CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER for: 020560, S018

MEDICAL REVIEW(S)

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

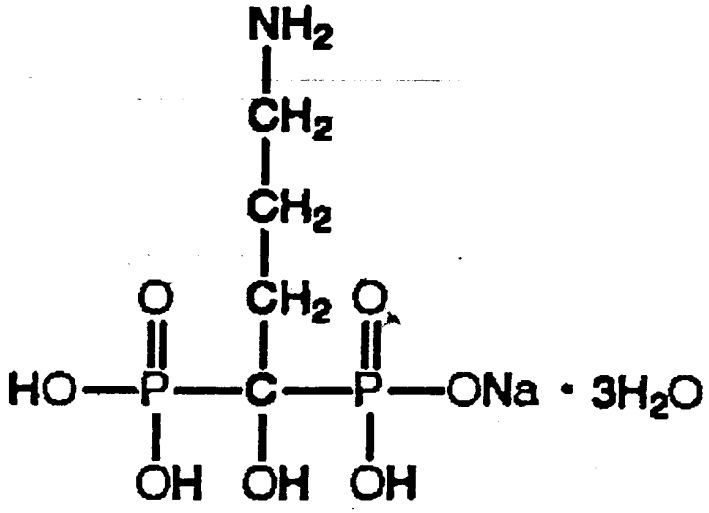
November 5, 1999

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, $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$, 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

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 in 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.

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[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 lumber spine BMD T-score $\leq$-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 $\leq$-2.0 and a BMD T-score $\leq$-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 ± 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*

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:

		Run-In		Study Day of the Month[1]									
		Month 1		Month 1		Month 2		Month 3			Month 4			
	Prestudy	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	Poststudy[2]
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			
Bone/mineral biochemistry		X[4]	X[4]		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 medroxyprogesterone acetate/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.

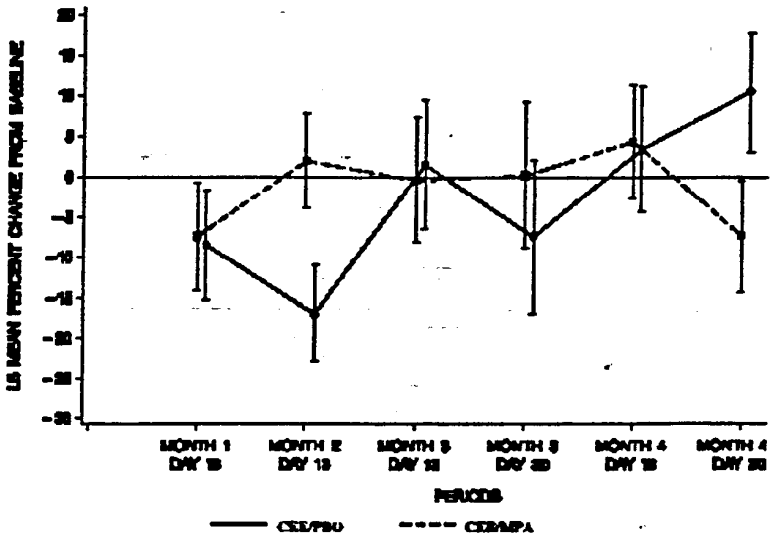
Urinary N-Telopeptide/Creatinine Excretion

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:



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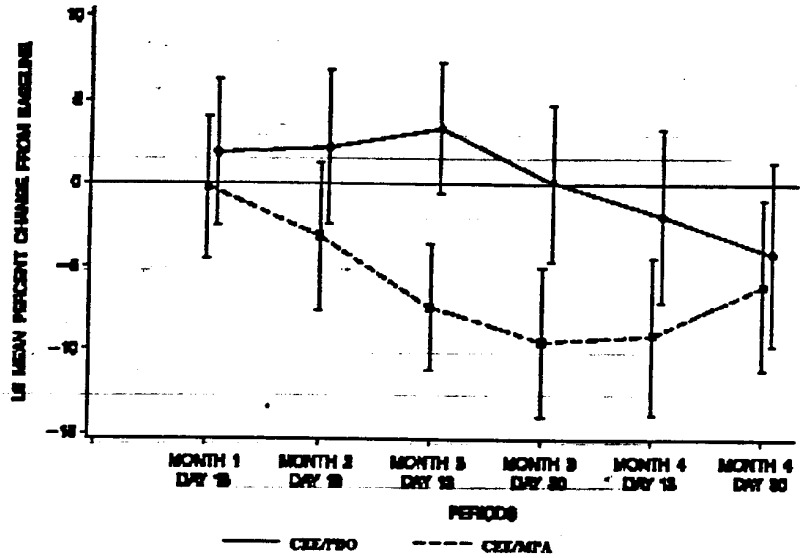
Results for BSAP: Results for serum bone-specific alkaline phosphatase (BSAP), a marker of bone formation, also showed no consistent differences between the two treatment groups. The difference between groups attained statistical significance only at month 3. The data are displayed in the figure below:



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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 [redacted] 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
Esterified 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

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

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 (≥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 μIU/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 progestin, 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:

Month	S1†	S2†	R	3‡	6	12‡
Visit	1	2	3	N/RA	4	5
CLINICAL						
Informed consent	X					
Medical history	X					
Complete physical exam (PE) with pelvic exam, pap		X				X
Dietary calcium assessment		X				
Interval PE‖			X		X	
Mammography¶		X				X
Adverse experiences			X	X	X	X
Treatment		X#	X††	X††	X††	X††
Tablet count			X		X	X
LABORATORY						
Laboratory tests-hematology, chemistry		X			X	X
Urine dipstick§§		X			X	X
TSH, PTH		X				
Urinary NTx			X		X	X
Serum BSAP			X		X	X
SPECIAL STUDY						
DXA‖‖	X				X	X

S1=screening Visit 1.
S2=screening Visit 2.
R=Randomization.
N/RA=Telephone contact only—no office visit.

† Screening may have required more than one visit. If more than one visit was required, all procedures scheduled were completed within a 3-week period.

‡ Telephone contact only.

§ If a patient did not complete the study, all clinical, laboratory, and special study procedures listed for Month 12 were done at the time of discontinuation.

‖ Interval PE included measurement of height, weight, heart rate, and blood pressure.

¶ Baseline screening mammogram was to be performed unless a mammogram performed within the preceding 6 months was available. If available, it was considered the "baseline" study and a repeat mammogram was performed at the Month 12 visit.

Single-blind placebo, usual HRT regimen, at least 1000-mg calcium daily between diet and supplement, and 400 IU vitamin D supplement during 2 week run-in period to assess compliance and tolerability.

†† ALN or placebo plus usual HRT regimen, at least 1000-mg calcium daily between diet and supplement, and 400 IU vitamin D supplement.

§§ Urinary blood or protein ≥1+ by dipstick required microscopic analysis.

‖‖ DXA of the PA lumbar spine and hip performed using Hologic or Lunar instrumentation.

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Visit	Visits 1 and 2 Screening	Visit 3 Randomization	Visit 4 Month 6	Visit 5 Month 12
Hematology				
Hemoglobin	X		X	X
Hematocrit	X		X	X
White blood cell count	X		X	X
Platelets	X		X	X
Blood Chemistry				
Blood urea nitrogen	X		X	X
Creatinine	X		X	X
AST	X		X	X
ALT	X		X	X
Glucose	X		X	X
Alkaline phosphatase (blinded)	X		X	X
Bicarbonate	X		X	X
Cholesterol	X		X	X
Triglycerides	X		X	X
Albumin	X		X	X
TSH	X			
Sodium	X		X	X
Potassium	X		X	X
Calcium	X		X	X
Phosphorous	X		X	X
PTH	X			
Protein	X		X	X
Uric acid	X		X	X
Bilirubin, total	X		X	X
LDH	X		X	X
GGT	X		X	X
Urinalysis				
Protein	X		X	X
Blood	X		X	X
WBC's	X		X	X
RBCs	X		X	X
Squamous epithelial cells	X		X	X
Renal epithelial cells	X		X	X
Casts	X		X	X
Biochemical Markers				
Bone-specific alkaline phosphatase		X	X	X
Urine N-telopeptides		X	X	X

Laboratory measurements:

As a marker of bone resorption, the sponsor used urinary N-telopeptides of type I collagen, corrected for creatinine (NTx, OSTEOMARK™). 5ml aliquots of first morning urine voids were frozen until assay.

Serum bone-specific alkaline phosphatase (BSAP) was used as a marker of bone formation. Serum samples were stored frozen until assay, using the Tandem™-R-Ostase™ (Hybritech) kit.

Bone densitometry was performed at each study site, using either Hologic or Lunar densitometers. User manuals were provided by the central quality assurance center. For each patient, measurements were taken on the same densitometer throughout the study. Quality control data were provided by each study site using hydroxyapatite phantoms. All study sites participated in a calibration program using a "gold standard" phantom. Further details on quality control are provided in the NDA submission. Densitometry of the lumbar spine and hip was performed at screening, Month 6, and Month 12. Fractured vertebrae were excluded from BMD analyses.

8.2.1.3.2 Endpoints

Efficacy

The primary efficacy endpoint was % change in BMD of the lumbar spine (L1-4) at 1 year. The % change from baseline after 1 year of treatment in femoral neck and trochanter BMD constituted secondary endpoints. Other secondary endpoints were % change from baseline in bone formation and resorption markers.

Safety

At each visit, adverse events were determined by direct questioning, as well as physical examination. Recording and coding of all AE's were performed according to standard procedures (full details provided by sponsor in NDA submission). Laboratory AE's were identified and recorded according to routine methodology (also included in submission). Predefined limits of change were defined for each laboratory parameter, in order to estimate the numbers of individuals with routine laboratory results that were considered possibly adverse. These establish limits are provided in the submission.

8.2.1.3.3 Statistical considerations

A complete statistics review accompanies this analysis. The primary and secondary hypotheses are indicated above. Briefly, the null hypothesis for all BMD efficacy endpoints was that the addition of alendronate to postmenopausal HRT will produce an increase in BMD that is the equivalent to that seen with HRT alone. The alternative hypothesis was that addition of alendronate will produce an increase in BMD that is greater than that seen with HRT alone. For the bone marker studies the secondary null hypothesis was that addition of alendronate to HRT regimen will produce decreases in markers of bone turnover that are equivalent to those seen on HRT alone. The alternative hypothesis is that addition of alendronate will produce decreases in markers that are greater than seen with HRT alone.

For safety/tolerability, the null hypothesis was that HRT alone will be safer and better tolerated than the combination alendronate+HRT. The alternative hypothesis was that addition of alendronate to HRT would be as safe as HRT alone.

The sponsor presents a power analysis. Based on extensive earlier experience, the standard deviation of spinal BMD measurements of the lumbar spine is estimated at about 4.0%. To detect a 1.5% difference, between treatment groups, in BMD changes from baseline, with 90% power at an alpha level of

0.05, 300 subjects would be required in a 1:1 allocation ratio. The sponsor enrolled 428 subjects in order to ensure that 300 were retained for evaluation at study end.

For the primary analysis, the sponsor employed an ANOVA model that included terms for treatment, center, stratum, and all 2-way interactions with treatment. Statistical significance for all treatment comparisons was set at the 0.05 alpha level (2-sided). This analysis was used to determine whether there was a significant difference between treatment groups in the mean % change from baseline in BMD of the lumber spine at 1 year of treatment. The analysis used an intent-to-treat approach. The ITT population included all patients who received at least 1 dose of study drug and had at least 1 post-treatment BMD determination. For patients with only a 6-month BMD determination, the 6-month value was carried forward. An identical analysis was used for BMD changes in the femur. In addition, a per-protocol analysis of BMD data is provided.

Mean % changes in biochemical markers were analyzed (using a log-transformed data) as a fraction of baseline. Analyses of these data used a per-protocol approach, with no carrying forward of data.

Clinical and laboratory ae's were summarized separately. Between-group differences in the incidence of ae's were compared using Fisher's exact test. The sponsor conducted analyses on all reported ae's, as well as on the set of ae's considered by the investigator to be drug-related.

Subgroup analyses of BMD data were done for the following pre-defined groups: duration of HRT use (< 2 years, >2 years), age (<65 years, >65 years), baseline lumbar spine T-score (≤2.5, > 2.5), and baseline calcium intake (≤800mg/day, >800mg/day).

Further details of the statistical analyses are provided in the submission.

8.2.2 RESULTS

8.2.2.1 Populations enrolled/analyzed

The sponsor enrolled 428 women, mean age 61.7 years. With the exception of smoking history and family history of osteoporosis, there was no difference in relevant baseline characteristics. These included age (mean was about 62 years, range 40-84 years), duration of menopause (mean about 15 years, range 1.6-44 years), height, weight, duration of prior HRT (mean about 9.5 years, range 0.6-42 years), and estimated calcium intake. More than 96% were Caucasian; 56.5% had experienced a previous fracture; 60% were receiving combined estrogen/progestin therapy, the remainder taking estrogen alone.

The proportion of subjects who had a history of smoking or a family history of osteoporosis was statistically significantly greater in the alendronate + HRT group than in PBO + HRT (for + smoking history, 46.7% alendronate+HRT vs 36.5% HRT+ PBO, p=0.039; for family history of osteoporosis, 59.2% vs 48.6%, alendronate vs PBO, p=0.044). There were no other significant between-group differences at baseline. Details on baseline characteristics are provided in Tables 7 and 8 of the NDA submission.

Baseline BMD values at the spine, femoral neck, trochanter, or Ward's triangle did not differ between treatment groups (Table 10 of the NDA submission).

Baseline values for biochemical bone turnover markers, NTx and BSAP) did not differ between the two treatment groups (data in Table 11 of submission). The values for both parameters were similar to those found in normal premenopausal women.

Comment: This was presumably due to the ongoing HRT. These markers are usually elevated in osteoporotic postmenopausal women.

A complete listing of secondary diagnoses is provided in Table 12 of the NDA submission. All but one subject in each treatment group had at least one secondary diagnosis.

Comment: At baseline, the two treatment groups were evenly balanced according to specific secondary diagnoses, including GI tract disorders.

The sponsor summarizes all prior drug therapies (Table 13 of the NDA) that were taken within 14 days of baseline. Of the 428 randomized patients, 397 had at least 1 prior therapy. Of note, about 25% of all subjects were taking anti-inflammatory drugs, and approximately 27% were using GI drugs.

Concomitant therapies were listed, by treatment group, in Table 14 of the NDA. Approximately 37% of all subjects used anti-inflammatory drugs, and 28% used GI medications (excluding calcium). Use of specific concomitant therapies did not differ by treatment group.

Patient accounting:

Of the 428 patients who entered, 394 (92.1%) completed the study. The sponsor provides a complete listing of all patients who discontinued the study, along with reasons for discontinuation. The overall data are summarized in the table below:

	Total	PBO + HRT	ALN + HRT
ENTERED:	428	214	214
Age Range (years)	40 to 84	42 to 84	40 to 82
	n (%)	n (%)	n (%)
COMPLETED 12 MONTHS	394 (92.1)	191 (89.3)	203 (94.9)
DISCONTINUED:	34 (7.9)	23*(10.7)	11 (5.1)
Clinical adverse experience	16 (3.7)	11 (5.1)	5 (2.3)
Laboratory adverse experience	0	0	0
Protocol deviation	1 (0.5)	1 (0.5)	0
Lost to follow-up	3 (0.7)	1 (0.5)	2 (0.9)
Patient withdrew consent	10 (2.3)	6 (2.8)	4 (1.9)
Other	4 (0.9)	4 (1.9)	0

* p=0.048.

For the BMD analysis, the number of patients included in the ITT and per-protocol analyses are given in the table below:

	PBO + HRT (N=214)	ALN + HRT (N=214)	Total (N=428)
Total Included In			
Intention-to-Treat Analysis	202	206	408
Per-Protocol Analysis	178	192	370
Total Excluded From			
Intention-to-Treat Analysis	12	8	20
Per-Protocol Analysis	36	22	58

To be included in the ITT analysis at a given time point, patients must have had a baseline measurement and at least one post-treatment measurement prior to or at that time point. Patients were excluded from per-protocol analyses for any of the following reasons: study drug non-compliance, postmenopausal<4.5 years, prior HRT <1year, BMD exclusion criteria.

Specific estrogen use: Data on specific estrogen preparations and doses are provided by the sponsor. The majority of patients (approximately 65%) were taking CEE, 0.625 mg/day, with the remainder receiving higher doses of CEE, or transdermal estradiol, micronized estradiol, estropipate, or esterified estrogen. One patient took ethinyl estradiol. There were no significant differences between treatment groups in the type or dose of estrogen. The sponsor has summarized estrogen use in the table below:

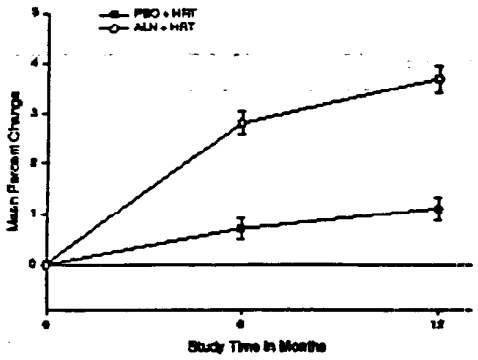
Preparation	Daily Dosage	PBO + HRT (N=214)	ALN + HRT (N=214)
Conjugated Equine Estrogens	0.625 mg	136 (63.6)	147 (68.7)
	0.9 mg	9 (4.2)	10 (4.7)
	1.25 mg	10 (4.7)	9 (4.2)
Transdermal Estradiol	0.05 mg	8 (3.7)	15 (7.0)
	0.075 mg	1 (0.5)	0
	0.1 mg	7 (3.3)	4 (1.9)
Micronized Estradiol	0.5 mg	4 (1.9)	4 (1.9)
	0.75 mg	1 (0.5)	0
	1.0 mg	13 (6.1)	11 (5.1)
	1.5 mg	1 (0.5)	1 (0.5)
	2.0 mg	8 (3.7)	0
Estropipate	0.625 mg	4 (1.9)	4 (1.9)
	0.75 mg	1 (0.5)	0
	0.937 mg	0	1 (0.5)
	1.25 mg	5 (1.9)	4 (1.9)
Esterified Estrogen	0.625 mg	7 (3.3)	3 (1.4)
Ethinyl Estradiol	0.02 mg	0	1 (0.5)

8.2.2.2 Efficacy outcomes

For bone mineral density, the mean % change from baseline constituted the primary outcome, using an ITT approach. In addition, a per-protocol analysis, which yielded comparable results, is included in the submission. The treatment-by-stratum (see above for definitions of strata) interaction analysis demonstrated no qualitative interactions. Thus each stratum showed the same differences between treatments. This analysis was done for each BMD outcome variable, with the same results.

Lumbar spine BMD:

Over the 12-month period, BMD increased in both treatment groups at this site, as shown by the sponsor in the figure below:



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The mean % change from baseline was significant ($p<0.001$) for both treatment groups at both the 6-month and 12-month time points. The % change from baseline was significantly greater ($p<0.001$) in the alendronate + HRT group than in the HRT+PBO group at both time points.
The sponsor provides a summary of these data in the table below:

Treatment	N	Observed Mean (g/cm²) Baseline	Observed Mean (g/cm²) Month 6	Percent Change From Baseline at Month 6: Mean	SD	Adjusted Mean	95% C.I.	Pairwise Comparison P Value ALN + HRT vs. PBO + HRT
PBO + HRT	213	0.853	0.858	0.7***	3.0	0.6	(0.1, 1.0)	
ALN + HRT	214	0.859	0.884	2.8***	3.4	2.7	(2.2, 3.2)	<0.001

Within-treatment test of means: ***p≤0.001.
p-Value for consistency of treatment across centers: 0.994.
p-Value for consistency of treatment across strata based on prior estrogen use: 0.715.
Pooled SD: 3.25.

Treatment	N	Observed Mean (g/cm²) Baseline	Observed Mean (g/cm²) Month 12	Percent Change From Baseline at Month 12: Mean	SD	Adjusted Mean	95% C.I.	Pairwise Comparison P Value ALN + HRT vs. PBO + HRT
PBO + HRT	213	0.853	0.862	1.1***	3.5	1.0	(0.4, 1.5)	
ALN + HRT	214	0.859	0.892	3.7***	3.9	3.6	(3.0, 4.1)	<0.001

Within-treatment test of means: ***p≤0.001.
p-Value for consistency of treatment across centers: 0.354.
p-Value for consistency of treatment across strata based on prior estrogen use: 0.568.
Pooled SD: 3.65.

Comments: The data clearly show an enhancement in BMD accrual at the lumbar spine in association with alendronate + HRT, compared to HRT

alone. The between-group differences were 2-2.6%; most of the difference was achieved by 6 months.

Femoral neck BMD:

Result: Both treatment groups demonstrated an increase in BMD at the femoral neck over the 12 months of the study. For both groups at both time points, the increases over baseline were significant at p≤0.05. There was a numerical difference between groups at both time points, with alendronate > PBO, but the differences were not statistically significant (p=0.318 at 6 months; p=0.072 at 12 months).

The data are summarized in the table below:

Treatment	N	Observed Mean (g/cm²) Baseline	Observed Mean (g/cm²) Month 6	Percent Change From Baseline at Month 6 Mean	SD	Adjusted Mean	95% C.I.	Pairwise Comparison P Value ALN + HRT vs. PBO + HRT
PBO + HRT	213	0.681	0.688	1.0*	5.2	0.9	(0.2, 1.7)	
ALN + HRT	214	0.684	0.694	1.5***	4.4	1.5	(0.7, 2.2)	0.318

Within-treatment test of mean = 0: *p≤0.05; ***p≤0.001.
p-Value for consistency of treatment across centers: 0.450.
p-Value for consistency of treatment across strata based on prior estrogen use: 0.906.
Pooled SD: 4.75.

Treatment	N	Observed Mean (g/cm²) Baseline	Observed Mean (g/cm²) Month 12	Percent Change From Baseline at Month 12 Mean	SD	Adjusted Mean	95% C.I.	Pairwise Comparison P Value ALN + HRT vs. PBO + HRT
PBO + HRT	213	0.681	0.687	0.8*	4.9	0.8	(0.0, 1.5)	
ALN + HRT	214	0.684	0.695	1.6***	5.1	1.7	(1.0, 2.5)	0.072

Within-treatment test of mean = 0: *p≤0.05; ***p≤0.001.
p-Value for consistency of treatment across centers: 0.838.
p-Value for consistency of treatment across strata based on prior estrogen use: 0.938.
Pooled SD: 5.06.

Trochanter BMD:

Result: For the alendronate + HRT group, trochanter BMD increased significantly (p≤0.001) from baseline at both (6- and 12-month) time points. For the HRT + PBO group, the increase was significant at 6 months (p≤0.05), but not at 12 months. At the trochanter, the increases in BMD in the alendronate + HRT group were significantly greater than those in the HRT + PBO group at both time points (p=0.003 at 6 months and p≤0.001 at 12 months). The differences between groups were 1.3-2.0%. The results are given in the sponsor's figure below:

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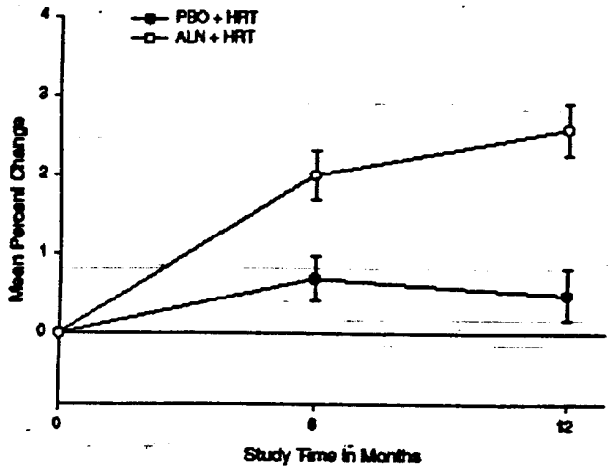
TROCHANTER BMD



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Summary data with statistics are provided by the sponsor in the table below:

Treatment	N	Observed Mean (g/cm²) Baseline	Observed Mean (g/cm²) Month 6	Percent Change From Baseline at Month 6 Mean	SD	Adjusted Mean	95% C.I.	Pairwise Comparison P Value ALN + HRT vs. PBO + HRT
PBO + HRT	213	0.592	0.595	0.7*	4.2	0.8	(0.2, 1.5)	
ALN + HRT	214	0.588	0.602	2.0***	4.7	2.3	(1.6, 2.9)	0.003

Within-treatment test of mean = 0: *p≤0.05; ***p≤0.001.
p-Value for consistency of treatment across centers: 0.889.
p-Value for consistency of treatment across strata based on prior estrogen use: 0.294.
Pooled SD: 4.41.

Treatment	N	Observed Mean (g/cm²) Baseline	Observed Mean (g/cm²) Month 12	Percent Change From Baseline at Month 12 Mean	SD	Adjusted Mean	95% C.I.	Pairwise Comparison P Value ALN + HRT vs. PBO + HRT
PBO + HRT	213	0.592	0.595	0.5	4.8	0.5	(-0.2, 1.2)	
ALN + HRT	214	0.588	0.604	2.6***	4.9	2.7	(1.9, 3.4)	<0.001

Within-treatment test of mean: *p≤0.05, ***p≤0.001.
p-Value for consistency of treatment across centers: 0.763.
p-Value for consistency of treatment across strata based on prior estrogen use: 0.428.
Pooled SD: 4.71.

Ward's triangle:

Result: At Ward's triangle, both treatment groups had significant increases in BMD at 6 and 12 months ($p \leq 0.05$); however, there was no difference between the groups at either time point (sponsor's figure below).

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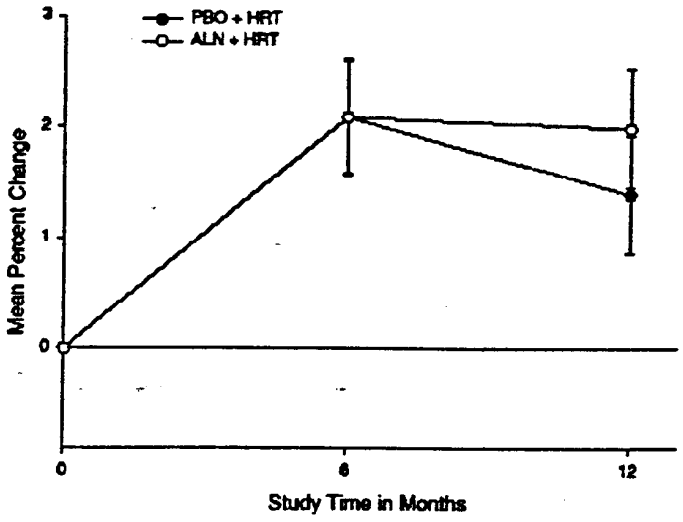
WARD'S TRIANGLE BMD



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For the BMD studies, there was no significant treatment-by-center interaction, at any skeletal site. As mentioned above, the per-protocol analysis, presented as part of the submission, yielded essentially the same results.

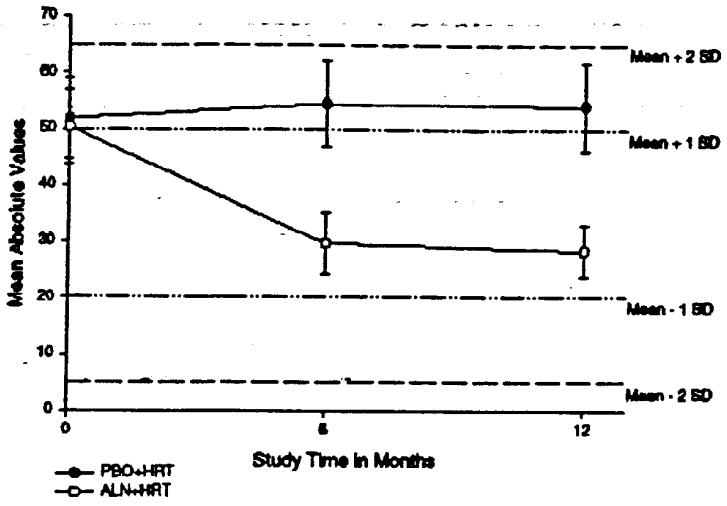
The subgroup analyses, described above, were based on age, HRT duration, lumbar spine BMD, and baseline calcium intake. The analyses showed no significant changes or responses by subgroup, suggesting that subjects in all the pre-defined subgroups responded similarly to treatment. Complete data from the subgroup analyses are provided with the submission.

Biochemical Efficacy

Biochemical marker endpoints were analyzed using a per-protocol approach, in which data were analyzed up to and including the last time point that subjects received study drug. No data were carried forward in this analysis.

For urine NTx, the mean values for both treatment groups (mean absolute values ± SE, NTx/Cr, in nmol/mmol) are presented in the sponsor's figure below. The figure includes the normal premenopausal mean NTx ±2 SD. The reason for the slight elevation in baseline mean NTx was the inclusion of a few patients with very high values in both treatment groups. The median NTx values for both groups were within the normal premenopausal range.

NTx/Cr



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As shown in this figure, and in the table below, there was no significant change in urine NTx in the HRT + PBO group over the 12 months, whereas the NTx decreased significantly ($p<0.001$) from baseline in the alendronate + HRT group at both 6 months (-41.7%) and 12 months (-45.5%). The differences between the two treatment groups were significant ($p<0.001$) at both time points. The changes from baseline were similar, using either mean or median values.

Treatment	N	Observed Mean		Observed Median		Percent Change From Baseline at Month 6	
		Baseline	Month 6	Baseline	Month 6	Geometric[1] Mean	Pairwise Comparison p-Value ALN + HRT vs. PBO + HRT
PBO + HRT	170	51.8	54.5	33	34	3.5	
ALN + HRT	184	50.4	29.7	34	18	-41.7***	<0.001

Within-treatment test of mean = 0: ***p≤0.001.
p-Value for consistency of treatment across centers: 0.938.
p-Value for consistency of treatment across strata based on prior estrogen use: 0.164.
[1]Transformed from ln (fraction of baseline)
Pooled SD: 0.65.

Treatment	N	Observed Mean		Observed Median		Percent Change From Baseline at Month 12	
		Baseline	Month 12	Baseline	Month 12	Geometric[1] Mean	Pairwise Comparison p-Value ALN + HRT vs. PBO + HRT
PBO + HRT	170	51.8	54.1	33	36	0.7	
ALN + HRT	184	50.4	28.4	34	18	-45.5***	<.001

Within-treatment test of mean = 0: ***p≤0.001.
p-Value for consistency of treatment across centers: 0.909.
p-Value for consistency of treatment across strata based on prior estrogen use: 0.403.
[1]Transformed from ln (fraction of baseline)
Pooled SD: 0.70.
Values greater than 5 SD from the overall mean were considered outliers and were removed from the estimation of means. All patients were included in the analysis of the ranked data which provides the comparison of treatments

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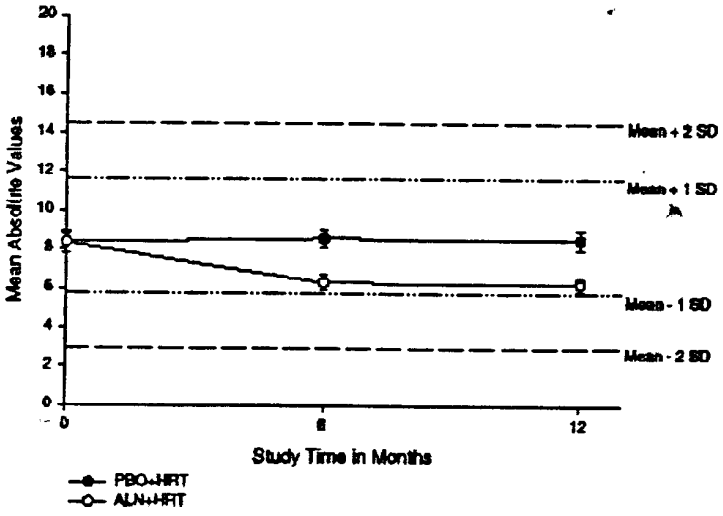
BSAP Results: For BSAP, a marker of bone formation, the HRT + PBO group had a small, but nonsignificant increase during the study. In contrast, the HRT + alendronate group showed a decrease at Month 6 that was maintained through Month 12. The decrease, which was about 21% from baseline, was statistically significant ($p<0.001$). These decreases in the alendronate group were statistically significantly greater than those seen in the placebo group at both time points ($p<0.001$).

The changes in BSAP over time are shown in the sponsor's figure below, which plots serum BSAP, in ng/ml, over time. Again, the normal premenopausal mean ± 2SD is included in the figure. As shown in the figure, and in the following table, the baseline mean and median values for BSAP in both treatment groups were essentially the same as those found in normal premenopausal women (premenopausal mean BSAP is 8.7 ng/mL, according to assay reference data).



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Summary data, with statistics, for changes in BSAP are shown in the sponsor's table below:

B S A P SUMMARY DATA

Treatment	N	Observed Mean		Observed Median		Percent Change From Baseline at Month 6	
		Baseline	Month 6	Baseline	Month 6	Geometric[1] Mean	Pairwise Comparison p-Value ALN + HRT vs. PBO + HRT
PBO + HRT	188	8.4	8.6	8.2	8.7	5.5	
ALN + HRT	193	8.3	6.3	7.8	6.1	-21.7***	<0.001

Within-treatment test of mean = 0: ***p≤0.001.
p-Value for consistency of treatment across centers: 0.424.
p-Value for consistency of treatment across strata based on prior estrogen use: 0.762.
[1]Transformed from ln (fraction of baseline)
Pooled SD: 0.44.

Treatment	N	Observed Mean		Observed Median		Percent Change From Baseline at Month 12	
		Baseline	Month 12	Baseline	Month 12	Geometric[1] Mean	Pairwise Comparison p-Value ALN + HRT vs. PBO + HRT
PBO + HRT	188	8.4	8.5	8.2	8.4	4.1	
ALN + HRT	193	8.3	6.2	7.8	6.1	-20.8***	<0.001

Within-treatment test of mean = 0: ***p≤0.001.
p-Value for consistency of treatment across centers: 0.978.
p-Value for consistency of treatment across strata based on prior estrogen use: 0.702.
[1]Transformed from ln (fraction of baseline)
Pooled SD: 0.45.
Values greater than 5 SD from the overall mean were considered outliers and were removed from the estimation of means. All patients were included in the analysis of the ranked data which provides the comparison of treatments.

Comments: The results of these studies show that the baseline biochemical markers of bone formation and resorption were, on average, essentially the same as in premenopausal women. This is most likely due to the estrogen replacement therapy (although this study lacked a control group of patients who were not taking HRT). These results suggest that these subjects were generally compliant with the HRT.

The addition of alendronate to the ongoing HRT produced additional, statistically significant, decreases in markers of bone turnover (formation and resorption) over those found in subjects taking HRT alone. These differences were seen at both the 6- and 12-month time points. In subjects receiving alendronate + HRT, the markers remained within the lower normal range of values found in premenopausal women.

8.2.2.3 Safety

This safety analysis compared the frequency of adverse events, as well as the % of patients with specific adverse events, between the two treatment groups. In the analysis, 214 alendronate and 214 placebo patients were evaluated. Upper GI AE's and fracture AE's were evaluated separately, because of concerns related specifically to alendronate.

No patients withdrew from this study because of a serious AE, and there were no deaths. A summary of clinical adverse experience, by treatment group, is provided by the sponsor in the following table:

	PBO + HRT (N=214)	ALN + HRT (N=214)
	n (%)	n (%)
Number of patients evaluated	214	214
Number (%) of patients:		
with one or more adverse experience	178 (83.2)	186 (86.9)
with a drug-related* adverse experiences	44 (20.6)	46 (21.5)
with a serious adverse experience	17 (7.9)	12 (5.6)
with serious drug-related* adverse experiences	0	0
withdrawn from therapy due to an adverse experience‡	14 (6.5)	8 (3.7)
deaths	0	0
withdrawn due to a drug-related adverse experience†,‡	11 (5.1)	4 (1.9)
withdrawn due to a serious adverse experience‡	2 (0.9)	1 (0.5)
withdrawn due to a serious drug-related adverse experience†,‡	0	0

* Determined by the investigator to be possibly, probably, or definitely drug related.
‡ Includes those patients who discontinued study drug therapy but completed the study on HRT alone (3 alendronate + HRT, 3 placebo + HRT).
This table does not include those adverse experiences that occurred during pretreatment, prior to randomization.

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The number of patients with clinical AE's, by body system, did not differ between groups, as shown below:

	PBO + HRT (N=214)	ALN + HRT (N=214)
	n (%)	n (%)
Body as a whole/site unspecified	40 (18.7)	39 (18.2)
Cardiovascular system disorders	26 (12.1)	18 (8.4)
Digestive system disorders	70 (32.7)	74 (34.6)
Endocrine disorders	2 (0.9)	3 (1.4)
Hematologic and lymphatic disorders	4 (1.9)	0
Metabolic, nutritional, immune disorders	12 (5.6)	13 (6.1)
Musculoskeletal disorders	63 (29.4)	78 (36.4)
Nervous system and psychiatric disorders	31 (14.5)	46 (21.5)
Respiratory system disorders	91 (42.5)	82 (38.3)
Skin or skin appendage	35 (16.4)	39 (18.2)
Eye, ear, nose	10 (4.7)	14 (6.5)
Urogenital system disorders	68 (31.8)	64 (29.9)

† This table does not include those adverse experiences that occurred during pretreatment. Although a patient may have had two or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

The sponsor provides a table of all clinical AE's occurring in at least 2% of patients in either treatment group. The most common of these were URI's, sinusitis, headache, back pain, and abdominal pain. Back pain was reported in a significantly greater proportion patients in the HRT + alendronate group than in the HRT + PBO group: 9.8% vs 3.3% ($p \leq 0.01$). Full details are provided in Table 26 of the submission.

Upper GI AE's: A separate analysis is presented for upper GI AE's. The following table summarizes the number and percent of patients with upper GI AE's. There were no significant between-group differences in any of these parameters. The sponsor provides narratives for all upper GI AE's that resulted in discontinuation from the study.

	PBO + HRT (N=214)	ALN + HRT (N=214)
	n (%)	n (%)
Number of patients evaluated	214	214
Number (%) of patients		
with one or more upper GI adverse experiences	49 (22.9)	52 (24.3)
with a drug-related† adverse experience	23 (10.7)	23 (10.7)
with a serious adverse experience	1 (0.5)	2 (0.9)
with a serious drug-related† adverse experience	0	0
withdrawn from therapy due to a adverse experience	7 (3.3)	3 (1.4)
withdrawn from therapy due to a serious adverse experience	0	0
withdrawn from therapy due to a drug-related† adverse experience	7 (3.3)	2 (0.9)
withdrawn from therapy due to a serious drug-related† adverse experience	0	0
Patients who died	0	0

† Determined by the investigator to be possibly, probably, or definitely related to treatment with study drug.

The number and % of patients with specific upper GI AE's is provided in the table below. There were no significant between-group differences.

	PBO + HRT (N=214) n (%)	ALN + HRT (N=214) n (%)
Patients with one or more upper GI adverse experiences	49 (22.9)	52 (24.3)
Abdominal distention	3 (1.4)	7 (3.3)
Abdominal pain	14 (6.5)	13 (6.1)
Acid regurgitation	8 (3.7)	9 (4.2)
Cholelithiasis	1 (0.5)	1 (0.5)
Dyspepsia	6 (2.8)	12 (5.6)
Eructation	2 (0.9)	0 (0.0)
Gastritis	2 (0.9)	2 (0.9)
Nausea	12 (5.6)	6 (2.8)
Reflux esophagitis	3 (1.4)	2 (0.9)
Vomiting	7 (3.3)	2 (0.9)

Serious Clinical AE's

A serious AE is defined by the sponsor as one that "resulted in death, permanent or substantial disability, new or prolonged hospitalization, was immediately life threatening, cancer, congenital anomaly, or the result of an accidental or intentional overdose with the study medication."

During this study, 29 individuals (7%) experienced at least one serious AE. There were no deaths during the study. A listing of all patients with serious AE's is provided in table 28 of the NDA. There were 2 lung neoplasms, one in the placebo group and one in the alendronate group. Cardiac AE's were slightly more frequent in the alendronate group, with one myocardial infarction, 2 cases of unstable angina, and one conduction disorder reported in the alendronate group and none in the placebo group. There was one deep vein thrombosis in the placebo (HRT alone) group and none in the alendronate+HRT group.

According to the sponsor, 22 patients discontinued due to clinical AE's: 8 in the alendronate group and 14 among placebo subjects. Three of these AE's were serious. There was no obvious difference in the nature or number of these AE's, according to treatment group. Complete narratives for all cases are provided in the NDA.

Non-vertebral fractures:

Twenty-four patients experienced a non-vertebral fracture: 9 PBO and 15 ALN. According to the sponsor, X-ray reports or other documentation of these fractures were available in only 4 of the PBO group and 12 in the ALN group. However, a fracture was not seen in one of these. There was no correlation between

baseline lumbar spine BMD, or biochemical bone resorption/formation markers, and incidence of fracture.

Comments: Therefore, documented non-vertebral fractures occurred in 4 PBO and 11 ALN subjects. However, a listing of specific non-vertebral fractures is provided in tabular form (Table 34). According to this table, there were only 3 undocumented or falsely + X-rays in the 9 PBO patients. In addition, there were 13 documented patients with non-vertebral fractures in the ALN group. The reason for this discrepancy is not clear.

I have summarized the data, in the table below, for the documented fractures in the 13 ALN subjects and for the 6 subjects in the PBO group for whom there was no specific exclusion on the basis of non-documentation. Each row indicates a separate individual.

HRT + PBO	HRT + ALENDRONATE
arm	rib (multiple)
foot	rib
radius	foot
ankle	metatarsal (foot)
metatarsal (foot)	wrist
radius	patella
tibia	hand
	ankle
	metatarsal (foot)
	foot
	foot
	foot
	foot

There are twice as many patients with documented non-vertebral fractures in the ALN group. The difference is accounted for by a large increase in the number of foot fractures (7 vs 2). The reason for the discrepancy between the narrative and the data in the table is unclear. Of note, this was not replicated in the next trial, 072, which was two years' duration (see below).

Laboratory AE's:

The sponsor summarizes the laboratory AE experience during this study in the table below. There were no unexpected changes in laboratory parameters during this study, in either treatment group.

	PBO + HRT (N=214) n (%)	ALN + HRT (N=214) n (%)
Number of patients with at least one laboratory test postbaseline	212	211
Number (%) of patients:		
with one or more adverse experiences	25 (11.8)	29 (13.7)
with drug-related[1] adverse experiences	8 (3.8)	7 (3.3)
with serious adverse experiences	0 (0.0)	0 (0.0)
with serious drug-related[1] adverse experiences	0 (0.0)	0 (0.0)
withdrawn from therapy due to an adverse experiences	0 (0.0)	0 (0.0)

[1] Determined by the investigator to be possibly, probably, or definitely drug related.
This table does not include those adverse experiences that occurred during pretreatment.

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Data for specific laboratory AE's, by test category and treatment group are given in Table 37 of the NDA and will not be reproduced here. The number and % of patients with specific laboratory AE's (incidence ≥1patient in 1 or more treatment groups) did not differ between treatment groups.

There were no serious laboratory AE's in either treatment group. No patients discontinued due to a laboratory AE.

Clinical safety measurements:

There were no significant changes from baseline in body weight, in either treatment group. Both treatment groups showed a statistically significant change in diastolic blood pressure from baseline at month 12 (mean increases of about 2 mm Hg). There was no difference between the groups. There were no changes in systolic blood pressure from baseline in either treatment group. Similarly, there were no changes from baseline in pulse rates in either group at any time.

Laboratory Safety Measurements

The mean percent changes in serum alkaline phosphatase, total serum calcium, and serum phosphorus are presented in tabular form in the NDA. In both treatment groups, the (total) serum alkaline phosphatase level decreased significantly from baseline at 6 and 12 months. The decline from baseline was significantly greater in the ALN group at 12 months (-14.3% vs –1.9%, $p \leq 0.001$).

Serum phosphorus decreased significantly, by 3.5% in PBO and 3.0% in ALN, at 6 and 12 months (between group differences NS at both time points).

At 6 and 12 months, the mean serum calcium level decreased significantly from baseline, by 1.2 and 0.8%, respectively, in the ALN group. In the PBO group, ther was a non-significant increase from baseline after 12 months (1.0%). At Month 6, the between-group differences were significant (p=0.026), but not at Month 12.

Comments: These changes are not likely to be of clinical significance. In no patient was the calcium level < 8.5mg/dl (Table 42).

Pre-defined limits of change:

As shown in Table 42 of the NDA, there were no significant between-group differences in any laboratory parameter except serum AST and monocyte count. The ALN group had 6 patients with increases in AST above the predefined limits compared with none in the PBO group (p=0.015). There were 12 subjects with a decrease in monocytes > predefined limits in the ALN group, vs 2 PBO subjects (p=0.012).

8.2.2.4 Assessment of efficacy and safety for Trial 097

This study enrolled 428 postmenopausal women (96% Caucasian, average age 61.7 years, average of 15.3 years post-menopause) who had taken HRT for an average of 9.6 years. 56.5% of the trial population had experienced previous fractures. No BMD data prior to onset of HRT are available, and it is therefore not possible to determine the subjects' BMD responses to the HRT. However, the average time between onset of menopause and initiation of HRT in these subjects was 5 years, and it is likely that many experienced a period of rapid bone loss that accompanies estrogen withdrawal. This possibility, together with the fact that the BMD responses to HRT begin to reach a plateau at around 3 years, most likely explain the presence of osteopenia and osteoporosis at baseline. That the baseline biochemical markers of bone turnover were within the premenopausal range suggests that subjects were compliant with HRT regimens during the period prior to study start, and that the HRT doses were adequate.

Efficacy:

1) BMD: At the 4 skeletal sites (lumbar spine, femoral neck, trochanter, and Ward's triangle) both treatment groups, HRT alone (PBO) and alendronate (10 mg) plus ongoing HRT (ALN), experienced statistically significant increases above baseline in BMD after 6 and 12 months. The single exception to this was trochanter BMD at 12 months in the PBO group. The increases were generally of the order of about 0.5-1% in the PBO group and 1.6-3.7% in the ALN group. A plausible explanation for the increases in

BMD over baseline in the PBO group is increased calcium and vitamin D intake.

Comparisons between groups: The BMD increases found in the ALN group were statistically significantly greater than those in the PBO group at the lumbar spine and hip trochanter at 6 and 12 months. The differences were a little over 2%. However, the differences between groups were not significant at the femoral neck and Ward's triangle.

2) Biochemical markers of bone turnover:

For both groups, the baseline median values for BSAP and NTx were similar to values found in premenopausal women, indicating long term effects of HRT.

For the PBO group, there was no significant change in BSAP or NTx during the 12 months of the study.

For the ALN group, there were statistically significant decreases from baseline in BSAP (by about 21%) and NTx (by about 42%) at 6 and 12 months. At both 6 and 12 months, the means both markers were slightly below the premenopausal means, but were within 1 SD and remained within the normal premenopausal range.

The between-group (ALN vs PBO) differences in levels of both markers were statistically significant at both 6- and 12-month time points.

Thus, the sponsor has demonstrated that, over the course of 12 months, the addition of alendronate, 10mg, to an ongoing regimen of HRT, further suppresses biochemical markers of bone turnover and further increases BMD at the spine and trochanter, but not at the femoral neck and Ward's triangle (where the differences between treatment groups were not significant).

Safety: The addition of alendronate, 10mg, to an ongoing regimen of HRT was generally safe and well tolerated over the course of a one-year study. There was no increase in adverse events in general, or in adverse events usually associated with either treatment alone. There appeared to be an increase in foot fractures in the alendronate-treated patients, but the level of documentation for all fractures remains unclear.

8.3 Reviewer's Trial #3, Sponsor's Trial #072

"A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate and Compare the Safety and Efficacy of Oral Alendronate Sodium, Conjugated Estrogens, and Combination Conjugated Estrogens With Alendronate Sodium for the Treatment of Postmenopausal Osteoporosis"

8.3.1.1 Objectives

As stated by the sponsor, the primary objectives of this trial were:

1) To evaluate and compare the effects over time of treatment with concomitant daily oral ALN (10 mg) and CE (0.625 mg), to CE (0.625 mg) alone, on BMD of the lumbar spine in hysterectomized, osteoporotic, postmenopausal women treated for 2 years

2) To evaluate and compare the safety and tolerability of daily oral administration of 10 mg ALN, 0.625 mg CE, both agents administered concomitantly, and PBO in hysterectomized, osteoporotic, postmenopausal women treated for 2 years, by comparing relevant safety parameters and by analyzing the incidence of adverse experiences and patient dropouts due to adverse experiences

The secondary objectives were:

1) To evaluate and compare the effects over time of daily oral administration of 10 mg ALN, 0.625 mg of CE, both agents administered concomitantly, and PBO on BMD of the lumbar spine, hip (total and region-specific) and total body in hysterectomized, osteoporotic, postmenopausal women treated for 2 years

2) To evaluate and compare the effects over time of daily oral administration of ALN (10 mg), CE (0.625 mg), both agents administered concomitantly, and placebo on biochemical markers of bone turnover (urinary N-telopeptides of type 1 collagen corrected for creatinine [NTx/Cr], serum bone-specific alkaline phosphatase [BSAP]), mineral metabolism (serum parathyroid hormone, 1,25-dihydroxyvitamin D, serum calcium, serum phosphate), and serum lipids (total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and triglycerides) in hysterectomized, osteoporotic, postmenopausal women treated for 2 years

3) To evaluate and compare the effects of daily oral ALN (10 mg), CE (0.625 mg), both agents administered concomitantly, and PBO on indices of bone turnover, bone mineralization, and bone architecture assessed by

histomorphometric analysis of bone biopsy samples in a subset of hysterectomized, osteoporotic, postmenopausal women treated for 18 months

The stated hypotheses were:

Primary

1) Treatment of hysterectomized, osteoporotic, postmenopausal women with concomitant daily oral ALN (10 mg) and CE (0.625 mg) will produce a mean increase in lumbar spine BMD at 2 years, which is significantly greater than that observed with treatment with CE (0.625 mg) alone.

2) Daily concomitant oral administration of ALN (10 mg) and CE (0.625 mg) will be sufficiently safe and well tolerated to be used in women with postmenopausal bone loss.

Secondary

1) Daily oral administration of ALN (10 mg) alone, CE (0.625 mg) alone, and both agents administered concomitantly to hysterectomized, osteoporotic, postmenopausal women for 2 years will each result in mean increases in lumbar spine and total hip BMD, relative to both baseline and to placebo.

2) Treatment of hysterectomized, osteoporotic, postmenopausal women with concomitant daily oral ALN (10 mg) and CE (0.625 mg) will produce a mean increase in total hip BMD at 2 years which is greater than that observed with treatment with CE (0.625 mg) alone.

3) Treatment of hysterectomized, osteoporotic, postmenopausal women with daily oral ALN (10 mg) alone will produce greater mean increases in lumbar spine and total hip BMD at 2 years than treatment with CE (0.625 mg) alone.

4) Treatment of hysterectomized, osteoporotic, postmenopausal women with concomitant daily oral ALN (10 mg) and CE (0.625 mg) will produce mean increases in lumbar spine and total hip BMD at 2 years equal to or greater than those observed in patients treated with ALN (10 mg) alone.

8.3.1.2 Study Design

This was a randomized, double-blind, placebo-controlled, multicenter, two-year study of 425 hysterectomized postmenopausal women with low spinal bone mineral density. The purpose of the study was to compare the safety, tolerability, and effects on BMD and bone turnover markers of daily oral alendronate (ALN) 10 mg, daily oral conjugated estrogens (CE) 0.625 mg, and the combination of

the two. The study consisted of 4 arms: placebo, CE, alendronate, and combination CE plus alendronate (1:2:3:3). The study was conducted at 19 sites in 16 states in the US.

Target enrollment was 360 women at 19 centers in the US, with the goal of at least 240 completing 2 years of treatment.

Randomized subjects were stratified according to prior estrogen use, which was defined as >1 month of oral or transdermal estrogen taken during the peri- or postmenopausal period, with or without a progestin. Patients who had taken estrogens were placed into Stratum I; patients with no prior estrogen use were assigned to Stratum II.

This trial began with a 2-week single-blind placebo run-in period, in which all subjects were given placebos for both ALN and CE. The purpose of this run-in was to assess compliance with dosing, and also to determine any adverse experiences in patients who were given calcium supplementation. Any patient who was < 85% compliant with placebo tablets was excluded from further participation.

The trial used a "double-dummy" design, in which each patient received both ALN or placebo for ALN, and CE or placebo for CE, as shown below. PREMARIN™ (Wyeth Ayerst) was used as CE.

Group	Treatment	N
PBO	Placebo for ALN + Placebo for CE	40
ALN	ALN 10 mg + Placebo for CE	80
CE	CE 0.625 mg + Placebo for ALN	120
ALN+CE	ALN 10 mg + CE 0.625 mg	120
Total		360

PBO: Placebo.
ALN: Alendronate.
CE: Conjugated estrogens (PREMARIN™).

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8.3.1.3 Protocol

8.3.1.3.1 Populations, Procedures, and Concurrent Medications

A complete listing of inclusion/exclusion criteria is given in the NDA submission. Of particular importance to this study, the inclusion criteria were:

"The patient was a woman, 45 to 75 years of age, who had undergone hysterectomy (with or without removal of the ovaries) at least 3 months prior to entry and had experienced menopause (either surgical or natural) at least 3 years prior to entry. Patients were considered to have met the latter criterion if they fell into one or more of the following categories:
(a) age >60, (b) a surgical/pathology report was available documenting

oophorectomy at least 3 years prior to entry, (c) absent menses for ≥6 months prior to hysterectomy, beginning ≥3 years prior to entry, or (d) onset of typical climacteric symptoms ≥3 years prior to entry in a woman who underwent hysterectomy without confirmed oophorectomy. If the patient gave no history of climacteric symptoms, an FSH level was obtained through the central laboratory and must have exceeded the lower end of the reference range for postmenopausal women for the patient to be eligible."

Other important inclusion criteria were that the patient had a lumbar spine BMD <0.86g/cm^2 by Hologic QDR measurement. Patients also agreed not to take systemic estrogens, except as prescribed, throughout the study.

A complete list of exclusion criteria is reproduced here:

"1) The patient had received treatment with estrogens within 6 months prior to randomization (other than topical estrogen-containing vaginal creams, which were acceptable if used up to twice weekly).
2) The patient was, in the opinion of the investigator, mentally or legally incapacitated such that informed consent could not be obtained.
3) The patient had participated in another therapeutic trial within 30 days of randomization.
4) The patient intended to move within 2 years of entry into the study, rendering per-protocol follow-up impractical.
5) The patient had a history of any illness or had significant abnormalities on prestudy clinical or laboratory evaluation that, in the opinion of the investigator, might have posed an unacceptable risk to the patient from participation in this study or complicated the interpretation of study data.
6) The patient was, at the time of the study, a current user of any illicit drugs or had a history of drug or alcohol abuse within the past 5 years.
7) The patient consumed more than 2 glasses of wine, 2 beers, or 2 standard alcoholic drinks on average per day.
8) The patient had any of the following: any severe malabsorption syndrome; moderate or severe hypertension that was uncontrolled; new onset angina or myocardial infarction within 6 months of entry into the study; evidence for impaired renal function defined as a serum creatinine greater than 1.6 mg/dL; endogenous hypercortisolism within 1 year of entry into the study; known symptomatic gallbladder disease not treated with prior cholecystectomy; history of porphyria; or other significant end organ diseases (genitourinary, cardiovascular, hepatic, psychiatric, renal, hematologic, or pulmonary) that, in the opinion of the investigator, posed an added risk to the patient or impaired her ability to complete the trial.
9) The patient had a history of major upper gastrointestinal (GI) (esophagus, stomach, duodenum) mucosal erosive disease as defined by:
(1) significant upper GI bleeding within the last 5 years resulting in hospitalization and/or transfusion; (2) recurrent ulcer disease documented by radiographic or endoscopic means (two episodes in the last 5 years); (3) dyspepsia treated on a daily basis, or (4) esophageal or gastric variceal disease.
10) The patient had a history of cancer. However, patients with the following cancers were considered eligible for the study: (a) superficial basal or squamous cell carcinoma of the skin that had been completely resected, or (b) other malignancies (with the exceptions indicated below) successfully treated >10 years prior to screening, where in the judgment of both the investigator and a consulting oncologist, appropriate follow-up had

revealed no evidence of recurrence from the time of treatment through the time of screening. However, patients with a history of leukemia, lymphoma, myeloproliferative disease, endometrial cancer, breast cancer (including histologic diagnosis of lobular carcinoma in situ), or known or suspected estrogen-sensitive neoplasia were excluded regardless of the time since treatment or disease status.

11) 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, Paget's disease of bone, osteomalacia, and osteogenesis imperfecta. Patients with surgically cured hyperparathyroidism due to parathyroid adenoma at least 1 year prior to randomization were eligible for the study.

12) If the screening 25-OH vitamin D level was below 50% of the lower limit of normal (central laboratory), the patient was excluded. If the screening 25-OH vitamin D level was below the normal range but ≥50% of the lower limit of normal, the patient was excluded if there was any other evidence for osteomalacia (e.g., clinical manifestations or abnormalities in calcium, phosphorus, or alkaline phosphatase). If the screening 25-OH vitamin D level was below the normal range but ≥50% of the lower limit of normal and there was no other evidence to suggest osteomalacia, the patient could be treated with oral vitamin D, 800 IU daily for a minimum of 2 months (preferably 3 to 4 months if time permitted), and subsequently entered if repeat 25-OH vitamin D level was normal.

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13) The patient had received treatment (other than estrogens) prior to randomization which might have influenced bone turnover, including: (a) within 6 months: anabolic steroids, calcitonin, or progestins; (b) thyroid hormone, unless on a stable dose for at least 6 weeks before randomization with serum thyroxine and thyroid stimulating hormone (TSH) within the normal range; (c) 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; (d) 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 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) during the course ofthe study; and (e) any previous treatment with a bisphosphonate for more than 2 weeks; if given for 2 weeks or less, it must have occurred more than 1 year before randomization.

14) The patient was receiving any medication that might alter bone or calcium metabolism, including vitamin A in excess of 10,000 IU per day or vitamin D in excess of 800 IU per day, anticonvulsants, or regular use of phosphate-binding antacids.

15) The patient had active rheumatoid arthritis.

16) The patient had active thrombophlebitis or a history of prior thromboembolic disease.

17) The patient's baseline mammogram (performed within 1 year of entry) raised any suspicion of malignancy requiring follow-up (e.g., repeat mammogram) within a 9-month period, unless proven benign by biopsy.

18) The patient was at increased risk for breast cancer to the degree that, in the judgment of the investigator or patient, the risks of possible estrogen therapy outweighed the benefits.

19) The patient had a history of genital bleeding within the preceding year for which a cause had not been identified or that, in the judgment of the investigator, placed the patient at increased risk from estrogen therapy.

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

21) The patient had any clinical condition (including climacteric symptoms) which she or the investigator believed could require systemic estrogen therapy within 2 years following enrollment.
22) The patient had a history of allergy, hypersensitivity, or intolerance to any bisphosphonate (including agents used for diagnostic testing) or any conjugated estrogen or other estrogen preparation.
23) The patient was a regular user (more than once per day) of any medication (including over-the-counter analgesics such as nonenteric coated aspirin, ibuprofen, or other nonsteroidal anti-inflammatory drugs) having the potential for GI irritation, unless taken at an unchanged dosage for >2 months without occurrence of symptoms referable to the upper GI tract.
24) The patient demonstrated noncompliance with taking study medication during the placebo run-in phase (consumption of <85% of all prescribed tablets) or anticipated significant difficulty in taking study medications precisely as directed."

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Comments: The sponsor's definition of "osteoporosis" is based solely on BMD. This definition is now widely but not universally accepted. Many authorities insist on evidence of bone fragility in addition to osteopenia.

The sponsor gives no description of methodology for recruitment of participants. There is no indication of the method of initial patient contact, number of patients initially contacted, number screened, number excluded at each level of selection prior to final randomization, and the reasons for exclusion at each step. As discussed in earlier alendronate reviews, the careful selection and screening of participants helps ensure a high level of compliance, as well as a remarkable retention rate during trials. For example, in the FIT trial (reviewed earlier this year), 96% of subjects originally randomized completed the study, with over 80% still on study drug. In this trial, the additional feature of a placebo run-in period further ensures enrichment of the trial population with compliant individuals. This approach increases the technical quality of a controlled trial and allows questions to be answered in a scientifically rigorous manner. The trade-off is that the trial population may not be representative of the population of patients who will receive the drug. Thus, a trial may show that treatment A is superior to treatment B, but in a population that inadequately represents the market population. One indication of inadequacy of representation of the trial populations is the discordance between the frequency of GI adverse events reported in all alendronate clinical trials and the number of GI adverse events that have marked post-marketing experience with alendronate.

