline to 3600 at the end of study). One patient experienced premature atrial contractions, most likely unrelated to study drug.

8.1.5 Conclusions regarding efficacy and safety for Trial 080

This small study demonstrated that the addition of MPA 10 mg daily for 12 days during each of 4 months to continuous estrogen therapy (conjugated equine estrogens 0.625 mg daily) had no discernible effect on biochemical markers of bone resorption, bone formation, or mineral homeostasis. There were no unanticipated adverse events. Since the study lacked a control arm (a group that had not been taking HRT and remained off HRT for the 4 months) the effects of estrogen alone are not demonstrated in this trial. These results are in agreement with previously published studies using biochemical markers of bone turnover. In addition, the results are consistent with those of the PEPI trial, which showed no differences in spine or hip BMD between patients receiving CEE alone and those receiving CEE/progestin. A link between short-term bone marker results and longer-term BMD results and even longer-term fracture prevention results is suggested but by no means proven. Nonetheless, there are no data which suggest that the addition of MPA to estrogen replacement therapy, a regimen which is mandatory in women with an intact uterus, diminishes the bone-sparing effects of estrogen.

8.2 Reviewer's Trial #2, Sponsor's Trial #097

"A triple-blind, randomized, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and tolerability of the addition of alendronate sodium to ongoing hormone replacement therapy in the treatment of osteoporosis in postmenopausal women"

8.2.1.1 Objectives

This was a study of postmenopausal women with osteoporosis (as defined above) who have received HRT for at least one year prior to entry. Women with intact uteri received estrogen/progestin combination; hysterectomized women received estrogen alone. In these women, the primary objective was, "to evaluate the effects of the addition of oral alendronate 10 mg daily to ongoing HRT in comparison to treatment with HRT alone on BMD of the poster-anterior (PA) lumbar spine at 1 year using dual energy X-ray absorptiometry (DXA)."

The secondary objectives were:

- 1) To evaluate the effects of the addition of oral alendronate 10 mg daily to ongoing HRT in comparison to treatment with HRT alone on BMD of the hip trochanter and femoral neck at 1 year using DXA.*
- 2) To evaluate and compare the safety and tolerability of the combination of oral alendronate 10 mg daily and HRT compared with HRT alone by comparing clinical and laboratory safety parameters and by analyzing the incidence of adverse experiences and patient dropouts due to adverse experiences.*
- 3) To evaluate the effects over time of the addition of oral alendronate 10 mg*

daily to ongoing HRT in comparison to treatment with HRT alone on biochemical indices of bone turnover (bone-specific alkaline phosphatase [BSAP], urinary type I collagen cross-linked N-telopeptide [NTx]).”

The stated hypotheses were:

“In postmenopausal women with osteoporosis who have received hormone replacement therapy with an estrogen/progestin combination (women with intact uteri) or estrogen alone (hysterectomized women) for at least the year prior to study entry:

Primary

1) Oral alendronate 10 mg daily added to ongoing HRT will produce a mean increase from baseline in lumbar spine bone mineral density at 1 year which is significantly greater than that observed with HRT alone.

Secondary

1) Oral alendronate 10 mg daily added to ongoing HRT will produce a mean increase from baseline in hip trochanter and femoral neck BMD at 1 year which is significantly greater than that observed with treatment with HRT alone.

2) Oral alendronate 10 mg daily added to ongoing HRT will be safe and well tolerated compared to a regimen of HRT alone.”

8.2.1.2 Study Design

This was a one-year, randomized, triple-blind, placebo-controlled multicenter trial (38 study sites in the US).

8.2.1.3 Protocol

8.2.1.3.1 Populations, Procedures, and Concurrent Medications

Populations

The following inclusion/exclusion criteria are reproduced from the NDA submission:

Inclusion criteria:

1) The patient was a community-dwelling, ambulatory woman, ≥ 40 years of age and postmenopausal (time since last natural menstrual period) for at least 5 years, or 25 years of age and surgically menopausal for at least 5 years.

2) The patient had osteoporosis defined as a BMD ≤ 2 standard deviations (SD) below peak bone mass for either the PA lumbar spine (L1 to L4) or femoral neck based on the normative database provided by and ≤ 1.5 SD below peak bone mass for the other site.

3) The patient had been treated with and was currently receiving combined estrogen and progestin replacement therapy (women with intact uteri) or estrogen alone (hysterectomized women) for at least the year prior to entry into the study. The dosage of any estrogen must have been at least equivalent to the lowest effective dose for the management of osteoporosis (0.625 mg of conjugated equine estrogen [CEE]). The progestin component of the combined estrogen and progestin replacement regimen must have been either micronized progestin or medroxyprogesterone acetate. The minimum acceptable estrogen dosages appear in the table below:

Estrogen Equivalency Table Used to Determine Entry Criteria

Generic	Trade	Minimum Dosage
Conjugated Equine Estrogens	Premarin™ Prempro™	0.625 mg daily
Micronized Estradiol	Estrace™	0.5 mg daily
Estriated Estrogens (Estrone Sulfate)	Estratab™ Menest™	0.625 mg daily
Estropipate	Ogen™ Ortho-est™	1.25 mg daily
Transdermal Estradiol	Estraderm™	0.05 mg patch, twice weekly
Ethinyl Estradiol	Estinyl™	0.02 mg daily

APPEARS THIS WAY
ON ORIGINAL

4) The patient was in a state of good health, based on medical history, physical examination, and laboratory screening evaluation, enabling her to complete the trial without anticipated serious comorbid events.

5) The patient understood the procedures of the study, had been informed of alternative treatments for osteoporosis, and voluntarily agreed to participate in the study.

6) The patient weighed less than 300 pounds.

7) The patient had spinal anatomy suitable for DXA of the lumbar spine. Significant scoliosis, bone deformity, and sequelae of orthopedic procedures which result in unsuitable anatomy were absent from the lumbar spine. At least three vertebrae from L1 to L4 were evaluable. Any patient with more than a total of four known thoracic or lumbar vertebral fractures was excluded.

8) The patient agreed to take the calcium supplement containing 500 mg of elemental calcium as carbonate up to twice a day if necessary and the 400 IU Vitamin D supplement daily and agreed not to take other calcium supplements unless specifically instructed to do so by the investigator.

Exclusion Criteria

1) The patient was mentally or legally incapacitated, or otherwise unable to

BEST POSSIBLE COPY

give informed consent.

- 2) The patient was a pregnant or lactating woman, or a woman of childbearing potential.
- 3) The patient had participated in another therapeutic trial within 30 days of randomization.
- 4) The patient had an intact uterus and had been treated with unopposed estrogen therapy, i.e., without a progestin, within 3 years prior to entry into the study.
- 5) The patient intended to move within the next year rendering per-protocol follow-up impractical.
- 6) The patient had a history of hypersensitivity to any component of FOSAMAX™ (Merck & Co., Inc., West Point, PA).
- 7) The patient had a history of any illness or had significant abnormalities on prestudy clinical or laboratory evaluation which, in the opinion of the investigator, might either pose an unacceptable risk to the patient from participation in this study or complicate the interpretation of study data.
- 8) The patient had bilateral hip replacements.
- 9) The patient was a current user of any illicit drugs or had a history of drug or alcohol abuse within the past 5 years.
- 10) The patient had any of the following: hypocalcemia; any severe malabsorption syndrome; moderate or severe hypertension which was uncontrolled; active or past history of thrombophlebitis, thromboembolic disorders, or stroke; new onset angina or myocardial infarction within 6 months of entry into the study; known symptomatic gallbladder disease not treated with prior cholecystectomy; evidence for impaired renal function defined as a creatinine clearance <35 mL/min or serum creatinine greater than 1.6 mg/dL; evidence for liver dysfunction or disease defined as an elevation twice the upper limit of normal in any one of the following tests of liver function: SGOT, SGPT, or alkaline phosphatase; endogenous hypercortisolism within 1 year of entry into the study; organ transplantation; or other significant end organ diseases (genitourinary, cardiovascular, endocrine, hepatic, psychiatric, renal, hematologic, or pulmonary) which, in the opinion of the investigator, posed an added risk to the patient or impaired the patient's ability to complete the trial.
- 11) The patient had a history of cancer. However, patients with the following cancers were considered eligible for the study: 1) superficial basal or squamous cell carcinoma of the skin which had been completely resected; 2) other malignancies completely treated without recurrence or treatment in the last 5 years, with the following exceptions: patients with a history of endometrial cancer or breast cancer (including histologic diagnosis of lobular carcinoma in situ), or other known or suspected estrogen-sensitive neoplasia were excluded regardless of the time since treatment or disease status.
- 12) The patient had an abnormal Pap smear (\geq CIN Grade I) at screening or

had had a previously abnormal endometrial biopsy (e.g., adenomatous hyperplasia, atypia, carcinoma) within the 12 months prior to randomization.