Concomitant medications:

If dietary calcium intake was assessed to be <1000 mg/day, subjects were advised to take 500 mg of supplemental calcium. The calcium was provided by

the investigator (OSCAL 250 + D™). If the estimated daily dietary calcium was >1000 mg, subjects were advised to continue current intake and were not given supplemental calcium.

Supplemental vitamin D was prescribed only if judged to be indicated by the investigator, in which case no more than 400 IU daily supplement was given.

Comments: This will probably be inadequate supplementation for many of the subjects in the trial. Postmenopausal women require 1500 mg elemental calcium per day and should also be given 400 IU of vitamin D per day.

Drugs that affect mineral metabolism were not permitted (see above for complete listing).

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Procedures (clinical observations and laboratory measurements):

The sponsor provides a schedule of clinical and laboratory assessments during the screening and randomization periods and throughout the 24 months of the trial:

Month:	Screening		Randomization	1	3	6	9	12	18	24
Visit No:	1	2	3	4	5	6	7	8	9	10
Informed consent	X								X[8]	
Mammography		X[1]						X[1]		X[1]
Dietary calcium assessment	X							X		X
History/adverse experiences	X		X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Physical examination	X		X[3]	X[3]	X[3]	X[3]	X[3]	X	X[3]	X
Height/weight	X		X		X	X	X	X	X	X
Electrocardiogram		X								
Routine hematology and chemistry	X		X		X	X	X	X	X	X
Screening chemistry	X									
Serum lipids	X							X		X
Bone-specific alkaline phosphatase	X		X	X	X	X		X	X	X
Parathyroid hormone; 1,25-OH vitamin D			X	X	X			X		X
Routine urinalysis		X			X	X	X	X	X	X
Special urine chemistry (creatinine and NTx)		X	X	X	X	X		X	X	X
Archival serum samples	X		X	X	X	X	X	X	X	X
Dual-energy X-ray absorptiometry (DXA)	X[4]	X[5]	X[6]		X[7]	X[7]		X[9]	X[7]	X[9]
Thoracolumbar spine X-rays	X									X

Month:	Screening		Randomization	1	3	6	9	12	18	24
Visit No:	1	2	3	4	5	6	7	8	9	10
Bone biopsy (with consent)									X[10]	
Study drugs		X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	
Tablet counts			X	X	X	X	X	X	X	X
Randomization			X							

[1] Baseline screening mammogram was performed unless a mammogram performed within the preceding year was available. In the latter case, it was considered the "baseline" study and repeat mammograms were performed at 1-year intervals from the date of that mammogram for the duration of the study.
[2] Interim medical history to identify changes in symptoms, adverse experiences and changes in medication usage.
[3] Limited physical examination was performed only if indicated by the occurrence of symptoms or for any other reason.
[4] DXA of the lumbar spine only.
[5] DXA of the hip and total body only.
[6] DXA of the lumbar spine, hip, and total body.
[7] DXA of the lumbar spine and hip only.
[8] Transiliac bone biopsy on a subgroup of approximately 100 consenting subjects.
[9] Placebo run-in (2 weeks).
[10] Study medications.
[11] For those patients who had a bone biopsy performed.

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Methodology: A complete description of the methodologies employed for all laboratory assessments is provided in the NDA. Blood and urine specimens were collected according to the schedule presented in the table above.

In addition, a subgroup of 98 individuals consented to have transiliac bone biopsies after approximately 18 months of treatment. Complete details of the methodology for bone histomorphometry are provided in the NDA. Standard techniques, including tetracycline labeling, were employed.

Subjects received demeclocycline (DECLOMYCIN™, Lederle) 300 mg b.i.d. for 2 days, followed by 12 days without demeclocycline, followed by an additional 2 days of demeclocycline 300 mg b.i.d. The bone biopsy was performed 4 to 6 days after the last demeclocycline dose. On the last day of demeclocycline administration, all subjects provided a urine specimen, which was stored frozen for future assay in the event that no tetracycline was detected in the bone biopsy. After local anesthesia, a bicortical transiliac biopsy, using a 7-mm trephine needle, was performed. Biopsy specimens, protected from UV light, were processed and stored according to routine, standard procedures. Following shipment to the central histomorphometry laboratory [redacted] specific histomorphometric parameters of bone turnover and mineralization were assessed on undecalcified sections.

The mineralization and turnover parameters measured were:

1) trabecular osteoid volume
2) combined trabecular and endocortical: a) osteoid thickness, b) mineral apposition rate
3) extent of surface undergoing mineralization

In addition, qualitative assessments of bone architecture were performed using polarized light microscopy (collagen fibrils) and study of the appearance of cellular components. Marrow fibrosis was also noted, if present.

Bone densitometry was assessed with [redacted] according to routine procedures (details in NDA). At each study site, the same densitometer was used for each subject throughout the study. Strict procedures were used for QA. Coss-calibration data, and phantom data were archived and analyzed by a central data management facility. BMD of spine and hip were assessed at 3, 6, 12, 18, and 24 months and total body BMD at 12 and 24 months. BMD data were not included for vertebrae that fractured during the study.

All patients had a baseline mammogram, unless results of mammography conducted during the previous year were available. Patients then had yearly mammograms for the remainder of the study.

At baseline, lateral thoracolumbar spine X-rays were obtained to determine the presence of fracture(s). These were repeated at Month 24. The X-rays were sent to Dr. Michael Nevitt, Ph.D, at the University of California at San Francisco (UCSF) for digitization and determination of fractures. As with the FIT trial, the readings were blinded to treatment but not to sequence, based on agreement with the FDA.

8.3.1.3.2 Endpoints

Efficacy

Clinical efficacy:

The primary efficacy endpoint was mean percent change in lumbar spine (L1 to L4) BMD from baseline to Month 24.

Secondary efficacy endpoints: mean percent changes in BMD (baseline to Month 24) of the total hip, femoral neck, trochanter, intertrochanteric, Ward's triangle hip and total body.

Biochemical Efficacy

Changes in biochemical markers of bone turnover (urine NTx and serum BSAP and total alkaline phosphatase) were secondary endpoints. The endpoint for this analysis was the log-transformed fraction of baseline at Month 24.

Changes in indices of mineral homeostasis (serum calcium and phosphate) were also analyzed as the log-transformed fraction of baseline at Month 24.

Safety

A comprehensive clinical and laboratory safety assessment and analysis was performed.

Clinical adverse experiences (obtained via history taken at each visit, plus spontaneous reporting to the investigator) were recorded on the Adverse Experience Case Report Form. These were rated as to severity (mild to severe).

Physical examinations were performed according to the schedule, provided above.

Laboratory safety tests were performed (by the central laboratory) according to the schedule provided in the table above. Specific tests and methodologies are provided in the NDA. The tests included a complete hematology profile and battery of serum chemistries, serum lipids, and urinalyses. Additionally, at visit 1, the sponsor determined levels of 25-hydroxyvitamin D, total thyroxine, and TSH.

In addition, the sponsor determined levels of total alkaline phosphatase, BSAP, PTH, and 1,25-dihydroxyvitamin D.

Predefined limits of change were established for laboratory safety parameters.

Bone histomorphometry (described above) was analyzed as a safety outcome.

8.3.1.3.3 Statistical Considerations

The primary efficacy parameter was change from baseline in BMD of the lumbar spine. BMD at other sites (total body, femoral neck, trochanter, intertrochanteric, and Ward's triangle) were secondary efficacy parameters.

For each of the 4 treatment groups, at the 3-, 6-, 12-, 18-, and 24-month time points, summary statistics for % change were calculated. Mean % change in BMD (with 95% CI's) was compared between treatment groups at the 2-year time point.

The safety/tolerability of each of the 4 regimens was assessed by clinical review of all relevant parameters. Proportions of subjects with AE's, with changes in laboratory variables outside of predefined limits, and with new vertebral fractures (X-ray) were compared among the 4 treatment groups. For continuous variables, (e.g., blood pressure) summary statistics of changes over the 24 months were employed.

For biochemical indices of mineral metabolism, the sponsor used the log-transformed fraction of baseline in each treatment group to compare changes among groups.

A correlation analysis of the relationship between baseline BMD and percent changes in BMD from baseline was performed. In addition, the sponsor performed an analysis of correlations between changes in BMD, and biochemical parameters (both baseline and changes from baseline). Other, exploratory (i.e., hypothesis-generating) correlations were determined.