13) The patient had a history of or evidence for metabolic bone disease (other than postmenopausal bone loss) including but not limited to hyper- or hypoparathyroidism; recent hyperthyroidism (suppressed TSH within the 6 months prior to entry into the study); Paget's disease of bone; osteomalacia; renal osteodystrophy; and osteogenesis imperfecta. Patients with surgically cured hyperparathyroidism due to parathyroid adenoma at least 1 year prior to randomization were allowed to enter the trial.

14) The patient had received treatment prior to randomization which might influence bone turnover, including: (1) within 1 year: estrogen analogues (e.g., tamoxifen), anabolic steroids, or calcitonin; (2) thyroid hormone, unless on a stable dose for at least 6 weeks before randomization with serum TSH within the normal range; patients found at screening to have mild hypothyroidism (as indicated by an elevation in TSH to no more than 15 μ U/mL) were eligible to enter the study provided they received careful thyroid replacement therapy, if needed, and TSH levels were monitored 3 months later and as appropriate during the study; (3) fluoride treatment at a dose greater than 1 mg/day for more than 1 month at any time; given for a shorter time than 1 month it must have been greater than 1 year before randomization; (4) glucocorticoid treatment for more than 1 month with >7.5 mg of oral prednisone (or the equivalent) per day within 6 months prior to randomization; patients who had received therapeutic glucocorticoids in the past must have been considered highly unlikely to require retreatment (with >7.5 mg of oral prednisone or the equivalent) for more than 1 month during the course of the study; (5) treatment with an immunosuppressant (e.g., cyclosporine, azathioprine) within the previous year and; (6) any previous treatment with a bisphosphonate during the year prior to randomization.

15) The patient was receiving any medication which might alter bone or calcium metabolism, including vitamin A in excess of 10,000 IU per day or vitamin D in excess of 1000 IU per day, phenytoin, phenobarbital, heparin, or lithium.

16) The patient had active rheumatoid arthritis.

17) The patient had fasting serum triglycerides >400 mg/dL.

18) The patient's baseline mammogram raised any suspicion of malignancy requiring follow-up (e.g., repeat mammogram) prior to the end of the 12-month treatment period of the study.

19) The patient had a history of abnormal vaginal bleeding within the preceding year for which a cause had not been identified. Abnormal bleeding was defined as any of the following:

- a) other than during progestational withdrawal in a patient receiving cyclical progestin therapy
- b) prolonged, i.e., more than 10 days
- c) heavy, i.e., heavier than the woman's premenopausal normal menses

20) The patient was noncompliant with taking the alendronate placebo during

the run-in period (consumption of <80% of all prescribed tablets) or anticipated significant difficulty in taking study medication precisely as directed.

21) The patient had an abnormality of the esophagus which delayed esophageal emptying such as stricture or achalasia.

22) The patient was unable to stand or sit upright for at least 30 minutes.

Treatment allocation: Patients were randomized to receive either alendronate or placebo in a 1:1 ratio. To ensure equal distribution of duration of HRT in each treatment arm, the randomization was distributed into 2 strata, according to duration of prior HRT (less than, or greater than, 2 years).

Treatment:

The 12 month triple blind treatment period was preceded by a single-blind placebo run-in period of 10 to 21 days, to determine compliance. Patients who were found to be <80% compliant were excluded from the study. Patients remained on their HRT regimens throughout the study period. Patients assigned to the alendronate treatment group received 10mg of the drug per day and were instructed to take the drug according to currently accepted procedure: first thing in the morning, standing or seated for at least 30 minutes after dosing, with a full glass of water, and without any other food, drink, or medication for the 30-minute period.

Concomitant medications:

All patients continued on HRT, either 0.625mg of CEE per day or equivalent as shown in the table above. If a patient had an intact uterus, she was required to take either MPA or micronized progesterin, either continuously (low dose) or cyclically. Calcium supplementation was given to all women, based on estimated calcium intake (estimated by questionnaire), as follows: if estimated intake of the mineral was > 1000mg/day, no supplementation; if 500-999, patients were given 500mg/day of open-label elemental calcium as carbonate; if <500 mg/day, patients were given 1000mg/day. All patients were also given vitamin D, 400 IU/day, open-label. Anticoagulants or any drugs that could influence bone turnover or calcium metabolism were prohibited. Any HRT that included an androgenic agent was also prohibited. Use of vaginal estrogen creams was permitted. Discontinuation of either study drug or HRT was a protocol violation. Use of vaginal estrogen creams was permissible.

Schedule of clinical observations and laboratory measurements are provided in the tables below: