CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 20-560/S03/S06

Trade Name: FOSAMAX TABLETS

Generic Name: Alendronate sodium

Sponsor: MERCK RESEARCH LABORATORIES

Approval Date: 04/25/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 20-560/S03/S06

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
Approvable Letter				X
Final Printed Labeling	X			
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI	X			
Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
Bioequivalence Review(s)				X
Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 20-560/S03/S06

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-560/S-003, S-006

APR 25 1997

Merck Research Laboratories
Attention: Michelle Kloss, Ph.D
Director, Regulatory Affairs
P.O. Box 4, BLA-20

Dear Dr. Kloss:

Please refer to your supplemental new drug applications, Supplement-003 and Supplement-006, dated April 29, and September 23, 1996, and received April 30, and September 24, 1996, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosamax (alendronate sodium) 10 and 40 mg Tablets.

The User Fee goal dates for these applications are April 30, 1997, for Supplement 003, and September 24, 1997, for Supplement 006.

We acknowledge receipt of your submissions for Supplement 003, dated June 10 and 12, August 28, September 3 and 27, October 11 and 29, November 12, and December 27, 1997; and January 21, February 11(2), 24, and 28, March 13 and 20, and April 10, 14, and 21, 1997, and for Supplement 006, September 27, November 12 and 20, and December 27, 1996; and January 9, February 14 and 28, March 20, and April 14 and 21, 1997.

Supplemental application S-003 provides for a new indication the prevention of osteoporosis in postmenopausal women, and supplemental application S-006 provides for expansion of the indication to include the prevention of fractures in the treatment of postmenopausal osteoporosis and for the incorporation of new clinical data in the *Clinical Studies* section of the package insert.

We have completed the review of these supplemental applications, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated April 21, 1997. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on April 21, 1997.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days

after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDAs 20-560/S-003, S-006. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Randy Hedin, R.Ph., Consumer Safety Officer, at (301) 443-3520.

Sincerely yours,

Solomon Sobel

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-560/S03/S06

FINAL PRINTED LABELING

MERCK & CO., INC.
West Point, PA 19486, USA

7957005

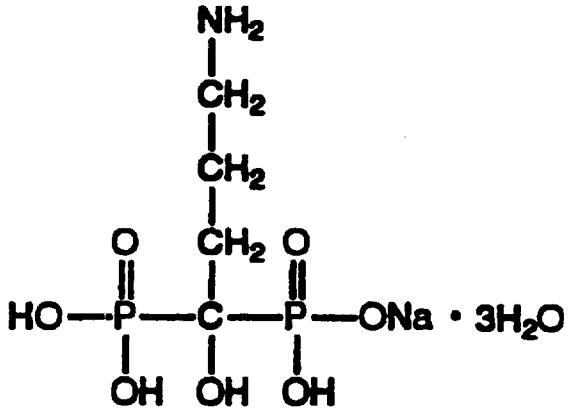
FOSAMAX®
(ALENDRONATE SODIUM TABLETS)

DESCRIPTION

FOSAMAX*(alendronate sodium) is an aminobisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.

Alendronate sodium is chemically described as (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate.

The empirical formula of alendronate sodium is $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$ and its formula weight is 325.12. The structural formula is:



Alendronate sodium is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.

Tablets FOSAMAX for oral administration contain 6.53, 13.05 or 52.21 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 5.0, 10.0 and 40.0 mg, respectively, of free acid, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, and magnesium stearate.

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*Registered trademark of MERCK & CO., Inc.

CLINICAL PHARMACOLOGY

Mechanism of Action

Animal studies have indicated the following mode of action. At the cellular level, alendronate shows preferential localization to sites of bone resorption, specifically under osteoclasts. The osteoclasts adhere normally to the bone surface but lack the ruffled border that is indicative of active resorption. Alendronate does not interfere with osteoclast recruitment or attachment, but it does inhibit osteoclast activity. Studies in mice on the localization of radioactive [^{3}H]alendronate in bone showed about 10-fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bones examined 6 and 49 days after [^{3}H]alendronate administration in rats and mice, respectively, showed that normal bone was formed on top of the alendronate, which was incorporated inside the matrix. While incorporated in bone matrix, alendronate is not pharmacologically active. Thus, alendronate must be continuously administered to suppress osteoclasts on newly formed resorption surfaces. Histomorphometry in baboons and rats showed that alendronate treatment reduces bone turnover (i.e., the number of sites at which bone is remodeled). In addition, bone formation exceeds bone resorption at these remodeling sites, leading to progressive gains in bone mass.

Pharmacokinetics

Absorption

Relative to an intravenous (IV) reference dose, the mean oral bioavailability of alendronate in women was 0.7% for doses ranging from 5 to 40 mg when administered after an overnight fast and two hours before a standardized breakfast. Oral bioavailability of the 10 mg tablet in men (0.59%) was similar to that in women (0.78%) when administered after an overnight fast and 2 hours before breakfast.

A study examining the effect of timing of a meal on the bioavailability of alendronate was performed in 49 postmenopausal women. Bioavailability was decreased (by approximately 40%) when 10 mg alendronate was administered either 0.5 or 1 hour before a standardized breakfast, when compared to dosing 2 hours before eating. In studies of treatment and prevention of osteoporosis, alendronate was effective when administered at least 30 minutes before breakfast.

Bioavailability was negligible whether alendronate was administered with or up to two hours after a standardized breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

Distribution

Preclinical studies (in male rats) show that alendronate transiently distributes to soft tissues following 1 mg/kg IV administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 L in humans. Concentrations of drug in plasma following therapeutic oral doses are too low (less than 5 ng/mL) for analytical detection. Protein binding in human plasma is approximately 78%.

Metabolism

There is no evidence that alendronate is metabolized in animals or humans.

Excretion

Following a single IV dose of [^{14}C]alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces. Following a single 10 mg IV dose, the renal clearance of alendronate was 71 mL/min, and systemic clearance did not exceed 200 mL/min. Plasma concentrations fell by more than 95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton. Based on the above, it is estimated that after 10 years of oral treatment with FOSAMAX (10 mg daily) the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed from the gastrointestinal tract.

Special Populations

Pediatric: Alendronate pharmacokinetics have not been investigated in patients <18 years of age.

Gender: Bioavailability and the fraction of an IV dose excreted in urine were similar in men and women.

Geriatric: Bioavailability and disposition (urinary excretion) were similar in elderly (≥65 years of age) and younger patients. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Race: Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency: Preclinical studies show that, in rats with kidney failure, increasing amounts of drug are present in plasma, kidney, spleen, and tibia. In healthy controls, drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after 3 weeks dosing with cumulative IV doses of 35 mg/kg in young male rats. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function.

No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). **FOSAMAX is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 mL/min) due to lack of experience.**

Hepatic Insufficiency: As there is evidence that alendronate is not metabolized or excreted in the bile, no studies were conducted in patients with hepatic insufficiency. No dosage adjustment is necessary.

Drug Interactions (also see PRECAUTIONS, *Drug Interactions*)

Intravenous ranitidine was shown to double the bioavailability of oral alendronate. The clinical significance of this increased bioavailability and whether similar increases will occur in patients given oral H_2-antagonists is unknown; no other specific drug interaction studies were performed.

Products containing calcium and other multivalent cations are likely to interfere with absorption of alendronate.

Summary of Pharmacokinetic Parameters in the Normal Population

	Mean	90% Confidence Interval
Absolute bioavailability of 5 mg tablet, taken 2 hours before first meal of the day	0.63% (females)	(0.48, 0.83)
Absolute bioavailability of 10 mg tablet, taken 2 hours before first meal of the day	0.78% (females)	(0.61, 1.04)
	0.59% (males)	(0.43, 0.81)
Absolute bioavailability of 40 mg tablet, taken 2 hours before first meal of the day	0.60% (females)	(0.46, 0.78)
Renal Clearance (mL/min) (n=6)	71	(64, 78)

Pharmacodynamics

Osteoporosis in postmenopausal women

Osteoporosis is characterized by low bone mass that leads to an increased risk of fracture. The diagnosis can be confirmed by the finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis, indicative of vertebral (spinal) fracture. Osteoporosis occurs in both males and females but is most common among women following the menopause, when bone turnover increases and the rate of bone resorption exceeds that of bone formation. These changes result in progressive bone loss and lead to osteoporosis in a significant proportion of women over age 50. Fractures, usually of the spine, hip, and wrist, are the common consequences. From age 50 to age 90, the risk of hip fracture in white women increases 50-fold and the risk of vertebral fracture 15- to 30-fold. It is estimated that approximately 40% of 50-year-old women will sustain one or more osteoporosis-related fractures of the spine, hip, or wrist during their remaining lifetimes. Hip fractures, in particular, are associated with substantial morbidity, disability, and mortality.

Alendronate is an aminobisphosphonate that binds to bone hydroxyapatite and specifically inhibits the activity of osteoclasts, the bone-resorbing cells. Alendronate reduces bone resorption with no direct effect on bone formation, although the latter process is ultimately reduced because bone resorption and formation are coupled during bone turnover. Alendronate thus reduces the elevated rate of bone turnover observed in postmenopausal women to approximate more closely that in premenopausal women. Alendronate is not an estrogen and does not have the benefits and risks of estrogen replacement therapy.

Daily oral doses of alendronate (5, 20, and 40 mg for six weeks) in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as deoxypyridinoline and cross-linked N-telopeptides of type I collagen). These biochemical changes tended to return toward baseline values as early as 3 weeks following the discontinuation of therapy with alendronate and did not differ from placebo after 7 months.

In long-term (two- or three-year) osteoporosis treatment studies, FOSAMAX 10 mg/day reduced urinary excretion of markers of bone resorption, including deoxypyridinoline and cross-linked N-telopeptides of type I collagen, by approximately 50-60% to reach levels similar to those seen in healthy premenopausal women. Similar decreases were seen in patients in osteoporosis prevention studies who received FOSAMAX 5 mg/day. The decrease in the rate of bone resorption indicated by these markers was evident as early as one month and at three to six months reached a plateau that was maintained for the entire duration of treatment with FOSAMAX. In osteoporosis treatment studies FOSAMAX 10 mg/day decreased the markers of bone formation, osteocalcin and total serum alkaline phosphatase, by approximately 50% and 25-30%, respectively, to reach a plateau after 6 to 12 months. In osteoporosis prevention studies FOSAMAX 5 mg/day decreased these markers by approximately 40% and 15%, respectively. These data indicate that the rate of bone turnover reached a new steady-state, despite the progressive increase in the total amount of alendronate deposited within bone.

As a result of inhibition of bone resorption, asymptomatic reductions in serum calcium and phosphate concentrations were also observed following treatment with FOSAMAX. In the long-term studies, reductions from baseline in serum calcium (approximately 2%) and phosphate (approximately 4 to 6%) were evident the first month after the initiation of FOSAMAX 10 mg, but no further decreases were observed for the three-year duration of the studies. Similar reductions were observed with FOSAMAX 5 mg/day. The reduction in serum phosphate may reflect not only the positive bone mineral balance due to FOSAMAX but also a decrease in renal phosphate reabsorption.

Paget's disease of bone

Paget's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disorderly bone remodeling. Excessive osteoclastic bone resorption is followed by osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganized, enlarged, and weakened bone structure.

Clinical manifestations of Paget's disease range from no symptoms to severe morbidity due to bone pain, bone deformity, pathological fractures, and neurological and other complications. Serum alkaline phosphatase, the most frequently used biochemical index of disease activity, provides an objective measure of disease severity and response to therapy.

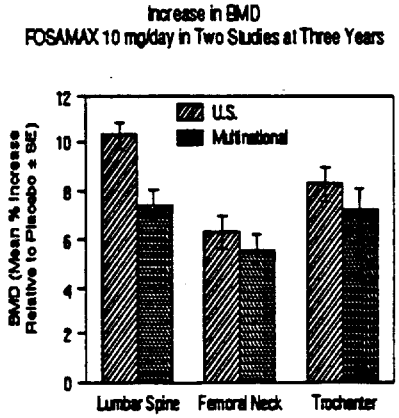
FOSAMAX decreases the rate of bone resorption directly, which leads to an indirect decrease in bone formation. In clinical trials, FOSAMAX 40 mg once daily for six months produced highly significant decreases in serum alkaline phosphatase as well as in urinary markers of bone collagen degradation. As a result of the inhibition of bone resorption, FOSAMAX induced generally mild, transient, and asymptomatic decreases in serum calcium and phosphate.

Clinical Studies

Treatment of osteoporosis in postmenopausal women

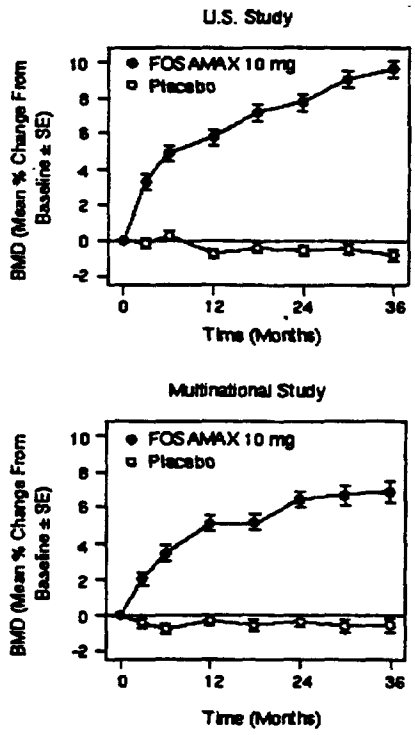
Effect on bone mineral density

The efficacy of FOSAMAX 10 mg once daily in postmenopausal women, 44 to 84 years of age, with osteoporosis (lumbar spine bone mineral density [BMD] of at least 2 standard deviations below the premenopausal mean) was demonstrated in four double-blind, placebo-controlled clinical studies of two or three years' duration. These included two large three-year, multicenter studies of virtually identical design, one performed in the United States (U.S.) and the other in 15 different countries (Multinational), which enrolled 478 and 516 patients, respectively. The following graph shows the mean increases in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving FOSAMAX 10 mg/day relative to placebo-treated patients at three years for each of these studies.



Highly significant increases in BMD, relative both to baseline and placebo, were seen at each measurement site in each study in patients who received FOSAMAX 10 mg/day. Total body BMD also increased significantly in each study, suggesting that the increases in bone mass of the spine and hip did not occur at the expense of other skeletal sites. Increases in BMD were evident as early as three months and continued throughout the three years of treatment. (See figures below for lumbar spine results.) Thus, FOSAMAX appears to reverse the progression of osteoporosis. FOSAMAX was similarly effective regardless of age, race, baseline rate of bone turnover, and baseline BMD in the range studied (at least 2 standard deviations below the premenopausal mean).

Time Course of Effect of FOSAMAX 10 mg/day Versus Placebo:
Lumbar Spine BMD Percent Change From Baseline



In patients with postmenopausal osteoporosis treated with FOSAMAX for one or two years, the effects of treatment withdrawal were assessed. Following discontinuation, there were no further increases in bone mass and the rates of bone loss were similar to those of the placebo groups. These data indicate that continuous daily treatment with FOSAMAX is required to maintain the effect of the drug.

Effect on fracture incidence

To assess the effects of FOSAMAX on vertebral fracture incidence, the U.S. and Multinational studies were combined in an analysis that compared placebo to the pooled dosage groups of FOSAMAX (5 or 10 mg for three years or 20 mg for two years followed by 5 mg for one year). There was a significant 48% reduction in the proportion of patients treated with FOSAMAX experiencing one or more new vertebral fractures relative to those treated with placebo (3.2% vs. 6.2%). A reduction in the total number of new vertebral fractures (4.2 vs. 11.3 per 100 patients) was also observed. In the pooled analysis, patients who received FOSAMAX had a statistically significant smaller loss in stature than those who received placebo (–3.0 mm vs. –4.6 mm). Furthermore, of patients who sustained any vertebral fracture, those treated with FOSAMAX experienced less height loss (5.9 mm vs. 23.3 mm) due to a reduction in both the number and severity of fractures.

The Vertebral Fracture Study of the Fracture Intervention Trial (FIT) included results from 2027 patients who had at least one baseline vertebral (compression) fracture. The results of this study demonstrated the reduction in fracture incidence due to FOSAMAX. In this three-year, randomized, double-blind, placebo-controlled study, 1022 patients received FOSAMAX and 1005 patients received placebo. Treatment with FOSAMAX resulted in statistically significant and clinically meaningful reductions in the proportion of patients experiencing fractures as shown in the table below.

Effect of FOSAMAX on Fracture Incidence Over Three Years in the Vertebral Fracture Study of FIT

	% of Patients		Reduction (%) in Fracture Incidence
	FOSAMAX	Placebo	
Patients with:			
≥1 new vertebral fracture	8.0	15.0	47
≥2 new vertebral fractures	0.5	4.9	90
≥1 painful vertebral fracture	2.3	5.0	55
Hip fractures	1.1	2.2	51
Wrist (forearm) fractures	2.2	4.1	48

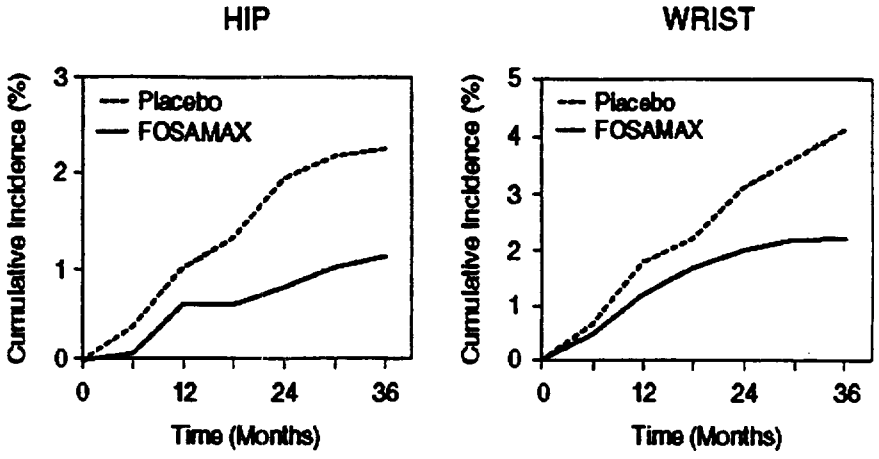
Furthermore, treatment with FOSAMAX significantly reduced the incidence of total hospitalizations (24.9% vs. 30.4%).

The reduction in the incidence of vertebral fractures (FOSAMAX versus placebo) in the Vertebral Fracture Study of FIT (in which all women had at least one baseline vertebral fracture) was consistent with that in the combined U.S. and Multinational (U.S./Mult) treatment studies (see above), in which 80% of the women did not have a vertebral fracture at baseline. During these three-year studies, treatment with FOSAMAX reduced the proportion of women experiencing at least one new vertebral fracture in both study populations by approximately 50% (FIT: 47% reduction, $p<0.001$; U.S./Mult: 48% reduction, $p = 0.034$). Similarly, FOSAMAX reduced the proportion of women experiencing multiple (two or more) new vertebral fractures by approximately 90% in both studies ($p<0.001$). Thus, FOSAMAX reduces the incidence of fractures whether or not patients have experienced a previous vertebral fracture.

The two figures below display the cumulative incidence of patients with hip and wrist fractures over 3 years in the Vertebral Fracture Study of FIT. In both figures, the cumulative incidence of patients with these types of fracture is lower with FOSAMAX compared with placebo at all time points. FOSAMAX reduced the proportion of women experiencing hip fracture by 51% and wrist fracture by 48%. Proportionately similar reductions of hip and wrist fractures were seen in pooled earlier osteoporosis treatment studies.

Cumulative Incidence of Patients with Hip and Wrist Fractures

FIT
(Vertebral Fracture Study)



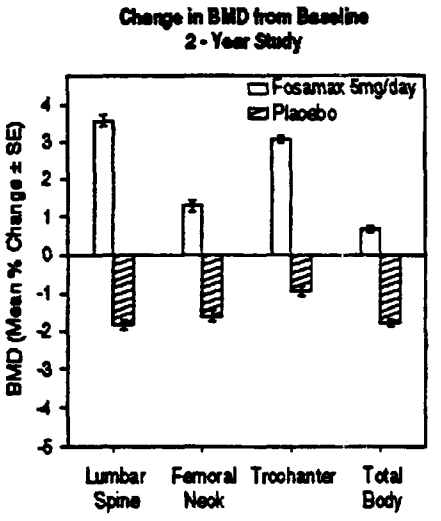
Overall, these results demonstrate the efficacy of FOSAMAX to reduce the incidence of fractures at the spine, hip and wrist, which are the three most common sites of osteoporotic fracture.

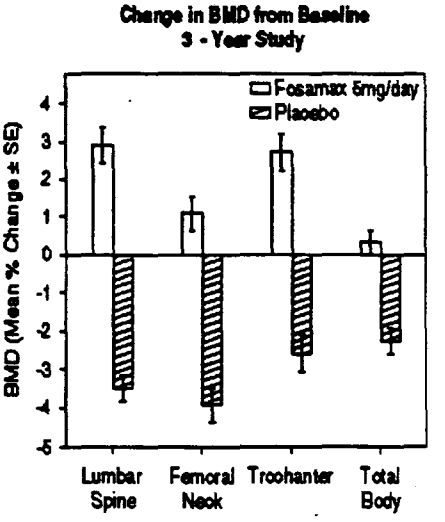
Bone histology

Bone histology in 270 postmenopausal patients with osteoporosis treated with FOSAMAX at doses ranging from 1 to 20 mg/day for one, two, or three years revealed normal mineralization and structure, as well as the expected decrease in bone turnover relative to placebo. These data, together with the normal bone histology and increased bone strength observed in rats and baboons exposed to long-term alendronate treatment, support the conclusion that bone formed during therapy with FOSAMAX is of normal quality.

Prevention of osteoporosis in postmenopausal women

Prevention of bone loss was demonstrated in two double-blind, placebo-controlled studies of postmenopausal women 40-60 years of age. One thousand six hundred nine patients (FOSAMAX 5 mg/day; n = 498) who were at least six months postmenopausal were entered into a two-year study without regard to their baseline BMD. In the other study, 447 patients (FOSAMAX 5 mg/day; n = 88), who were between six months and three years postmenopause, were treated for up to three years. In the placebo-treated patients BMD losses of approximately 1% per year were seen at the spine, hip (femoral neck and trochanter) and total body. In contrast, FOSAMAX 5 mg/day prevented bone loss in the majority of patients and induced significant increases in mean bone mass at each of these sites (see figures below). In addition, FOSAMAX 5 mg/day reduced the rate of bone loss at the forearm by approximately half relative to placebo. FOSAMAX 5 mg/day was similarly effective in this population regardless of age, time since menopause, race and baseline rate of bone turnover.

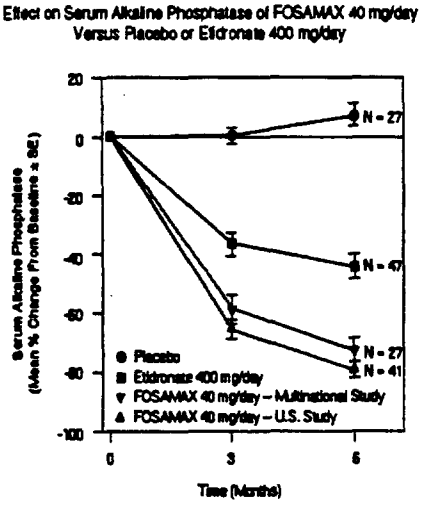




Bone histology was normal in the 28 patients biopsied at the end of three years who received FOSAMAX at doses of up to 10 mg/day.

Paget's disease of bone

The efficacy of FOSAMAX 40 mg once daily for six months was demonstrated in two double-blind clinical studies of male and female patients with moderate to severe Paget's disease (alkaline phosphatase at least twice the upper limit of normal): a placebo-controlled multinational study and a U.S. comparative study with etidronate disodium 400 mg/day. The following figure shows the mean percent changes from baseline in serum alkaline phosphatase for up to six months of randomized treatment.



At six months the suppression in alkaline phosphatase in patients treated with FOSAMAX was significantly greater than that achieved with etidronate and contrasted with the complete lack of response in placebo-treated patients. Response (defined as either normalization of serum alkaline phosphatase or

decrease from baseline ≥60%) occurred in approximately 85% of patients treated with FOSAMAX in the combined studies vs. 30% in the etidronate group and 0% in the placebo group. FOSAMAX was similarly effective irrespective of age, gender, race, prior use of other bisphosphonates, or baseline alkaline phosphatase within the range studied (at least twice the upper limit of normal).

Bone histology was evaluated in 33 patients with Paget's disease treated with FOSAMAX 40 mg/day for 6 months. As in patients treated for osteoporosis (see *Clinical Studies, Treatment of osteoporosis in postmenopausal women, Bone histology*), FOSAMAX did not impair mineralization, and the expected decrease in the rate of bone turnover was observed. Normal lamellar bone was produced during treatment with FOSAMAX, even where preexisting bone was woven and disorganized. Overall, bone histology data support the conclusion that bone formed during treatment with FOSAMAX is of normal quality.

ANIMAL PHARMACOLOGY

The relative inhibitory activities on bone resorption and mineralization of alendronate and etidronate were compared in the Schenk assay, which is based on histological examination of the epiphyses of growing rats. In this assay, the lowest dose of alendronate that interfered with bone mineralization (leading to osteomalacia) was 6000-fold the antiresorptive dose. The corresponding ratio for etidronate was one to one. These data suggest that alendronate administered in therapeutic doses is highly unlikely to induce osteomalacia.

INDICATIONS AND USAGE

FOSAMAX is indicated for the treatment and prevention of osteoporosis in postmenopausal women.

- For the treatment of osteoporosis, FOSAMAX increases bone mass and prevents fractures, including those of the hip, wrist, and spine (vertebral compression fractures). Osteoporosis may be confirmed by the finding of low bone mass (for example, at least 2 standard deviations below the premenopausal mean) or by the presence or history of osteoporotic fracture. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics*.)

- For the prevention of osteoporosis, FOSAMAX may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of future fracture.

  Bone loss is particularly rapid in postmenopausal women younger than age 60. Risk factors often associated with the development of postmenopausal osteoporosis include early menopause; moderately low bone mass (for example, at least 1 standard deviation below the mean for healthy young adult women); thin body build; Caucasian or Asian race; and family history of osteoporosis. The presence of such risk factors may be important when considering the use of FOSAMAX for prevention of osteoporosis.

FOSAMAX is indicated for the treatment of Paget's disease of bone.

- Treatment is indicated in patients with Paget's disease of bone having alkaline phosphatase at least two times the upper limit of normal, or those who are symptomatic, or those at risk for future complications from their disease.

CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 minutes
- Hypersensitivity to any component of this product
- Hypocalcemia (see PRECAUTIONS, *General*)

WARNINGS

FOSAMAX, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa.

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding, have been reported in patients receiving treatment with FOSAMAX. In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue FOSAMAX and seek medical attention if they develop dysphagia, odynophagia or retrosternal pain.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking FOSAMAX and/or who fail to swallow it with a full glass (6-8 oz) of water, and/or who continue to take FOSAMAX after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see DOSAGE AND ADMINISTRATION). In patients who cannot comply with dosing instructions due to mental disability, therapy with FOSAMAX should be used under appropriate supervision.

Because of possible irritant effects of FOSAMAX on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when FOSAMAX is given to patients with active upper gastrointestinal problems, (such as dysphagia, esophageal diseases, gastritis, duodenitis, or ulcers).

PRECAUTIONS

General

There have been rare (post-marketing) reports of gastric and duodenal ulcers, some severe and with complications, although no increased risk was observed in pre-marketing clinical trials.

FOSAMAX is not recommended for patients with renal insufficiency (creatinine clearance <35 mL/min). (See DOSAGE AND ADMINISTRATION.)

Causes of osteoporosis other than estrogen deficiency and aging should be considered.

Hypocalcemia must be corrected before initiating therapy with FOSAMAX (see CONTRAINDICATIONS). Other disturbances of mineral metabolism (such as vitamin D deficiency) should also be effectively treated. Presumably due to the effects of FOSAMAX on increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients with Paget's disease, in whom the pretreatment rate of bone turnover may be greatly elevated. Adequate calcium and vitamin D intake should be ensured to provide for these enhanced needs.

Information for Patients

Patients should be instructed that the expected benefits of FOSAMAX may only be obtained when each tablet is swallowed with plain water the first thing upon arising for the day at least 30 minutes before the first food, beverage, or medication of the day. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of FOSAMAX (see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Absorption*).

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation patients should be instructed to swallow FOSAMAX with a full glass of water (6-8 oz) and not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take FOSAMAX at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they develop

symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking FOSAMAX and consult their physician.

Patients should be instructed to take supplemental calcium and vitamin D, if daily dietary intake is inadequate. Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as excessive cigarette smoking, and/or alcohol consumption, if these factors exist.

Physicians should instruct their patients to read the patient package insert before starting therapy with FOSAMAX and to reread it each time the prescription is renewed.

Drug Interactions (also see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Drug Interactions*)

Estrogen

The safety and effectiveness of the concomitant use of hormone replacement therapy and FOSAMAX in postmenopausal women has not been established.

Calcium Supplements/Antacids

It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of FOSAMAX. Therefore, patients must wait at least one-half hour after taking FOSAMAX before taking any other drug.

Aspirin

In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving concomitant therapy with doses of FOSAMAX greater than 10 mg/day and aspirin-containing compounds.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

FOSAMAX may be administered to patients taking NSAIDs. In a 3-year, controlled, clinical study (n=2027) during which a majority of patients received concomitant NSAIDs, the incidence of upper gastrointestinal adverse events was similar in patients taking FOSAMAX 5 or 10 mg compared to those taking placebo. However, since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with FOSAMAX.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Harderian gland (a retro-orbital gland not present in humans) adenomas were increased in high-dose female mice (p=0.003) in a 92-week carcinogenicity study at doses of alendronate of 1, 3, and 10 mg/kg/day (males) or 1, 2, and 5 mg/kg/day (females). These doses are equivalent to 0.5 to 4 times the 10 mg human dose based on surface area, mg/m^2.

Parafollicular cell (thyroid) adenomas were increased in high-dose male rats (p=0.003) in a 2-year carcinogenicity study at doses of 1 and 3.75 mg/kg body weight. These doses are equivalent to 1 and 3 times the 10 mg human dose based on surface area.

Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation, in an *in vitro* mammalian cell mutagenesis assay, in an *in vitro* alkaline elution assay in rat hepatocytes, and in an *in vivo* chromosomal aberration assay in mice. In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate was weakly positive at concentrations ≥5 mM in the presence of cytotoxicity.

Alendronate had no effect on fertility (male or female) in rats at oral doses up to 5 mg/kg/day (four times the 10 mg human dose based on surface area).

Pregnancy

Pregnancy Category C:

Reproduction studies in rats showed decreased postimplantation survival at 2 mg/kg/day and decreased body weight gain in normal pups at 1 mg/kg/day. Sites of incomplete fetal ossification were statistically significantly increased in rats beginning at 10 mg/kg/day in vertebral (cervical, thoracic, and lumbar), skull, and sternebral bones. The above doses ranged from 1 times (1 mg/kg) to 9 times (10 mg/kg) the 10 mg human dose based on surface area, mg/m^2. No similar fetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (50 times the 10 mg human dose based on surface area, mg/m^2).

Both total and ionized calcium decreased in pregnant rats at 15 mg/kg/day (13 times the 10 mg human dose based on surface area) resulting in delays and failures of delivery. Protracted parturition due to maternal hypocalcemia occurred in rats at doses as low as 0.5 mg/kg/day (0.5 times the recommended human dose) when rats were treated from before mating through gestation. Maternotoxicity (late pregnancy deaths) occurred in the female rats treated with 15 mg/kg/day for varying periods of time ranging from treatment only during pre-mating to treatment only during early, middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment. Calcium supplementation either in the drinking water or by minipump could not ameliorate the hypocalcemia or prevent maternal and neonatal deaths due to delays in delivery; calcium supplementation IV prevented maternal, but not fetal deaths.

There are no studies in pregnant women. FOSAMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers

It is not known whether alendronate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FOSAMAX is administered to nursing women.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in the Elderly

Of the patients receiving FOSAMAX in the two large osteoporosis treatment studies and Paget's disease studies (see CLINICAL PHARMACOLOGY, *Clinical Studies*), 45% and 70%, respectively, were 65 years of age or over. No overall differences in efficacy or safety were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

Use in Men

Safety and effectiveness in male osteoporosis have not been established.

ADVERSE REACTIONS

Clinical Studies

In clinical studies adverse experiences associated with FOSAMAX usually were mild, and generally did not require discontinuation of therapy.

FOSAMAX has been evaluated for safety in approximately 3800 postmenopausal women in clinical studies.

Treatment of osteoporosis

In two large, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational), discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with FOSAMAX 10 mg/day and 6.0% of 397 patients treated with placebo. Adverse experiences reported by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either FOSAMAX 10 mg/day or placebo are presented in the following table.

Drug-Related** Adverse Experiences Reported in ≥1% of Patients	FOSAMAX 10 mg/day % (n = 196)	Placebo % (n = 397)
Gastrointestinal		
abdominal pain	6.6	4.8
nausea	3.6	4.0
dyspepsia	3.6	3.5
constipation	3.1	1.8
diarrhea	3.1	1.8
flatulence	2.6	0.5
acid regurgitation	2.0	4.3
esophageal ulcer	1.5	0.0
vomiting	1.0	1.5
dysphagia	1.0	0.0
abdominal distention	1.0	0.8
gastritis	0.5	1.3
Musculoskeletal		
musculoskeletal (bone, muscle or joint) pain	4.1	2.5
muscle cramp	0.0	1.0
Nervous System/Psychiatric		
headache	2.6	1.5
dizziness	0.0	1.0
Special Senses		
taste perversion	0.5	1.0

**Considered possibly, probably, or definitely drug related as assessed by the investigators

Rarely, rash and erythema have occurred.

One patient treated with FOSAMAX (10 mg/day), who had a history of peptic ulcer disease and gastrectomy and who was taking concomitant aspirin developed an anastomotic ulcer with mild hemorrhage, which was considered drug related. Aspirin and FOSAMAX were discontinued and the patient recovered.

The adverse experience profile was similar for the 401 patients treated with either 5 or 20 mg doses of FOSAMAX in the United States and Multinational studies.

In the Vertebral Fracture Study of the Fracture Intervention Trial, discontinuation of therapy due to any clinical adverse experience occurred in 7.6% of 1022 patients treated with FOSAMAX 5 mg/day for 2 years and 10 mg/day for the third year and 9.4% of 1005 patients treated with placebo. Similarly, discontinuations due to upper gastrointestinal adverse experiences were comparable: FOSAMAX, 2.6%; placebo, 2.6%. The overall adverse experience profile was similar to that seen in other studies with FOSAMAX 5 or 10 mg/day.

Prevention of osteoporosis

The safety of FOSAMAX in postmenopausal women 40-60 years of age has been evaluated in three double-blind, placebo-controlled studies involving over 1,400 patients randomized to receive FOSAMAX for either two or three years. In these studies the overall safety profiles of FOSAMAX 5 mg/day and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 7.5% of 642 patients treated with FOSAMAX 5 mg/day and 5.7% of 648 patients treated with placebo. The adverse experiences reported by the investigators as possibly, probably or definitely drug related in ≥1% of patients treated with either FOSAMAX 5 mg/day or placebo are presented in the following table.

Drug-Related** Adverse Experiences Reported in ≥ 1% of Patients

	FOSAMAX 5 mg/day % (n = 642)	Placebo % (n = 648)
Gastrointestinal		
abdominal pain	1.7	3.4
acid regurgitation	1.4	2.5
diarrhea	1.1	1.7
dyspepsia	1.9	1.7
nausea	1.4	1.4

**Considered possibly, probably, or definitely drug related as assessed by the investigators.

Paget's disease of bone

In clinical studies (osteoporosis and Paget's disease), adverse experiences reported in 175 patients taking FOSAMAX 40 mg/day for 3-12 months were similar to those in postmenopausal women treated with FOSAMAX 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking FOSAMAX 40 mg/day (17.7% FOSAMAX vs. 10.2% placebo). One case of esophagitis and two cases of gastritis resulted in discontinuation of treatment.

Additionally, musculoskeletal (bone, muscle or joint) pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was reported by the investigators as possibly, probably, or definitely drug related in approximately 6% of patients treated with FOSAMAX 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with FOSAMAX 40 mg/day and 2.4% of patients treated with placebo.

Laboratory Test Findings

In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking FOSAMAX versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dL (2.0 mM) and serum phosphate to ≤2.0 mg/dL (0.65 mM) were similar in both treatment groups.

Post-Marketing Experience

The following adverse reactions have been reported in post-marketing use:

Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema.

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers and oropharyngeal ulceration. Rarely, gastric or duodenal ulcers, some severe and with complications have been reported (see

WARNINGS, PRECAUTIONS, *General* and *Information for Patients,* and DOSAGE AND ADMINISTRATION).

OVERDOSAGE

Significant lethality after single oral doses was seen in female rats and mice at 552 mg/kg (3256 mg/m^2) and 966 mg/kg (2898 mg/m^2), respectively. In males, these values were slightly higher, 626 and 1280 mg/kg, respectively. There was no lethality in dogs at oral doses up to 200 mg/kg (4000 mg/m^2).

No specific information is available on the treatment of overdosage with FOSAMAX. Hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, heartburn, esophagitis, gastritis, or ulcer, may result from oral overdosage. Milk or antacids should be given to bind alendronate. Due to the risk of esophageal irritation, vomiting should not be induced and the patient should remain fully upright.

Dialysis would not be beneficial.

DOSAGE AND ADMINISTRATION

FOSAMAX must be taken *at least* one-half hour before the first food, beverage, or medication of the day with plain water only (see PRECAUTIONS, *Information for Patients*). Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of FOSAMAX (see PRECAUTIONS, *Drug Interactions*). Waiting less than 30 minutes, or taking FOSAMAX with food, beverages (other than plain water) or other medications will lessen the effect of FOSAMAX by decreasing its absorption into the body.

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, FOSAMAX should only be swallowed upon arising for the day with a full glass of water (6-8 oz) and patients should not lie down for at least 30 minutes and until after their first food of the day. FOSAMAX should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of esophageal adverse experiences (see WARNINGS).

Patients should receive supplemental calcium and vitamin D, if dietary intake is inadequate (see PRECAUTIONS, *General*).

No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). FOSAMAX is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 mL/min) due to lack of experience.

Treatment of osteoporosis in postmenopausal women (see INDICATIONS AND USAGE)

The recommended dosage is 10 mg once a day.

Prevention of osteoporosis in postmenopausal women (see INDICATIONS AND USAGE)

The recommended dosage is 5 mg once a day.

Safety of treatment or prevention of osteoporosis with FOSAMAX for longer than four years has not been studied; extension studies are ongoing.

Paget's disease of bone

The recommended treatment regimen is 40 mg once a day for six months.

Retreatment of Paget's disease

In clinical studies in which patients were followed every six months, relapses during the 12 months following therapy occurred in 9% (3 out of 32) of patients who responded to treatment with FOSAMAX. Specific retreatment data are not available, although responses to FOSAMAX were similar in patients who had received prior bisphosphonate therapy and those who had not. Retreatment with FOSAMAX may be considered, following a six-month post-treatment evaluation period in patients who have relapsed, based on increases in serum alkaline phosphatase, which should be measured periodically. Retreatment may also be considered in those who failed to normalize their serum alkaline phosphatase.

HOW SUPPLIED

No. 3759 — Tablets FOSAMAX, 5 mg, are white, round, uncoated tablets with an outline of a bone image on one side and code MRK 925 on the other. They are supplied as follows:

NDC 0006-0925-31 unit-of-use bottles of 30

NDC 0006-0925-58 unit-of-use bottles of 100.

No. 3600 — Tablets FOSAMAX, 10 mg, are white, round, uncoated tablets with a bone image and code MRK 936 on one side and a bone image and FOSAMAX on the other. They are supplied as follows:

NDC 0006-0936-31 unit-of-use bottles of 30
(6505-01-424-1106, 10 mg 30's)
NDC 0006-0936-58 unit-of-use bottles of 100
NDC 0006-0936-28 unit dose packages of 100
(6505-01-424-1113, 10 mg 100's)
NDC 0006-0936-82 bottles of 1000.

No. 3592 — Tablets FOSAMAX, 40 mg, are white triangular-shaped, uncoated tablets with code MRK 212 on one side and FOSAMAX on the other. They are supplied as follows:

NDC 0006-0212-31 unit-of-use bottles of 30
(6505-01-424-1111, 40 mg 30's).

Storage

Store in a well-closed container at room temperature, 15-30°C (59-86°F).

Dist. by:
MERCK & CO., INC., West Point, PA 19486, USA

Issued ~~November 1996~~
Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-560/S03/S06

MEDICAL REVIEW(S)

FEB 27 1997

NDA 20560,S003
Alendronate (Fosamax)

Merck Research Laboratories
Comments written February 25, 1997

Team Leader's Comments on NDA Supplement

This supplement provides for labeling to indicate that prophylactic use of alendronate to prevent bone loss by BMD is safe and effective. This drug is approved for treatment of established osteoporosis, and a supplement has been received indicating that the BMD increase that was the basis of that approval is associated with a reduction in fracture rate in the population with very low bone density and/or with osteoporotic fracture.

Supplement 003 reports three studies conducted in women who do not have established osteoporosis, intended to show that BMD is conserved by doses of alendronate of 2.5, 5, or 10 mg daily. All of these studies were randomized and double blind and were conducted in postmenopausal women with established osteoporosis. In all of them, the primary endpoint was BMD of the lumbar spine, and the secondary endpoint was BMD of the hip and total body.

The data are persuasive that alendronate at any of the studied doses can prevent significant bone loss in a majority of women during the early postmenopausal period when bone loss is usually substantial. The application should be approved, but it is still important to see if it is possible to say in labeling who is going to benefit substantially from drug administration. The advisory committee seemed to be very interested in having as liberal a definition of the target population as possible with the idea that individual patient decisions be made by patients and their physicians. I believe they would like to have 2.5 mg (Merck suggests only 5 mg) available for the patients who are borderline in their need for therapy, who manifest some intolerance, or who otherwise might be treated with a low dose.

Study 029: 36 month treatment with placebo, 1, 5, or 10 mg daily or 24 mo treatment with 20 mg followed by 12 month placebo.

Study 038: Table shows BMD change to month 24 even though treatment was stopped at 6 mo.

Study 055: An estrogen/progestin arm was included. The two strata (based on blinding and type of estrogen and progesterone used) were combined in the table.

Populations in table are intention to treat. Ns are given for entered and completed subjects separated by / in some studies. Changes in BMD from baseline and % responders are given first followed by &, then the difference between drug and placebo. The change in BMD for hip is given for femoral neck and total hip separated by / in some studies. Per cent of responders is the percent with better response than -2% change from baseline.

Dose mg/d	Dura-tion	Ns enter/ complet	% Change in BMD		%patient ≤ 2% BMD
			spine &-P	hip neck/total&-P	
Study #029					
Placebo	36 mo	90/63	-3.5 ---	-4.0/-3.1 -------	37 ---
1 mg		92/66	-1.2 &2.3	-1.7/-1 & 2.3/2.1	61 & 24
5 mg		88/63	+2.9 &6.4	+1.1/+1 & 5.1/4.1	89 & 52
10 mg		88/62	+4 & 7.5	+2.3/+2.3&6.3/5.4	96 & 59
20 mg	24 mo	89/57	+4.4 &7.9	+1.9/+1.8&5.9/4.9	95 & 58
Study #038					
Placebo	24 mo	56/38	-1.5 ----	-0.4 & ------	
5 mg	6 mo	59/38	-1.5 & 0	-1.0 & -0.6	
5 mg	24 mo	56/43	+2.0 &3.5	+0.4 & 0.8	
10 mg	6 mo	69/40	+0.5 & 2	-0.9 & -0.5	
10 mg	24 mo	61/44	+4.4 &5.9	+1.3 & 1.7	
Study #055					
Placebo	24 mo	502	-1.8 ----	-1.6/-1.4 & -----	54 -----
2.5 mg		499	2.3 & 4.1	0.8/1.1 & 2.4/2.5	90 & 36
5 mg		498	3.5 & 5.3	1.3/1.9 & 2.9/3.3	95 & 41
E/P Er		49	5.1 & 6.9	3.2 & 4.8	
E/P US		53	4.0 & 5.8	1.8 & 3.4	

Safety is good, with only rare serious, drug-related GI AEs.

Recommendation: Drug is approvable with need for label changes.

Gloria Troendle/2-26-97

cc Orig NDA
Div File
HFD-510/GTroendle
HFD-340

FEB 5 1997

1.Title and General Information

1.1 Title/Heading- Medical Officer's Review

1.1.1 NDA # 20-560
Supplement S-003
1.1.2 Submission date- April 29, 1996
1.1.3 Review completed- January 15, 1997.

1.2 Drug Name

1.2.1 Generic- Alendronate sodium tablets
1.2.2 Trade name-Fosamax
1.2.3 Chemical name-(4-amino-1-hydroxybutylidene) bisphosphonic acid, monosodium salt, trihydrate

1.3 **Sponsor** Merck Research Laboratories
P.O.Box 4, BLA-20
West Point, PA 19486-0004
Attention-Bonnie J.Goldman, M.D.
Executive Director
Reg. Affairs

1.4 Pharmacologic category- Antiresorptive agent
1.5 **Proposed Indication**-
"Prevention of osteoporosis in postmenopausal women

Progressive bone loss occurs following menopause and commonly leads to osteoporosis. Prevention (5 mg dose) should be considered in all postmenopausal women, especially those under age 60 years, who do not have osteoporosis and for whom the desired clinical outcome is to maintain bone mass."

1.6 Dosage form and route of administration- 5 mg tablets for p.o. use. Fosamax, 10 mg tablets are available for the treatment of postmenopausal osteoporosis, an approved indication.

1.7 NDA drug classification- Standard (S)
1.8 Important related drugs-

Approved for the treatment of Paget's disease of bone- Etidronate (p.o.), pamidronate (i.v) and alendronate (p.o.).

Approved for the treatment of postmenopausal osteoporosis- Alendronate sodium tablets.

1.9 Related reviews- Pharmacology, Chemistry, Biopharm., and Statistical reviews.

2. **Table of Contents**

3. **Material Reviewed:** This supplemental submission consists of a total of 122 volumes. Materials reviewed are summarized in Table 1.

Table 1. Materials covered in the review.

	Description of Materials	Volume(s)
1.	Application Synopsis/Ref.	1
2.	Nonclinical Data	7
3.	Clinical Background Inf.	8-9
4.	Clinical Pharm.	8
5.	Efficacy and safety Data	8-26
6.	Selected Statistical Data	27
7.	Selected CRF Tabulations	36-104
8.	Selected CRF	104-122

4. **Chemistry and Manufacturing Controls:** This is an approved drug for the treatment of postmenopausal osteoporosis (PMO) indication. For the proposed indication, a 5 mg tablet of Fosamax will be taken p.o., daily. See Chemistry review for comments.

5. **Pharmacology**: Sponsor has submitted some additional preclinical data in this submission. See Pharmacology review for comments on additional new data.

6. **Clinical Background**

6.1 Relevant human experience-

Osteoporosis is a major public health problem in the

U.S.A. Extensive literature reports exist with regard to its epidemiology (including fractures), diagnosis, prophylaxis, and treatment.

The proposed indication of Fosamax is for the prevention of PMO. Fosamax is a bisphosphonate and bisphosphonates are known to inhibit bone resorption *in vitro and in vivo*. These drugs are being investigated in the treatment of diseases characterized by increased bone resorption, (e.g., Paget's disease of bone, hypercalcemia of malignancy, skeletal metastases in malignancy, and **osteoporosis)**. These drugs have the potential for use as an alternative oral agent for the prevention of PMO.

Fosamax was recently approved for the treatment of PMO, i.e., for patients with established osteoporosis. Except for estrogens, currently there is no other approved treatment regimen available for the prevention of PMO. A large volume of literature reports exist on the therapeutic efficacy and safety of bisphosphonates in the treatment of metabolic bone diseases, including PMO.

Approved estrogen preparations for the prevention of PMO include conj. estrogen (Premarin), estradiol transdermal, estradiol tablets, and estropipate tablets. Estrogen is an antiresorptive agent also. Estrogen therapy has demonstrated decreased rate of bone loss in estrogen-deficient women. However, there are limited reports on the ability of estrogen therapy to achieve any net gain in bone mass. Because of the potential association of long-term estrogen therapy and increased risk of breast and endometrial cancer, a large percentage of postmenopausal women avoid estrogen therapy. Therefore, a nonhormonal antiresorptive agent would be desirable for the prevention of PMO. Estrogen therapy is likely to be beneficial in hysterectomized women and for those with high risk for developing coronary heart disease.

In addition to Fosamax, salmon calcitonin formulations (Calcimar injection and Miacalcin nasal spray) are also approved for the treatment of PMO. Their efficacy and safety data are well documented in the literature.

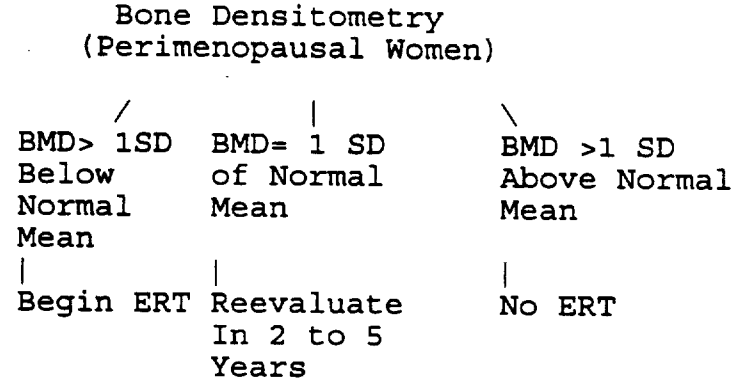
Since Fosamax is an approved drug for the treatment of PMO, literature reports relevant to prevention of PMO will be reviewed briefly.

1. Riggs BL, and Melton LJ(1992). The prevention and

treatment of osteoporosis. NEJM 327 (9):620-7.

This is a review article in which the authors have suggested that preventive pharmacologic intervention should be taken in patients with "low or relatively low bone density." Because of exponential increase in the incidence of fractures in old age, a treatment regimen that will slightly decrease the rate of bone loss may reduce the risk of fractures. At this time, estrogen replacement therapy (ERT) is the only treatment regimen approved for the prevention of PMO. BMD measurements may help to identify women at high risk of developing fractures. Combined measurements of BMD and biochemical markers of bone turnover (e.g., serum osteocalcin and urinary excretion of pyridinium crosslinks) may have more predictive value in identifying increased risk of fractures.

Most of the information available regarding preventive therapy of PMO, are related to the use of ERT. The authors have presented an algorithm(*) for initiating ERT for the prevention of PMO even though the optimum BMD threshold for such treatment has yet to be determined:



* Based on reports by Jhonston et al (1991) NEJM 324:1105-9.

Authors have recommended estrogen therapy for postmenopausal women (up to the age of 75 years) who have vertebral BMD values 1 SD or more below the age-adjusted normal mean.

2.Cooper C and Melton JL. Epidemiology of osteoporosis (1992). Trends Endocrinol. Metab. 3:224-29.

A review article in which preventive strategies for the risk of falls have been discussed.

Based on the results of many epidemiological studies, it is now generally recognized that most fractures in elderly men and women are partly due to low bone mass, which appears to be the best single predictor of future fractures in elderly subjects.

Bone loss is attributed to the aging process, the menopause, and risk factors such as lifestyle characteristics, thin stature, use of certain drugs, and other disease conditions (e.g.,Cushing's disease, thyrotoxicosis, rheumatoid arthritis, etc.)

Vertebral fractures are often regarded synonymous with the diagnosis of PMO. Based on objective morphometric evaluation of vertebral fractures, the prevalence rate of vertebral fractures "among women rises from 3% at age 50-54 years to 40% at 85-89 years." However, more than 60% of vertebral fractures in the general population remain "undetected." The medical and social consequences of osteoporosis-related fractures are of great importance.

Falls/trauma have been reported to play some role in the pathogenesis of osteoporotic fractures. The mechanics of falling and fractures are not fully understood.

The authors have discussed possible prevention strategies in the general population. Two general strategies were identified:

a. High-risk approach, and b) population-based approach.

High-risk approach- This involves use of pharmacologic interventions in individuals who are at high risk of developing fractures as determined by "some short of screening investigation." Currently, a single measurement of bone density coupled with measurement of resorption marker(s) appear to be the most rational way to determine the risk of fractures. This assessment should be performed at time of menopause and if the BMD falls below a certain cutoff value, ERT should be started. Initiation of ERT soon after menopause has been reported in the literature as the most effective way to prevent further bone loss, but the risk/benefit ratio needs to be evaluated for each subject. The authors have cautioned that from a social point of view, targeting of ERT based on BMD measurement alone may be inappropriate. The use of estrogens based on high-risk approach may not be desirable in this subset of the population.

The population-based approach- This approach covers increased daily intake of calcium and improved physical activity. There is little evidence in support of this approach to achieve reduction in fracture incidence.

3. Cummings et al (1985). Epidemiol rev. 7:178-208.

The authors have reviewed the advantages and disadvantages of estrogens, calcium and physical exercise, and thiazide diuretics as prophylactic measures in preventing bone loss and fractures. It is estimated that between 1985 and 2050, the proportion of persons over age 85 will increase from 1% to 5%, and the number of hip fractures is likely to be increased many fold by the year 2050.

4. Cummings et al (1990). The future of hip fractures in the United States: numbers, costs, and potential effects of postmenopausal estrogen. Clin. Orthop. 252: 163-5.

In this epidemiologic report, the potential effect of widespread use of estrogens on the future number of hip fractures has been studied.

The authors have utilized data from 1974-1979 National Hospital Discharge Survey in calculating age-specific incidence rate for hip fractures. The following assumptions were made in order to assess the potential effects of ERT on hip fracture: i) ERT will start at age 50 in 50% or 100 % of the cohort and ii) long-term (probably life-long) use of ERT will reduce the risk of hip fracture by 50%. However, considering increased life expectancy following long-term ERT, the risk of hip fracture may be increased in this target population. The projected number of hip fractures among white women age 50 years and older is going to be increased by years 2020-2040. For controlling the increasing numbers of hip fractures in postmenopausal women, effective prevention measures (including interventions to decrease falls) need to be developed. This report also stresses the need for developing interventions that could be applied to non-white women and men also.

5. Melton et al (1992). Perspective: How many women have osteoporosis. JBMR 7: 1005-10.

In this report the authors have attempted to relate the data on bone losses in women to the occurrence of fractures. Using several statistical methods the

lifetime risks of proximal femur, vertebrae, and distal forearm fractures were estimated. The report suggests that about 425,000 of 1,070,000 white women who will reach menopause annually in the U.S., will be affected.

Of the various factors (i.e., bone mass, architectural arrangement, abnormal bone matrix, presence of stress fractures) that affect bone fragility, bone mineral measurement is the only one that can be objectively assessed in vivo. Numerous epidemiological studies have shown that fracture incidence for proximal femur, lumbar vertebrae, and distal forearm increases with declining BMD/BMC at those sites. Thus, it is necessary to identify a specific level of bone mineral content at which the bone loss can be considered pathologic. The report stresses the importance of developing measures to decrease the high risk of fractures in postmenopausal women with osteopenia. Osteopenia has been defined on the basis of 2 SD below the mean BMD of normal young women.

6. Law et al (1991). Strategies for prevention of osteoporosis and hip fracture. BMJ 303: 453-9.

A review article in which the authors have mainly discussed the strategies for prevention of osteoporosis and hip fracture. Prospective studies of bone densities and hip fracture have not been carried out long enough to determine the BMD value at menopause for the prediction of future hip fracture. The report states that there is no scientific case for routine BMD screening.

Strategies that help to reduce the loss of bone mass include preventive therapeutic interventions (e.g., ERT/HRT), regular exercise, and cessation of smoking. These preventive measures could be directed toward the general population or targeted to postmenopausal women.

7. Chapuy et al (1995). Prevention and treatment of osteoporosis. Aging Clin. Exp. Res. 7: 164-73.

A review article in which clinical perspectives of investigational and currently available pharmacologic regimens for osteoporosis have been discussed.

With the advent of precise and accurate methods for detection of bone mineral density (BMD) it is relatively easy to detect the risk of osteoporosis and fractures. Diagnosis of osteoporosis (before fractures) can now be made based on criteria recommended by a study group of the WHO. Such patients are those with

BMD or bone mineral content (BMC) value more than 1 SD below the young adult mean (T score) but less than 2.5 SD below this value, at any site (spine, hip, or radius).

Studies have shown that a slower rate of bone loss persists in elderly women after the rapid loss following the onset of menopause. Changes in the hip BMD and biochemical indices of bone turnover support such a concept. Prevention appears to be the best mode of treatment since it is difficult to restore bone mass and "disrupted" trabecular architecture after the first fracture. The authors advocate preventive therapy over treatment at any age.

"Whole-life" prevention strategy- Directed toward improving peak bone mass at maturity by exercise, calcium supplementation, avoidance of smoking and alcohol consumption, and correction of estrogen deficient states.

Prevention strategy at menopause- Directed toward decreasing the accelerated rate of bone mass at onset of menopause. Benefits of ERT/HRT as a preventive measure are now well documented in the literature. Recent reports have shown ERT/HRT as being "extremely effective in treating older women (more than 65 years of age)."

With respect to benefits of non-hormonal agents (calcium and bisphosphonates) for prevention, their effects on the fracture rate have not been prospectively demonstrated. Considering the magnitude of the public health problem associated with postmenopausal osteoporosis, attention should be focussed on its prevention with pharmacological interventions.

Reviewer's comments: The above-mentioned 7 reports appear to be relevant to the benefits of preventing in postmenopausal osteoporosis.

All of these reports first addressed the relationship between progressive loss of bone mass (attributable to estrogen deficiency and/or ageing process), and increased risk of subsequent fracture. Several reports indicate bone density as the most important predictor of osteoporotic fractures. Beside loss of bone mass, there are other factors which contribute to increased risk of osteoporotic fractures.

Two of these articles have discussed strategies for the prevention of osteoporotic fractures. The "whole-life"/population-based strategy for prevention is directed toward improving peak bone mass at maturity by calcium supplementation, exercise program, avoidance of smoking or alcohol consumption, and correction of estrogen deficiency.

Chapuy and Meunier suggested that postmenopausal subjects before first fracture could be identified by measuring BMD at any site (spine, hip, radius). These subjects with *low bone mass* (*osteopenia*) were identified on the basis of BMD/BMC cutoff point recommended by a study group of the WHO. Subjects with a BMD/BMC value more than 1 SD below the young adult mean (T score) but less than 2.5 SD below this value.

At the present time, only estrogens are approved for the prevention of PMO. In addition to oral conjugated estrogens and estropipate, transdermal formulations of 17-beta estradiol have demonstrated prevention of early menopausal bone loss. ERT has been shown to be associated with substantial reductions in both vertebral and non-vertebral (including hip) fractures.

Long-term estrogen therapy is known to increase the risk of endometrial and breast cancers. **It is desirable to develop other non-hormonal agents for the prevention of postmenopausal bone loss and subsequent fractures.**

6.2 Important information from related INDs and NDAs

Fosamax (alendronate sodium tablets) was the first bisphosphonate approved for the treatment of PMO.

Adverse events of bisphosphonates as a class of compound include:

- Impairment of renal function
- Inhibition of normal skeletal mineralization
- **Gastrointestinal disturbances**
- Acute Phase reactions (transient pyrexia, myalgia, arthralgias)
- Hypocalcemia, hyperphosphatemia
- Suspected hematologic abnormalities

When given intravenously, large doses of clodronate, etidronate and pamidronate have been reported to cause impairment of renal function including renal failure. This has been attributed to the formation of insoluble aggregates of calcium bisphosphonates. All i.v. infusions should be given slowly (over 2 hours or longer) and in a large volume of fluid (250-500 ml).

Bisphosphonates are taken up by the skeletal system. Etidronate has been reported to induce focal or generalized osteomalacia. Since the bisphosphonates can stay in bone for life, their safety has to be demonstrated in long-term studies.

Previously in clinical trials with oral formulations, a small number of patients were reported to experience mild G-I disturbances (epigastric pain, nausea , vomiting, and diarrhea). Pamidronic acid and other amino-bisphosphonates are known to cause more frequent G-I disturbances. These adverse events have been reported to be dose-related and result from chemical injury of the mucosae of the esophagus and stomach.

In recent years, postmarketing experiences with etidronate and alendronate led to an improved understanding of the adverse events of oral formulations of bisphosphonates. Tolerability of oral formulations of bisphosphonates may be increased if taken with large amounts of plain water and if the subject avoid laying down for at least 30 minutes after administration. Serious esophageal (esophagitis, ulcer, erosion, and perforation) and gastric or duodenal (gastritis, ulcer, bleeding, and perforation) events

have been reported in postmenopausal women with or without proper administration of the drug. Patients with prior history of esophageal or gastric pathological conditions and concurrent administration of NSAIDs are likely to increase the occurrence of G-I adverse events with alendronate.

Additional studies are needed to understand the causal relationship between alendronate and upper G-I adverse events.

6.3 Foreign experience

The sponsor has listed 31 countries where Fosamax has received marketing approval for the treatment of PMO. In 33 additional countries applications are pending for the indication of treatment of PMO. Marketing approval of Fosamax for PMO has not been withdrawn anywhere.

Sponsor states that as of the submission date for this application, it has not filed an application for the prevention of PMO in any other country.

6.4 Human pharmacology, pharmacokinetics and pharmacodynamics

Alendronate is an approved drug for the treatment PMO. This application has no new data to review. Current package insert of alendronate sodium contains relevant information on human pharmacology including pharmacokinetics.

6.5 Relevant background information on meetings and commitments

Only the information relevant to osteoporosis prevention is presented here.

a. Date: 9/14/1990: The sponsor met with the members of the Division and discussed the clinical development program and safety of ALN.

b. Date 12/17/1990: End of Phase II meeting. The objectives of this meeting were to discuss the Phase III programs for metastatic bone disease and osteoporosis indications. The sponsor presented the plans for two controlled studies for the prevention of PMO and stated that at a future date bone loss prevention studies will be discussed in details and prevention claim will be submitted as a supplement to the original NDA.

c. Date 2/11/1992: End of Phase II meeting for osteoporosis prevention. We agreed that,contingent upon 3-year positive data for the treatment of PMO, the protocol for the proposed 2-year study for the prevention would be acceptable. The use of unopposed premarin was considered acceptable as a single estrogen preparation to be used one of these studies.

The Division recommended that BMD be evaluated for one year after the last dose of ALN in all patients for protocol 029. The sponsor responded that this could be done in patients treated at doses of 10 and 20 mg per day. The Division suggested that patients on 5 mg dose should also be followed up for 12 months after termination of treatment.

d. Date 9/14/1992 (correspondence): The sponsor submitted data in support of selecting the dose (5 mg daily) for ALN for the prevention of PMO. The rationale for dose selection were the following:

i) The mean effect of treatment with ALN at 5 mg dose is expected to achieve a modest gain in BMD at one or more sites. This is acceptable provided ALN at this dose is "very safe and well tolerated." Previous clinical experiences with ALN seem to indicate that lower doses, such as 1,2.5, and 10 mg daily were associated with fewer adverse experiences. Modest gain is likely to occur in the majority of treated subjects at this dose.

ii). A 10% or 20% increase in BMD over 6 years, is likely to restore bone mass lost and reduce the risk of future fracture.

iii). At this dose ALN would induce significant reduction in bone turnover as reflected by changes in biochemical markers of bone turnover.

iv. Dose-ranging information obtained from previous studies included: 1) Protocol 026 (Phase IIb treatment study), which provided one-year data on BMD changes, 2) Protocol 029 (Phase IIb prevention study), which provided one-year BMD data, and 3) Protocol 054 (Phase III treatment trial in elderly osteopenic women), which provided 3-month data on BMD, biochemical indices of bone turnover and bone histomorphometry.

The sponsor concluded that it is unlikely that ALN at 1 mg dose level would be an effective dose for

the prevention of PMO. ALN 2.5 and 5 mg dose will be tried in the Early Postmenopausal Intervention Cohort study.

e. June 16,1995: The firm presented background information on the development of ALN for osteoporosis prevention and discussed plans for submission of a supplemental application for this indication. The firm mentioned the submission date of a supplemental application and the possibility of presenting the prevention data before the EMDAC.

October 13, 1995 (General correspondence): The sponsor submitted Data Analysis Plan for three pivotal trials for the prevention of PMO. This plan was reviewed by our statistician.

Reviewer's comments

During the process of development of ALN for use in the prevention of PMO, the sponsor met or corresponded with the Agency on several occasions as stated above. These meetings and communications were very helpful in developing the drug according to our predefined guidelines and to fulfill the regulatory requirements.

6.6 Direction for use:

The direction for administration of 5 mg tablets is the same as for the 10 mg tablets for the approved treatment indication.

In three pivotal clinical trials for the prevention of PMO, alendronate was used at the following doses:

Table 2. Alendronate dose (p.o.) in three pivotal trials.

Protocol #	029	038	055
Doses of ALN	1,5,10,and 20 mg/day	5 and 10 mg/day	2.5 and 5 mg/day
Duration of Treatment	3 Yr	2 Yr	2 Yr

In a Phase IIa study involving subjects similar to prevention studies, ALN administration at doses of 5, 20 and 40 mg daily for 6 weeks led to dose-dependent decreases (28%-48%) in urinary excretion of deoxypyridinoline. Based on these data, ALN was tried

at doses of 5,10,20, and 40 mg daily in a subsequent osteoporosis treatment study. At a dose of 40 mg daily, ALN was found to cause G-I adverse events more frequently. Therefore, ALN doses of 5,10 and 20 mg daily were selected for the prevention studies.

In Study # 29, the sponsor carried out an interim analysis (prespecified) after one year of treatment, and the results indicated that at 5 mg daily dose, ALN caused a moderate increase in bone mass. ALN at 1 and 2 mg daily doses showed suboptimal response in BMD at all sites. Based on the results of this study, 2.5 and 5 mg daily doses were selected for Study # 55. At 5 mg daily dose, bone loss was prevented at spine, total hip, and total body BMD in about 90%, 82% and 73% of treated patients, respectively. Whereas, at 2.5 mg/day dose, prevention of loss of bone mass (at above-mentioned sites) was observed in about 81%,72% and 55% of patients, respectively. The increase in BMD at these sites with 10 mg daily was marginally greater(≈1%) than that observed with a dose of 5 mg/day.

In general, a small percentage of orally administered bisphonates is absorbed from the G-I tract. The presence of food or liquid (other than plain water) interferes with the absorption. Therefore, the timing of dosing of oral bisphosphonates with relation to food or drinking is important. The dosing instruction for the 5 mg dose will be the same as already noted for 10 mg dose which was approved for the treatment indication.

7. Description of Clinical Data Sources

7.1 Study type and Design/Patient Enumeration, Demographics, and Extent of Exposure

Clinical trials with ALN for the prevention of PMO were carried out under sponsor's IND All information (including chemistry, preclinical pharmacology, and clinical) relevant to the use of Fosamax for the treatment indication were contained in the original NDA (# 20-560) submission. The latter submission also contained clinical data for its use in treatment of Paget's disease of bone. The latter indication was also approved at the same time (September 29, 1995) when the osteoporosis indication was approved.

Data derived from two large randomized, double-blind, placebo-controlled studies were submitted in support of the efficacy and safety of Fosamax for the treatment of

PMO. These data were reviewed and presented before the EMDAC on July 13, 1995. The data submitted to original NDA were also supported by published literature.

In this supplemental submission, data from three controlled clinical trials have been included in support of efficacy and safety of ALN for the **prevention of PMO**. Table 3 provides brief descriptions of types of studies, objective, design, number of patients, demographics, doses of ALN and extent of exposure:

Table 3. Brief descriptions of clinical trials.

Protocol No.	#029	#038	#055*
Design	R,D-B,P-C**	R,D-B, P-C	R,D-B,P-C
No. of Pt.randomized	447	291	1609
Age range (Yr)	40-59	40-60	45-59
Yr. since menopause	0.5-3	1-4	≥ 0.5
Sp. BMD at entry (g/Cm2)-Lunar	0.87-1.28	0.87-1.2	T
Sp.BMD at entry-Non-LunarT	0.76-1,12	0.75-1.04	≥ 0.80
Treat. dose/N per Gr.	Placebo/90 ALN 1 mg/92 ALN 5 mg/88 ALN 10 mg/88	Placebo/56 ALN 5 mg/56 ALN 10 mg/61 ALN 10 mg/PBO/59‡	Placebo/502 ALN 2.5 mg/499 ALN 5 mg/498 E/P/110
Duration of treat.(Years)	3	2	2

* This study included an open-label estrogen/progesterone (E/P) parallel subgroup for comparison.

** R,D-B, P.C- Randomized, double-blind, placebo-controlled.

τ Hologic densitomer was used only.

ǂ Fifty percent of ALN treated patients were switched to placebo (for 18 months) after 6 months of treatment.

Reviewer's comments:

As required in our current Osteo-Guidelines, all three studies (Protocols 029,038 and 055) were randomized, double-blind, placebo-controlled. Protocols 029 and 055 provide most of the information on the efficacy of continuous ALN therapy for the prevention of PMO. These two studies randomized about 50 and 500 patients per treatment group, respectively. Protocol 038 randomized about 58 patients per treatment group, and this study was meant to examine the effect of termination of ALN treatment on resolution of BMD and other effects.

Patient populations for the clinical trials were chosen on the basis of entry spinal BMD (g/cm^2) as measured either by Lunar or non-lunar densitometers. All patients with a history of osteoporotic fractures or radiologic evidence of a previous fracture were excluded from the studies. At the time of developing the protocol for the prevention study, the cutoff point for the vertebral BMD was discussed. It was agreed upon that subjects with osteopenia (without fracture); spinal BMD less than 2 SD below the mean for young normal women would be recruited. In Studies 029 and 038, patients with spinal BMD either too low (($\leq$ 0.87 g/cm^2 by Lunar, or $\leq$ 0.75 g/cm^2 by non-Lunar) or too high ($\geq$ 1.28 g/cm^2 by Lunar or $\geq$ 1.2 g/cm2 by non-Lunar) were excluded. In Study 055, about 10% of total patients enrolled, had spinal BMD $\leq$ 0.80 g/cm^2 by Hologic (equivalent to approx.-2.2 SD from normal young women).

In the proposed labeling, the sponsor has mentioned that Fosamax is indicated for all postmenopausal women. If Fosamax is approved for the prevention of osteoporosis, then this issue needs further discussion in order to define a target population at risk of developing osteoporotic fractures.

The primary efficacy endpoint in all three studies was the percent change from baseline in lumbar spine BMD. The secondary efficacy endpoints were similar changes in BMD of the hip (total, femoral neck and trochanteric

region) and total body. Data for BMD changes in forearm were derived from a small subset of subjects. These primary and secondary efficacy endpoints are appropriate for the prevention of PMO. The same endpoints were used to demonstrate its efficacy for the treatment of PMO.

Protocol 038 which was carried out in Italy and it differed from Protocols 029 and 055 in the following ways:

- Four different densitometers (as opposed to two in other studies) were used.
- Different BMD Quality Assurance method was used.
- Large variations in baseline BMD values were noted compared to other two studies.
- Failure to perform BMD measurements particularly in relation to baseline hip scans, as specified in the protocol.

The overall size of the study population (N=2347) for all three studies seems to be adequate

7.2 Post-Marketing Experience

In the original NDA for the treatment of PMO only one nonserious AE was submitted to the agency from the Italian site. Subsequently, in the Safety Update Report, which covered the period from November 1,1994 through March 31, 1995, there were three patients who experienced one serious and three nonserious AEs. These cases were previously reviewed and considered clinically insignificant. From April 1, 1995 through November 30, 1995, one hundred eighty patients were reported to experience 19 serious and 330 nonserious adverse events. These AEs were also reviewed previously.

As of November 30, 1995, information on postmarketing AEs are available from the following countries: Argentina, Brazil, Chile, Costa Rica, Denmark, El salvador, Guatemala, Italy, Mexico, New Zealand, Peru, Panama, South Africa, Sweden, U.K., and U.S.A. In the U.S.A., alendronate 10 mg/day and 40 mg/day was approved for the treatment of osteoporosis and Paget's disease of bone, respectively. In the remaining countries (except for Italy) alendronate 10 mg daily is approved for the same two indications.

Esophageal and gastrointestinal AEs were most common in postmerketing reports which were based on World Adverse

Experience System. Esophageal reactions included esophagitis, esophageal ulcer, reflux esophagitis, and esophageal erosion. Gastric and duodenal AEs included ulcer and bleeding.

On March 20, 1996, representatives from MRL met with our Division and discussed the postmarketing reports of esophageal reactions. Prior to this meeting, MRL decided to communicate to the health professionals regarding dosing instructions and to alert them to the symptoms of esophageal irritation. Both package insert and patient information sheet for the product were revised to emphasize the importance of proper dosing of alendronate for the treatment of PMO and Paget's disease of bone. Currently, the U.S. and world-wide incidence of esophageal AEs are being closely monitored and the sponsor will periodically review the esophageal and gastric AEs in patients treated with alendronate and submit the results to the Agency. The current package insert and patient information sheet reflect recent revisions.

7.3 **Literature:**

The sponsor has provided a long list of published articles, abstracts, and review articles on alendronate. The relevant literature reports will be reviewed briefly.

Passeri et al(1993)reported analgesic effect of alendronate in postmenopausal women. But sponsor's own pilot study showed no apparent pain reduction at a dose of 5 mg p.o.

Rossini et al(1994)reported smaller increase in hip BMD following treatment with alendronate at a dose of 20 mg/day for 6 months. The sponsor has attributed this smaller increase in BMD to the use of alendronate not manufactured by the MRL. A lesser response by the biochemical markers to alendronate seem to support sponsor's explanation.

Apseloff et al(1991) suggested that alendronate treatment may affect bone quality adversely, based on a rat study. Sponsor's own study in rats contradicted the results of the study carried out by Apseloff and his associates.

Several preclinical studies were reported as of November 30, 1995, and the results are consistent with those studies carried out by MRL and reported in the

original NDA.

Information provided in recent clinical reports are mostly consistent with the information submitted to the original NDA submission and the current submission.

8. Clinical Studies

8.1 Reviewer's Traial #-1 Sponsor's Protocol # 029

8.1.1 Objective/Rationale

To determine the safety, tolerability, and effect on BMD of lumbar spine, proximal femur, whole body, and forearm of daily ALN therapy for 2-3 years in recently postmenopausal women. The rationale for use of ALN for the management of PMO is its selective inhibition of increased bone resorption and resultant inhibition of the rate of skeletal turnover. If the formation rate is not inhibited, bone mass will be either preserved or increased (as demonstrated in treatment trials), thereby decreasing the risk of developing osteoporosis and fractures

8.1.2 Design:

Double-blind, placebo-controlled, parallel group study. Such a study is required to demonstrate the safety and efficacy of ALN for the proposed indication.

8.1.3 Protocol

8.1.3.1 Population

Postmenopausal (6 months to 3 years since menopause) women aged 40-59 years old and women (post-hysterectomy) with a clear history postmenopausal symptoms within the last 3 years were recruited for the study. Other inclusion criteria were appropriate.

Subjects with established osteoporosis, as defined by previous a traumatic spine or femur fracture or marked osteopenia (lumbar sp. BMD $\leq$ 0.87 g/cm2 by Lunar DPX, or $\leq$ 0.76 g/cm2 by Hologic QDR

measurement) were excluded from the study. Other exclusion criteria were appropriate for the study.

Reviewer's comments: Subject selection and exclusion for the study were in agreement with our current Osteo-Guidelines.

Procedures- all subjects received dietary calcium supplement of 500 mg of elemental calcium as the carbonate salt. Supplemental calcium tablet was to be taken with food, preferably with the evening meal, or 4 hours before or after taking study medication.

Subjects were not allowed to take other drugs within two weeks of the start of study drug treatment. Subjects were also restricted from taking medications that could influence calcium metabolism. The sponsor has provided a list of concomitant medications. The most concomitant medications (taken by 5% or more subjects in any particular treatment group) are summarized in Table 4 (see also Table 13, vol 10, p.1058)

Table 4. Common concomitant medications

Concomitant Drugs	PBO N=90	ALN 1mg N=92	ALN 5 mg N=88	ALN 10mg N=88	ALN* 20mg N=89
Percent of Subjects with Conc.Therapy	93.3	91.3	90.9	90.9	91.0
Anti-infective agents	63.3	62.0	61.4	52.3	57.3
Anti-inflammatory agents	35.6	45.7	39.8	42.0	42.7
CNS drugs	62.2	63.0	65.9	56.8	75.3
Hormone/synthetic substitutes	34.4	29.3	38.6	18.2	21.3

* 20 mg/day for 2 years followed by daily placebo for 1 year.

Ibuprofen, acetaminophen, and aspirin

were the most common concomitant medications used by the patients on either treatment groups.

Drug administration-One tablet of placebo or ALN (four doses levels)was self-administered by the subjects with four ounces of plain water each morning. Placebo or ALN tablet was taken at least one hour before breakfast (or any other food or drink),or at least 2 hours after breakfast.

During the first 6 months of treatment, subjects received two tablets each day (larger ALN 5-20 mg or larger placebo, and smaller ALN, 1mg or smaller placebo). Thereafter, all subjects received a single study drug each day. Table 5 presents the treatment regimens.

Table 5 (Table 1 vol. 10,p. D-1020 of this submission).

Table 1

Daily Treatment by Group

Group	Two-Week Placebo Run-In	Treatment Months 1 Through 6	Treatment Months 7 Through 24	Treatment Months 25 Through 36
A	Placebo A* and Placebo B*	Placebo A* and Placebo B*	Placebo A	Placebo A
B	Placebo A and Placebo B	1 mg/day ALN and Placebo A	1 mg/day ALN	1 mg/day ALN
C	Placebo A and Placebo B	5 mg/day ALN and Placebo B	5 mg/day ALN	5 mg/day ALN
D	Placebo A and Placebo B	10 mg/day ALN and Placebo B	10 mg/day ALN	10 mg/day ALN
E	Placebo A and Placebo B	20 mg/day ALN and Placebo B	20 mg/day ALN	Placebo A

* Placebo A matched the 5 to 20-mg alendronate tablet image and Placebo B matched the 1-mg tablet image. The new 1-mg tablets formulated for Months 7 to 36 had the same image as the 5- to 20-mg tablets. Therefore, the smaller placebo (Placebo B) was not required after the first 6 months of dosing.

Data Source: [3.2.3; 3.2.4]

Reviewer's comments on the dose- Dose selection of ALN for the prevention study was based on the results of previous trials carried out for the treatment and also on the results of dose-ranging studies. The results of Phase II studies showed dose-related decreases in the biochemical markers of bone turnover, including serum alk. phosphatase and serum osteocalcin, and

urinary excretion of calcium, hydroxyproline, deoxypyridinoline, and N-teolopeptide of type I collagen. in addition, a 6-week ALN treatment resulted in a dose-related increase in the lumbar spine BMD of recently menopausal women. The results of Phase III trials demonstrated the long-term effects of ALN on bone mass and provided the rationale for continuous dosing.

Timing of other procedures- Bone mass (BMC and BMD) measurements at all sites were performed every 6 months. Routine serum and urine chemistries, and hematology were performed every 3 months for 24 months and thereafter, every 6 months.

Lateral thoracic and lumbar spine x-rays were performed at baseline and at Month 36.

Transiliac bone biopsy materials were collected between 33 and 36 months of the study from subsets of patients in the placebo and ALN groups. These samples were subjected to histomorphometric analysis.

8.1.3.2 **Endpoints**

Efficacy

Primary endpoint- PA lumbar spine BMD.

Secondary endpoints- Femoral neck, trochanter, total body, L3 lateral spine, Ward's triangle, total hip (hologic only),ultra-distal (radius + ulna)forearm (Hologic only) BMD.

Study of the effects of ALN therapy on mineral homeostasis variables such as serum calcium, phosphate, PTH, and 1,25 $(OH)_2$ D. Additionally, effects of ALN therapy on biochemical markers (formation and resorption) of bone turnover were evaluated. The formation

markers included bone specific serum alk. phosphatase (b-SAP), total SAP, and serum osteocalcin (OC). The resorption markers were urine deoxypyridinoline (DPyr), urine pyridinoline (Pyr), and N-telopeptide of type I collagen (NTX). All urinary markers were corrected for urine creatinine.

Safety

Clinical adverse signs and symptoms (graded as mild, moderate, and severe)

Laboratory (blood, urine, hematology) abnormalities. **Bone histomorphometric** changes to evaluate the effect of ALN therapy on mineralization, turnover, and architecture.

Reviewer's comments on endpoints

It is well known that postmenopausal women are likely to lose bone mass immediately after menopause.The risk of osteoporotic fracture increases exponentially as BMD decreases. ALN is approved for the treatment of postmenopausal osteoporosis and the drug demonstrated its efficacy based on statistically significant increases in spine, hip, and total body bone mass in postmenopausal women with osteoporosis. Timely measurement of BMD at axial and appendicular sites plays an important role in determining the response to treatment regimen. In a prevention study, preservation of bone mass or a small increase in bone mass following treatment with inhibitors of bone turnover is an appropriate endpoint to demonstrate the efficacy. The evidence of therapeutic benefits should be supplemented with evidence of normal bone strength and architecture.

Secondary efficacy endpoints are to provide evidence in support of primary efficacy endpoint, and to indicate the direction of changes in skeletal status as a result of ALN therapy.

Safety endpoints are routine clinical and laboratory parameters similar to those generally monitored in clinical trials with long-term use of bisphosphonates (including upper G-I disorders, hematological profile, serum electrolytes, and renal function).

In addition, transiliac bone biopsies were performed in a subset of the study population (both placebo and ALN) to assess the effect of ALN on bone mineralization, turnover, and architecture.

8.1.3.3 Statistical Considerations

The null and alternative hypotheses adopted to compare the effects of ALN with that of placebo were routine. Power calculations were based on estimated sample size of 60 patients per treatment group with 95% power to detect a 3% difference in mean percent change from baseline in lumbar spine BMD ($\alpha = 0.05$, two-sample, two-tailed test). The current study used about 83 subjects per treatment group. **(See statistical review for additional comments).**

Additional BMD parameters for total body, femoral neck, trochanter, total hip, Ward's triangle, forearm (one-third distal, and ultra-distal) were analyzed.

Data were also subjected to subgroup analysis based on baseline spine BMD, renal function, age, number of months since menopause, weight, race, and smoking status.

An interim clinical study report was prepared after 1 year of the study for a regulatory filing in a foreign country. The sponsor assures that the study continued in a blinded fashion without any adjustment.

Intention-to-Treat (ITT) and Per-Protocol (P-P) approaches were used for statistical analyses of results. The ITT

approach was primary for all BMD and subgroup analyses. The P-P approach was primary for biochemical efficacy-related parameters and for correlation analyses.

Routine statistical methods were used in all of these analyses.(See Statistical review for additional comments).

8.1.4 RESULTS

8.1.4.1 Patient Disposition- The number of subjects entered into the study by treatment groups are presented in Table 6.

Table 6. Number of subjects enrolled and completed the study by treatment groups.

	Placebo	ALN 1 mg	ALN 5mg	ALN 10mg	ALN 20/0mg	Total
No.of Pt.	90	92	88	88	89	447
No. of Pt. Completed (36 mo.)	63	66	63	62	57	311

One hundred thirty-six patients were reported to discontinue the study for the following reasons: clinical AEs (33pt.),withdrawal of consent(43 pt.),lost to follow-up (4 pt.),protocol deviation (6 pt.), and other (who did not participate in the 3rd year blinded treatment).

Relative day ranges window was used for the efficacy and safety analyses, since the patients did not came in on an exact day for their clinical visits. Examples: Month 6 BMD between Days 2-284; Months 12 BMD between Days 285 to 464; Month 18 BMD between Days 465 to 824; Month 24 BMD between Days 645 to 824; and Month 36 BMD between Days 1005 to 1166. The baseline value for BMD was the mean of

values determined between Days -100 to 1.

The sponsor has provided a list of subjects who were excluded from the ITT and P-P analyses for spine BMD. A patient was excluded from the ITT analysis at a particular time point, if the patient had no baseline or posttreatment measurement prior to that time point. The reasons for exclusion of patients in the P-P analysis were mentioned earlier in the review.

Few additional patients were excluded from the ITT and P-P analyses for total body BMD and forearm BMD, due to methodological problems (See Statistical review for comments).

Table 7 (Sponsor's Table 16, vol.10, p.D-1064)

Table 16

Number of Subjects in the Lumbar Spine BMD Analysis at Month 36

	PBO	ALN 1 mg	ALN 5 mg	ALN 10 mg	ALN 20/0 mg
Total Entered	90	92	88	88	89
Total Included In					
Intention-to-Treat Analysis	82	88	84	84	78
Per-Protocol Analysis	47	57	56	62	53
Total Excluded From					
Intention-to-Treat Analysis	8	4	4	4	11
Per-Protocol Analysis	43	35	32	26	36

8.1.4.2 **Efficacy**

Bone Mineral Density (BMD)

Lumbar Spine BMD- The subjects in 20/0-mg group did not receive ALN during

the third year of the study. The primary BMD analysis for spine was percent change from baseline at Month 36. This allowed evaluation of the resolution of the effect of ALN treatment.

The lumbar spine BMD increased from baseline significantly in 5,10, and 20/0 mg doses of ALN at Month 36.(Table 8). At Month 12, increase in BMD appeared to reach the maximum and stabilized thereafter. At higher doses (10 and 20/0 mg)BMD appeared to increase further (but at a slower rate) at Months 24 and 36. At Month 36 (12 months after cessation of ALN treatment), the 20/0mg group showed some decrease from the peak increase at Month 24.The ALN 1 mg group showed some increase at Month 12, but thereafter, started to loose bone mass despite treatment with ALN. The placebo group manifested progressive loss of BMD throughout the course of the study.

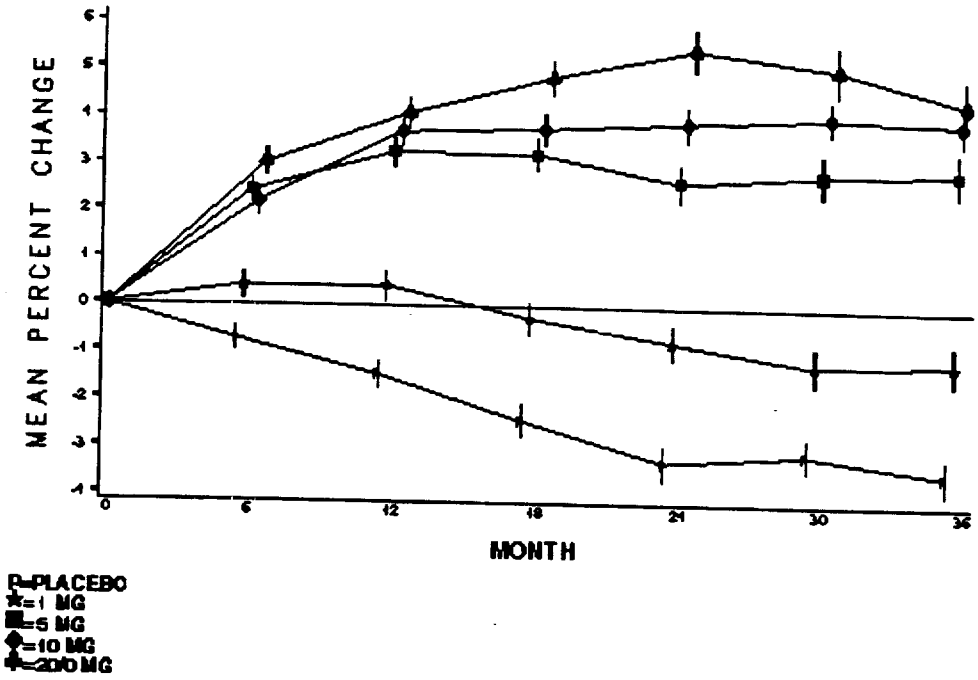
Table 8.Lumbar spine mean BMD changes from baseline at Month 36 (ITT analysis). See also Figure 1 (Sponsor's Figure 1, vol.10,p.D-1069)

Treatment	No. of Pt.	Mean % Change From Baseline	SD	Adjusted Mean	LSD Interval
Placebo.	82	-3.51***	3.28	-3.54	(-4.12,-2.95)
ALN:					
1 mg	88	-1.16**	3.79	-1.1	(-1.66,-0.53)
5 mg	84	2.89***	4.17	2.86	(2.28,3.44)
10 mg	84	3.95***	3.62	3.99	(3.41,4.57)
20/0 mg	78	4.37***	4.43	4.26	(3.66,4.86)

***: $p \leq 0.001$; ** $p \leq 0.01$-Within treatment test

Figure 1

Lumbar Spine BMD (g/cm^2)
Mean Percent Change ± SE of the Mean
(Intention-to-Treat Approach)



When the mean changes in BMD at Month 36 were compared between different doses, all ALN doses were superior to placebo ($p < 0.001$).

During the second year of the study, in the 1 and 5 mg groups, there were significant decreases in BMD at Month 24 compared to mean values at Month 12. The 10 mg dose showed no change and the 20/0 mg group manifested significant increase ($p < 0.001$). In the third year of the study, there were no significant differences in BMD changes between Month 24 and 36 in all groups except for a significant decrease in 20/0 mg group (on placebo during this period).

About 9.5% to 16.7% of patients in 5, 10, and 20/0 mg groups showed about 8%

increase in BMD at Months 36, There were no significant differences between these three treatment groups with respect to proportion of patients with a set percent increase in BMD. Seventy percent to 80% of patients in these three treatment groups achieved at least 1% increase in spine BMD compared to 28.4% and 7.3% in the 1 mg and placebo groups, respectively.

Femoral neck BMD- The femoral neck BMD showed significant increase from baseline at Month 36 in the 5,10, and 20/0 mg groups and are shown in Table 9 (Sponsor's Table 22, vol.10,p.1078).

Table 22

Femoral Neck BMD (g/cm^2)
Analysis of Percent Change From Baseline at Month 36
(Intention-to-Treat Approach)

Treatment	N	Means (Observed)		Percent Change From Baseline			
		Baseline	Month 36	Mean	SD	Adjusted Mean	LSD Interval
Placebo	76	0.80	0.77	-3.95***	4.08	-3.89	(-4.51, -3.27)
1 mg	83	0.79	0.78	-1.65***	3.91	-1.46	(-2.05, -0.87)
5 mg	83	0.76	0.77	1.10*	4.13	1.23	(0.64, 1.83)
10 mg	80	0.79	0.81	2.27***	4.14	2.39	(1.79, 2.99)
20/0 mg	74	0.77	0.79	1.87***	4.16	2.01	(1.38, 2.64)
Within-treatment test of mean = 0***: $p \le 0.001$**: $p \le 0.01$*: $p \le 0.05$							
Treatment-by-center interaction p-value 0.451							

Adjusted Trend-Test		Overall		Comparison Between Doses				Pooled
Dose Included	p-Value	p-Value		Placebo	1 mg	5 mg	10 mg	SD
Placebo through 10 mg	<0.001	<0.001	1 mg	<0.001				3.80
Placebo through 5 mg	<0.001		5 mg	<0.001	<0.001			
Placebo through 1 mg	<0.001		10 mg	<0.001	<0.001	0.053		
			20/0 mg	<0.001	<0.001	0.203	0.533	

Data Source: [4.7]

Increase in BMD mainly occurred at Month 12 and was mostly maintained during the second year of treatment. In the 20/0 mg group, during the third year of the study (on placebo) BMD decreased slightly from Month 24. The placebo and ALN 1 mg groups showed decreases in BMD during the course of the study. All ALN groups showed significant differences compared to the placebo group. ALN 5-20/0 mg doses appear to be more

effective than 1 mg dose with respect to change in femoral neck BMD.

The results showed approximately 60% to 70% of patients in ALN doses 5-20/0 mg doses with increased femoral neck BMD as opposed to 15% to 30% of patients in the placebo and ALN 1 mg groups, respectively.

Trochanter BMD-Trochanter BMD (about 50/50 distribution of trabecular and cortical bone) showed significant ($p < 0.001$) increases at ALN doses of 5 to 20/0 mg. About 70% to 90% of patients in these ALN groups achieved an increase (about 1%) in BMD. The 1mg group showed some increase at Month 18 and thereafter stabilized at or near baseline mean values. The placebo group showed progressive decrease over the entire duration of the treatment period. Forty-seven percent and 26% of patients in the 1 mg and placebo groups, respectively, showed a similar increase (from baseline) BMD.

Total Body BMD- Changes in total body BMD followed similar pattern as observed in trochanter BMD. The mean changes (at Month 36) were -2.26,-1.00,0.32,1.03, and 0.52% for the placebo, 1,5,10, and 20/0 mg groups, respectively. However, the difference from baseline mean was significant ($p < 0.01$) only for the 10 mg group. The loss of total body BMD was significant in both placebo and 1 mg groups. Approximately, 60% to 80% of patients in the ALN 5 to 20/0 mg doses showed increases in total body BMD.

The sponsor has further analyzed the BMD data for spine, femoral neck, and total body in order to assess any differential effect due to the type of densitometers (Hologic and Lunar machines) used. There was no treatment-by-densitometer interaction. However, for the trochanter BMD, the densitometer effect approached significance at $p < 0.06$ level.

Total Hip BMD-At Month 36, mean changes

in BMD were -3.07,-1.04,1.02,2.34, and 1.75% for the placebo, 1,5,10, 20/0 mg groups, rspectively. ALN at all doses significantly increased BMD compared to the placebo group ($p < 0.001$).

One-Third Distal Forearm (radius + ulna) BMD- The BMD at one-third distal forearm showed decrease at Month 36 in all treatment groups. The 20/0 mg group showed some increase in BMD up until 24 months and decreased thereafter. The degree of total loss of BMD was less at 5,10, and 20/0 mg groups at Month 36, compared to ALN 1 mg and placebo groups. Except for the 10 mg group, changes (decrease) from the baseline to Month 36 for the 5 and 20/0 mg groups were statistically significant.

Biochemical Efficacy Parameters

These parameters were evaluated to determine the mechanism of action of the drug and its effect on bone turnover. The previous long-term studies (two- or three-year) with alendronate in postmenopausal women showed an early decrease followed by a plateau that was maintained during the rest of the study duration.

Other biochemical parameters related to calcium and phosphorus homeostasis, included serum PTH, $1,25(OH)_2D$, calcium, and phosphorus.

Urine deoxypyridinoline corrected for creatinine (DPyr/Cr)- DPyr/Cr decreased by about 40% to 50% by the third month of treatment with ALN at doses of 5,10, and 20/0 mg and then the reduced level was maintained until Month 24. At Month 30 there was a rising spike with a decrease at Month 36.

Urine N-Telopeptide Corrected for Creatinine(NTX/Cr)-NTX/Cr decreased by about 65% to 75% by Month 6 of treatment with ALN at doses of 5,10, and 20/0 mg. The decrease was maintained thereafter

up to Month 36. The placebo group showed no appreciable change during the course of the study.

Urine Pyridinoline Corrected For Creatinine (Pyr/Cr) - The results were similar to DPyr/Cr data reviewed earlier.

Serum Alkaline Phosphatase (SAP) - SAP decreased by about 10% to 25% by Month 3 and thereafter remained decreased until Month 36 except for the 20/0 mg group. In the latter group, SAP tended to increase toward pretreatment level. The placebo group showed no significant change from the baseline mean value.

Bone-Specific Serum Alkaline Phosphatase (BSAP) - BSAP decreased by 40% to 50% at doses of 5, 10, and 20/0 mg at Month 6. Thereafter, the decreased level was maintained until Month 24 followed by a rise toward pretreatment value. The placebo group showed a progressive rise during the course of the study and increased about 45% at Month 36.

Serum Osteocalcin - Serum osteocalcin decreased by about 30% to 63% at all groups (including placebo) by Month 12. Decreases in ALN 5, 10, and 20/0 mg groups were significantly greater ($p \leq 0.01$) than the placebo group. After Month 12, decreased level was maintained for the remainder of the study except for 20/0 mg group in which it increased at Month 36.

Osteocalcin is a very unstable protein, and if serum samples are not properly frozen erroneous results may occur. Therefore, sponsor analyzed serum samples from the U.S. study sites separately. The results of the separate analysis were similar to those from the pooled analysis.

Parameters Related to Calcium Homeostasis and Mineral metabolism - Serum calcium showed a decrease by 2% to 3% in the ALN 5 to 20/0 mg groups and

then returned toward baseline at Month 36.The placebo and 1 mg groups showed appreciable change from baseline during the course of the study. In 10 and 20/0 mg groups decreases were significant ($p \leq 0.05$).

Serum phosphorus showed similar patterns of change for the ALN and placebo groups. ALN 5 mg or greater caused 4% to 8% decrease from baseline mean.

Serum PTH increased in all ALN groups at Month 1 and then gradually returned toward baseline at Month 36.The placebo group also showed some increase by Month 1 and returned toward baseline at Month 12.

Parallel to the increase in PTH, serum 1,25 $(OH)_2D$ increased in ALN 5 to 20/0 mg groups and thereafter returned toward baseline at Month 36.

Correlation Analysis of Baseline Spine BMD with Subject Characteristics and biochemical variables (per-protocol approach)

There was a small positive correlation with baseline spine BMD, height and weight. There were no other significant correlations between BMD and subject characteristics.

With respect to correlation between percent change in spine BMD at Month 36 and baseline biochemical markers, the results were not consistent.(See Appendices 4.24.1-4.24.3, vol. 11,pp.D-2476-2478).

Subgroup Analysis (ITT approach)

a.Baseline lumbar spine BMD subgroup analysis for percent change in spine BMD at Month 36- There was no significant treatment-by-subgroup interaction (p=0.68).

b. Baseline U/DPyr/Cr subgroup analysis for percent change in spine BMD at month 36- Treatment-by-subgroup interaction analysis was significant at a level of p=0.05.

c. Subgroup analysis by race and smoking status showed no significant treatment-by-subgroup interactions (p> 0.10-0.58).

Bone Histomorphometry

Those patients who underwent bone biopsy between 33 and 36 months of treatment were similar to a group of subjects who did not receive any treatment with respect to age, baseline spine BMD, and number of months since menopause.

In the ALN 20/0 mg group, bone biopsies were performed 9 to 12 months after the termination of treatment.

The following histomorphometric parameters were compared across treatment groups for assessment of the effects of ALN therapy on the "quality of bone mineralization."

The following histomorphometric parameters were evaluated:

Osteoid thickness (OTh; μm)-Mean thickness of the osteoid.

Mineral Apposition Rate (MAR; μm/day)-The rate of progression of active mineralization fronts.

Osteoid Volume/Bone Volume (OV/BV; %)-Percentage of bone volume in unmineralized osteoid.

Mineralizing Surface(MS/BS;%)-Percentage of total bone surface that takes up tetracycline label (which fluoresces under UV light).

The results are presented in Table 10. (Sponsor's Table 62,vol.10,p.D-1158).

Table 62

Summary of Bone Histomorphometry Parameters
(Intention-To-Treat Approach)

Parameter	Unit	Treatment	N	Mean	SE	Median	Range
Osteoid Thickness	µm	Placebo	15	8.90	0.60	9.06	
		1 mg	8	6.57	0.44	6.81	
		5 mg	11	8.06	0.87	7.85	
		10 mg	9	7.56	0.92	6.79	
		20/0 mg	8	8.11	0.75	7.93	
Mineral Apposition Rate	µm/day	Placebo	15	0.73	0.04	0.73	
		1 mg	8	0.78	0.03	0.77	
		5 mg	10	0.78	0.05	0.73	
		10 mg	9	0.77	0.04	0.79	
		20/0 mg	7	0.73	0.07	0.70	
Osteoid Volume/Bone Volume	Percent	Placebo	15	1.20	0.19	1.04	
		1 mg	8	0.73	0.22	0.49	
		5 mg	11	0.65	0.16	0.50	
		10 mg	9	0.74	0.23	0.48	
		20/0 mg	8	0.83	0.18	0.64	
Mineralizing Surface	Percent	Placebo	15	6.25	0.84	5.14	
		1 mg	8	1.88	0.20	1.84	
		5 mg	11	2.53	0.72	1.73	
		10 mg	9	2.13	0.28	2.38	
		20/0 mg	8	4.40	0.99	4.83	

Osteoid thickness slightly decreased in ALN groups (except for 20/0 mg) compared to the placebo group. This small decrease could be due to expected inhibitory effect of ALN on the rate of bone turnover.

The MAR results showed no significant differences among various treatment groups.

The mean osteoid volume decreased in all ALN groups compared to the placebo group. Decrease in osteoid volume is in agreement with the expected inhibitory effect of ALN on the rate of bone turnover. Smaller OV represents formation of a smaller portion of new bone (per unit of time)under the influence of ALN. Impairment of mineralization is likely to increase osteoid volume.

Means for mineralization surface in all ALN groups (except for the 20/0 mg

group) were lower than the mean of the placebo group. In the ALN 20/0 mg group, the mean MS value was higher than those in other three ALN groups. This probably happened due to resolution of the effect on mineralization after cessation of ALN treatment.The data showed no evidence of complete suppression of bone turnover.

Sponsor states that qualitative bone histology findings showed normal lamellar bone formation "without any evidence of woven bone.."

Sponsor's summary of histomorphometric findings - Observed changes (decreases) in OTh and OV/BV were not in the direction of impaired mineralization. The overall changes in histomorphometric parameters were consistent with the pharmacodynamic effect of ALN on bone turnover.

8.1.4.3 **Safety**

Clinical Adverse Experiences

The overall AEs are summarized in Table-11. (Sponsor's Table 63. Summary of clinical AEs, vol.10;p. D-1165)

Table 63

Clinical Adverse Experience Summary--Subject Count (%)

	PBO (N = 90)	ALN 1 mg (N = 92)	ALN 5 mg (N = 88)	ALN 10 mg (N = 88)	ALN 20/0 mg (N = 89)
Number (%) of subjects with one or more adverse experiences	82 (91.1)	85 (92.4)	81 (92.0)	86 (97.7)	84 (94.4)
with drug-related adverse experiences	21 (23.3)	32 (34.8)	22 (25.0)	29 (33.0)	34 (38.2)
with serious adverse experiences	9 (10.0)	5 (5.4)	10 (11.4)	13 (14.8)	8 (9.0)
with serious drug-related adverse experiences	0	0	0	1 (1.1)	1 (1.1)
withdrawn from therapy due to adverse experiences	6 (6.7)	6 (6.5)	6 (6.8)	6 (6.8)	9 (10.1)
withdrawn from therapy due to a serious adverse experience	2 (2.2)	0	2 (2.3)	1 (1.1)	2 (2.2)
withdrawn from therapy due to a drug-related adverse experience	1 (1.1)	3 (3.3)	3 (3.4)	5 (5.7)	4 (4.5)
withdrawn from therapy due to a serious drug-related adverse experience	0	0	0	0	0
Subjects who died	0	0	0	0	0

PBO = Placebo
ALN = Alendronate

Data Source: [4.12], [4.28]

During the course of the study, 91% to 98% of patients in the ALN groups experienced one or more AEs, compared to 91% in the placebo group. Slightly more patients during the third year of the study experienced clinical AEs compared to the first year of the study (93.5% vs 77.4%). One patient each in 10 and 20/0 mg groups experienced serious drug-related AEs. There were no significant differences between placebo and ALN 1-10 mg groups with respect to the number (%) of subjects withdrawn from therapy due to AEs. Three to 5 patients in ALN groups withdrew from the therapy due to drug-related AEs. There were no deaths in any of the treatment groups.

Table 12 presents clinical AEs by body system.

Table 12. Summary of AEs by body system

AEs	Placebo N=90	ALN 1mg N=92	ALN 5mg N=88	ALN 10mg N=88	ALN 20/0mg N=89
Body as a Whole	35(38.9%)	33(35.9%)	29(33.0%)	34(38.6%)	26(29.2%)
Digestive System	35(38.9%)	38(41.3%)	38(43.2%)	41(46.6%)	46(51.7%)
Hemat.and Lymph. Syst.	2(2.2%)	2(2.2%)	0	2(2.3%)	2(2.2%)
Musc.Sk. Syst.	43(47.8)	51(55.4%)	51(58.0%)	48(54.5%)	56(62.9%)

There were no significant differences among treatment groups with respect to AEs associated with various body systems. Nevertheless, higher proportions of patients with G-I and musculo-skeletal AEs were in the 20/0 mg group.

The most common AEs were upper respiratory tract infection, influenza, headache, **abdominal pain**, and back pain (Table 13).

Table 13. Most common AEs.

Common AEs	Placebo N=90(%)	ALN 1mg N=92(%)	ALN 5mg N=88(%)	ALN 10mg N=88(%)	ALN 20/0mg N=89
Up.Resp. Inf.	28(31.1)	27(29.3)	22(25.0)	29 (33.0)	30 (33.7)
Influenza	13 (14.4)	12 (13.0)	17 (19.3)	14 (15.9)	25 (28.1*
Abd. Pain	**11 (12.2)**	**14 (15.2)**	**8 (9.1)**	**14 (15.9)**	**11 (12.4)**
Headache	22 (24.4)	20 (21.7)	28 (31.8)	16 (18.2)	21 (23.6)
Back Pain	10 (11.0)	23 (25.0)	13 (14.8)	10 (11.4)	16 (18.0)

Upper respiratory tract infection and influenza were not considered to be drug related.

Of G-I AE, flatulence, odynophagia, and ulcer of mouth showed increasing trend with increasing dose, particularly in 10 and 20/0 mg groups.

Flatulence, finger pain, and hip pain were the common AEs considered possibly, probably, or definitely drug-related. Significantly higher proportions of patients experienced flatulence at 10 and 20/0 mg groups compared to the placebo group. The trend was not significant for the 5mg dose. The number of finger pain events increased with increasing dose and the number of hip pain **decreased** with increasing dose.

Reviewer's Comments: The number of patients with these frequent drug-related AEs were too small in this study. Postmarketing clinical experience will probably provide adequate information on these AEs with respect to their incidence).

Ten percent, 5.4%,11.4%,14.8%,and 9.0% in the placebo, 1, 5, 10, and 20/0 mg groups, respectively experienced one or

more serious AEs. One patient at 10 mg dose and another patient at 20/0 mg dose developed seizures (possibly drug-related) and "esophageal disorder" (probably drug-related), respectively. In case of the seizure disorder, the investigator felt that the episode was possibly drug-related. But its mechanism was not clear. This patient's serum calcium was normal and the event occurred after about 5 months on the drug. Following a second episode of seizure, treatment was discontinued. The patient with esophageal disorder presented with neck and chest pain. Concomitant medications included calcium carbonate (55 mg/day)and famotidine (40 mg/day). Coronary angiogram revealed no abnormality. The patient was diagnosed to have esophageal reflux and treated with antireflux regimen (famotidine 20 mg b.i.d.) for about 30 days. The patient completely recovered and resumption of ALN therapy resulted in no recurrence of the symptoms.

The following subjects were discontinued from the study due to drug-related AEs:

ALN 1mg-

One patient(AN 049) developed episodes of mild diarrhea. Diarrhea was considered possibly ALN-related.

One patient(AN 528)experienced worsening of dizziness that was considered possibly drug-related.

ALN 5mg-

Patient (AN 0127)developed swelling in both lower legs that was considered possibly drug-related.

ALN 10mg-

Patient (AN 0118) with a history of diverticulosis developed increased frequency of dyspepsia. Dyspepsia was considered study drug related.

Patient (AN 0136) with a history of heartburn discontinued ALN therapy on study Day 981 due to acid regurgitation, which was considered possibly drug-related.

Patient (AN 241) developed erythematous and pruritic rash on study Day 34; the AE was considered probably drug related.

Patient (AN 0361) developed diarrhea on study Day 558 that led to discontinuation of ALN therapy.

ALN 20/0 mg-

Patient (AN 047) developed pruritic rash first on her face and spread beyond to her neck. The AE was considered probably drug related.

Patient (AN 146) developed **severe abdominal pain** on Day 7 on ALN. The AE was considered drug related.

Patient(AN 160) developed severe odynophagia starting on Day 18 of therapy. Endoscopy revealed **exudative esophagitis**. ALN therapy was discontinued, patient was treated with omeprazole (20 mg/day). Symptoms were resolved. The AE was considered probably drug related.

Patient (AN 343) developed **dyspepsia and moderate nausea** on study Day 65. The AE was considered **definitely drug related**.

Summary of upper G-I adverse experiences

In all ALN groups, about 28.3% of patients experienced at least one upper G-I AE, compared to 28.9% of patients in the placebo group. In the placebo group, 13.3% of patients experienced possibly, probably, or definitely drug related upper G-I AEs, compared to 1.9%,12.5%,13.6%, and 19.1% of patients in the 1, 5,10, and 20/0 mg

ALN groups, respectively. There were significant trends in increased incidence of odynophagia in higher doses (10 and 20/0 mg) of ALN. One of 6 subjects with odynophagia was diagnosed to have esophagitis by endoscopy.

Reviewer's comments: There were no significant differences between the placebo and ALN groups with respect to proportion of patients with upper G-I AEs (including those considered serious by the investigators). However, there were isolated cases of upper G-I AEs which occurred at higher doses of ALN.

Clinical fractures- Twenty-eight patients (of N=44) experienced fractures during the study. The were no significant differences amongst the treatment groups. In the placebo group, 6.7% of patients suffered fractures, compared to 8.7%,4.5%,3.4%, and 7.9% of patients in the 1,5,10, and 20/0 mg ALN groups, respectively. These fractures were not considered to be drug-related. One patient each in the placebo, 1 and 5 mg groups suffered a vertebral fracture. The remaining fractures were nonvertebral and all were associated with trauma (fall, automob. accident, skiing accident, etc). Three subjects suffered wrist fractures (1 in the 10 mg dose and another in the 20/0 mg dose of ALN; showing a positive trend (p=0.03).

Skin rash- The overall incidence of drug related rash was low in this study, but it was reported to be significant at ALN 20/0 mg dose.

Taste disturbances- Three patients in the ALN groups (one each at 1,5, and 10 mg) developed taste disturbances during the first year of treatment. These were considered to be possibly, probably, or definitely drug-related. Taste disturbances resolved with continued treatment.

Laboratory Adverse Experiences

Laboratory AEs were evaluated in a total of 445 subjects. Two subjects discontinued the study prior to any laboratory determinations at the first visit.

About 40.7% of patients (181 of 445 pt.) experienced at least one laboratory AE. More patients (24.4%)in the placebo group experienced drug related AEs compared to 13.6% to 18.2% in the ALN groups.

Of the protocol-required measurements, increased urine RBC and urine WBC were the most commonly reported laboratory AEs. Despite numerical increases in these AEs, there were no consistent or dose-related increases in either of these AEs. Several of the patients suffered UTI and/or vaginitis or vaginal bleeding. No subject discontinued the study due to these AEs.

During the first year of the study, there was an increasing trend (at the 20/0 mg dose in the proportion of patients with decreased serum WBCs. But this trend was not seen at Year 3 of the study. Some of these episodes were isolated findings or preexisting conditions, and were normalized without interruption of treatment.

There were few patients (N=2 to 4)in the 10 and 20/0 mg doses that showed a decreases in hematocrit(but values were > 32.0%) and hemoglobin (but values were > 11.3 g/dL). One subject in the ALN 20/0 mg dose had hematocrit value of 28.7% and hemoglobin of 9.4 g/dL. This patient was previously diagnosed with breast cancer during the study. There were two additional cases with low hemoglobin values during the study, one recovered and the other was found to have colon cancer.

In the ALN 10 mg group, one subject was

tested positive for fecal guaiac.

Sponsor's Discussion on Efficacy and Safety:

The study was carried out involving a very wide cross section (with centers in U.S., Europe, South America, Australia, and New Zealand) of recently menopausal women.

Spinal BMD was selected as the primary efficacy endpoint of the study, because vertebral fractures are common in postmenopausal osteoporosis and they are associated with considerable morbidity (back pain, spinal deformity, and height loss). Furthermore, substantial bone loss occurs at this site immediately following menopause, and in untreated subjects the loss of bone mass is rapid. The treatment is targeted to prevent loss of BMD and not to increase BMD as it occurs in patients with established osteoporosis. The spinal BMD measurement with DXA (with a coefficient of variation of about 1%) would have sufficient power to detect a treatment effect.

The secondary endpoints (BMD of proximal hip, total body, and forearm) were also clinically relevant with respect to evaluation of the efficacy of ALN for prevention of osteoporosis.

Daily quality control procedures adopted at study sites provided assurance that changes due to software did not influence spine BMD measurements. Another problem with BMD measurements was "machine drift." This happened in the study by Dr. Eric Orwoll. Orwoll used a correction factor (from daily phantom data) to offset this problem. Sponsor states that "none of the conclusions from this study were altered by the use of correction factors."

The study demonstrated that ALN at a dose of 5 or 10 mg. day for 3 years or

20 mg/day for 2 years + follow-up for additional one year with placebo caused **significant increases (~3% to 4.5%), compared to a loss of about 3.5% in the placebo group (on adequate daily calcium supplementation)**. The mean differences from the control group were 6.4,7.5, and 7.9% in 5, 10, and 20/0 mg groups, respectively. At1 mg/day dose, ALN significantly prevented the loss of BMD.

ALN at a dose of 5 mg/day increased hip BMD at femoral neck, Ward's triangle, trochanter, and total hip. Significant differences between the effects of 5 and 10 mg/day were evident only at the trochanter and total hip BMD. At 5 mg dose, about 75% of patients achieved spine, femoral neck, and trochanter, compared to losses at these sites in about 80% of placebo-treated subjects. Thus, ALN therapy seems to provide a protective effect "to decrease the risk of vertebral and hip fracture" through reversal of bone mass loss and significant increases in vertebral and hip BMD. The effect of ALN therapy on forearm BMD was less "defined" than its effect on spine and hip BMD. ALN treatment (at all three doses) did not prevent the loss of forearm BMD. Increases in the total body BMD at 36 months in all three ALN groups indicated that "a simple redistribution of bone mass..." did not occur.

Alendronate, being an antiresorptive agent, is expected to decrease the biochemical markers of bone resorption (i.e., deoxypiridinolone and N-telopeptide of Type I collagen). ALN at all three doses, caused inhibition of urinary excretion of DPyr 1 month after initiation of treatment and plateaued around 30% to 40% of baseline mean. Similar effect was seen with changes in urinary excretion of N-telopeptide, which plateaued around 65% to 75% of baseline. Withdrawal of ALN treatment showed return of these markers toward baseline. Thus, the data on urinary

excretion of markers of bone resorption tend to indicate that ALN-induced "inhibition is far from total" and "the effect of alendronate to decrease turnover is not cumulative or progressive despite its continued administration and continued skeletal uptake." (**Comments**; The sponsor has presented a hypothesis that only recently administered drug and not the accumulated drug is responsible for the inhibitory action on bone turnover. More objective data in support of this hypothesis are lacking at this time).

With regard to the effect of ALN on bone formation, the data showed maximum reduction in formation markers (i.e.,serum bone-specific alk. phosphatase, and osteocalcin) occurred by 6 to 12 months of treatment.

Lack of progressive suppression after the initial several months of therapy showed achievement of a new steady state of bone turnover.

Changes in indices of calcium homeostasis are related to ALN-induced positive calcium balance. Net accumulation of calcium in bone led to decrease in serum calcium, increase in iPTH. Decreased urinary excretion of calcium occurred due to decreased filtered load and increased tubular resorption of calcium due to increase in PTH secretion. Changes in serum phosphate and 1,25 $(OH)_2$ D were in agreement with changes in overall calcium balance. Also, the time course of these changes were related to a positive effect of ALN on bone mass.

Increases in spine and hip BMD mostly occurred during the first year of ALN treatment. Whereas, the placebo group lost bone mass continuously and progressively during the course of the study. Stoppage of ALN treatment after 2 years, resulted in resumption of BMD loss at spine, femoral neck, trochanter,

and total body. These data suggest continuous daily ALN therapy for the prevention of osteoporosis in postmenopausal women.

The safety profile of ALN in this study was similar to that seen in 3-year controlled treatment studies submitted in the previous NDA for the treatment indication.

The G-I AEs appeared to be related to ALN were flatulence, esophageal irritation (causing odynophagia) at 10 and 20/0 mg doses. The number of patients discontinued from the study due to drug related AEs were higher at the 20/0 mg dose. All of subjects who discontinued the study due to upper G-I AEs did so during the first three months of treatment. In general, the upper G-I AEs occurred at similar rates in the placebo and active treatment groups (28.9% vs 26.1 to 31.5% range). Nevertheless, more patients (19.1%) in the 20/0 mg experienced drug-related upper G-I AEs, compared to 10.9-13.3% in lower doses of ALN and 13.3% in the placebo. Odynophagia was the only upper G-I AE that showed statistically significant dose-related increase in 10 and 20/0 mg doses. Five of 6 cases of odynophagia occurred in one study center. The true causal relationship between ALN and odynophagia is unclear. Flatulence is another AE which more frequently occurred with doses of ALN 10 mg or greater.

Skin rashes (including erythema and urticaria) showed a trend of occurrence with higher doses of ALN.

The data on fracture rate were too small to draw any conclusion. There was no evidence of adverse effect of ALN on fractures.

Bone histomorphometric data showed normal lamellar bone formation during ALN therapy.

All treatment groups showed similar rates of laboratory AEs. Based on predefined criteria of analyses, there was "no clinically important decrease in WBC."

In conclusion, ALN therapy at doses of 5 or 10 mg/day for 3 years or 20 mg/day for 2 years and 1 year on placebo resulted in increased BMD of spine (lumbar),femoral neck, trochanter, and total body relative to baseline and placebo in recently postmenopausal women. Bone loss resumed after stoppage of ALN at 20/0 mg dose. ALN at 1 mg/day dose,showed attenuated bone loss at spine, hip, and total body compared to placebo, but significant bone losses occurred at all sites except for the trochanter, L3 lateral spine, and Ward's triangle.

ALN therapy resulted in decreases in biochemical markers of bone turnover (i.e.,U/DPyr,U/N-telopeptide, serum osteocalcin, and bone-specific alk. phosphatase) after 3 to 6 months. Changes in indices of calcium homeostasis could be correlated with the positive effect of ALN therapy on calcium balance.

Histologically ALN therapy at all three doses showed normal mineralization.

Oral ALN therapy for up to 20 mg/day was well tolerated.

8.1.5 Reviewer's Comments and Conclusions

Alendronate (Fosamax), is an approved drug for the treatment of established osteoporosis in postmenopausal women. The rationale for use of ALN for the treatment of postmenopausal osteoporosis is well documented in the literature and in the NDA for this indication.

Pathophysiology of postmenopausal osteoporosis/osteopenia is also covered extensively in numerous publications.

Bone mass declines after menopause and prospective studies have shown that low bone mass is a major risk factor for fractures and it is preventable. Following menopause, women lose approximately 15% of their bone mass and most of the loss occurs within the first five years after menopause.
Low bone mass along with poor architecture and fatigue damage leads to skeletal fragility. Early intervention with ALN was expected to prevent bone loss, irreversible "microarchitectural" damage and decrease the risk of fracture.

The study(Phase III)design was appropriate to achieve the stated primary and secondary objectives relative to the efficacy and safety of ALN for 3 years. The subjects chosen for this controlled study were early postmenopausal (between 6 months and 3 years) with lumbar spine BMD of 0.87g/cm^2 and 1.25 g/cm^2 (by Lunar DPX) or between 0.76 g/cm^2 and 1.12 g/cm^2 (by Hologic QDR).
Posthysterectomized subjects with clear history of menopausal symptoms within past 3 years were also enrolled. Subjects who had established osteoporosis based on lumbar spine BMD ($\leq$ 0.87 g/cm^2 by lunar DPX or $\leq$ 0.76 g/cm^2 by Hologic QDR), previous nontraumatic fractures of the spine or proximal femur were excluded from the study. Inclusion and exclusion criteria for the study were appropriate.

Dose selection for ALN and duration of study were appropriate for the stated objectives. ALN is approved at a dose of 10 mg/day for the treatment of established postmenopausal osteoporosis. The dose of ALN was correctly examined over a range of 1 to 20/0 mg/day to determine the optimum dose of ALN for the prevention indication.

The sample size was adequate to provide a 95% power to detect a 3% difference in mean percent change from baseline in lumbar spine BMD (L1-L4) between treatment groups with α = 0.05 2-sample, 2-tailed test).

For clinical efficacy, percent change in BMD from baseline to Month 12, from Month 12 to Month 24, and Month 24 to Month 36 were

analyzed. For safety, proportion of patients with clinical or laboratory AEs or with change (outside the predefined limits) from baseline to the end of the study were analyzed. Procedures for analyses of efficacy and safety parameters of the study were appropriate.

There were no significant differences between treatment groups with respect to demographic characteristics.

Of the total 447 subjects who entered the study, 311 subjects completed 36 months of treatment. Sponsor has provided satisfactory subject accountability. A total of 33 subjects discontinued the study prior to Month 36 due to clinical AEs, but there was no significant difference between treatment groups with respect to number of discontinued subjects.

The efficacy results demonstrated significant increases in BMD of lumbar spine, femoral neck, trochanter, and total body from baseline to Month 36 at ALN 5,10, and 20/0 mg doses. The placebo group lost BMD (-2.26-3.95%) at all sites at Month 36. The ALN 1 mg group also lost BMD, but less than the placebo group. There were no significant differences (at the 0.05 level) between 5 and 10 mg doses for the spine BMD, and between 10 and 20/0 mg doses for the trochanter BMD. Increases in BMD at these sites were comparable to the effect observed with ALN treatment (primary Phase III studies), where increases on ALN were greater, but the decrease in BMD in the placebo group was less.

Sixty to 75% of patients treated with ALN 5 mg/day showed increases in spine, femoral neck, or trochanter BMD compared to the loss of BMD in about 80% of the placebo patients. Stoppage of ALN treatment at 24 months (20/0 mg group) resulted in significant loss of BMD of spine, femoral neck, trochanter, and total body. At the forearm site, ALN therapy did not prevent bone loss completely.

These data on BMD suggest a protective effect of ALN therapy against increased risk of vertebral and hip fractures in this study population, through augmentation of bone mineral density. Third year BMD data in the 20/0 mg group suggest continued ALN therapy in order to prevent bone loss.

In the beginning of the study (1-year interim analysis), a possible difference in measuring the BMD of total body and spine was detected and thought to be due to densitometer (Hologic or Lunar) used. But at 3 years, the differences between Hologic and Lunar machines at total body and spine sites were not evident.

The effect of ALN therapy on biochemical markers of bone turnover were similar to those seen in osteoporosis treatment trial. Plateauing of the effect of ALN on urinary excretion of DPyr and N-telopeptide at 6 months (at 65% to 75% of baseline mean), showed total inhibition of resorption. The overall changes in markers of bone turnover also indicated that ALN effect on bone remodeling was not cumulative and progressive with 2-3 years of therapy.

The safety profile of ALN was similar to that seen in the controlled treatment trials (previously reviewed). Flatulence and esophageal irritation (including odynophagia) were the G-I AEs observed with 10 and 20/0 mg groups. The higher numbers of G-I related AEs that occurred at 20/0 mg group were ALN related. There was no clear evidence of any excess of upper G-I AEs at ALN doses of 10 mg/day or less.

Formation of normal lamellar bone was noted for up to 3 years of treatment with ALN.

In conclusion, the results of this controlled study have demonstrated significant increase (relative to placebo and baseline) in BMD of lumbar spine, femoral neck, trochanter, and total body. At 1 mg/day dose, the effect (on BMD) of ALN therapy for 3 years was not significantly different from that of placebo.

There were more patients with upper G-I AEs

at 10 and 20/0 mg groups. At lower doses, the overall safety profile of ALN was not significantly different from that of the placebo group.

ALN therapy at doses of 1,5, 10mg/day for 3 years or 20 mg for 2 years and then placebo for one year showed no evidence of impaired mineralization of bone (histomorphometric evaluation), and preservation of normal lamellar bone formation histologically.

8.2 Reviewer's Trial #-2 Sponsor's Protocol # 038

This multicenter (14 investigators) study was carried out in Italy and U.K.

8.2.1 **Objective/Rationale**

The rationale for use of ALN in the prevention of osteoporosis in early postmenopausal women was the same as of the Study carried out under Protocol # 029. The primary objective of this controlled study was to determine the efficacy (in terms of BMD changes in lumbar spine, prox. femur, and total body) and safety of ALN 5 or 10 mg/day for 6 or 24 months. Additionally, changes in BMD during the second year of the study (i.e., 12 to 24 months) were compared between groups on ALN 5 and 10 mg/day for 6 months or continuously for 24 months. The objectives of this study were similar to those of the study conducted under Protocol # 029.

8.2.2 **Design**

Double-blind, randomized, placebo-controlled, multicenter study. Study was triple-blind for the first 6 months, After an interim analysis (maintaining blind status) after 6 months, the study was double-blind from Months 7 through 24.

8.2.3 **Protocol**

8.2.3.1 Population, procedure

Criteria for subject selection and exclusion were similar to those of the Protocol # 029.

After selection, subjects were randomly assigned to one of five treatment groups Table 14 shows the treatment regimens.

Table 14. Treatment regimens

Treatment	Duration of Treatment	
	Months 1 to 6	Months 7 to 24
Group A	Placebo	Placebo
Group B	ALN 5 mg	Placebo
Group C	ALN 5 mg	ALN 5 mg
Group D	ALN 10 mg	Placebo
Group E	ALN 10 mg	ALN 10 mg

ALN or placebo tablet was administered once daily in the morning with 250 mL of water. One hour before breakfast (or any other food or drink) or 2 hours after breakfast. Subjects were told not to lie down for at least one hour after taking medication.

All subjects took 500 mg of elemental calcium supplementation daily. Subjects were instructed to avoid taking other medications (with potentiality of causing gastrointestinal irritation) "as much as possible" during the entire course of the study.

Clinical observations and laboratory measurements were performed at similar intervals as of Protocol # 029.

Sponsor has assured that all investigators were qualified.

8.2.3.2 Endpoints

BMD of lumbar spine, proximal femur, and total body was evaluated (as a primary efficacy endpoint) at designated intervals. Definition of baseline BMD was similar to that used in Protocol # 029.

Biochemical markers of bone turnover and parameters related to calcium homeostasis were similar to those of Protocol # 029.

For the safety evaluation, clinical and routine laboratory parameters were evaluated at designated Visits.

8.2.3.3 Statistical Considerations

Null hypotheses proposed for the efficacy and safety of ALN vs placebo therapy were similar to those of the first study.

Sample size calculations indicated 95% power to detect "between and within-group differences in mean percent change from baseline of 3.4% and 2.4%, respectively. With 80% power, these figures are 2.7% and 1.9% for between and within-group comparisons, respectively with a SD of 4.67% change from baseline between-subject.

Based on the actual sample size for the ITT analysis, the study provided a 90 to 95% power to detect clinically meaningful differences between groups and within-group.

Tukey trend test was applied to assess the effect of ALN (5 and 10 mg/day for 2 years) treatment relative to placebo.

Subgroup analyses were also carried out for changes (from baseline) in BMD of spine with respect to variables such as smoking, oophorectomy status, age, number of months since menopause, height, weight, baseline lumbar spine BMD, and baseline U/DPyr/Cr.

Furthermore, correlation analysis was

performed to assess the relationship between changes in biochemical markers and spine BMD

Interim analysis was performed for the regulatory submission in Italy after 6 months of patient exposure. Sponsor assures that investigators, patients, and all persons connected to this study remained blinded until the study was complete after 24 months.

In statistical analyses of data both intention-to-treat (ITT) and per-protocol (P-P) approaches were used. In P-P approach, subjects with protocol violations were excluded from the analyses. Routine statistical methods were used for all data analyses.

8.2.4 **Results**

8.2.4.1 Patient disposition, comparability

The number of subjects entered into this controlled study by treatment group is shown in Table.

Table 15. Number of subjects by the treatment group.

	PBO*	ALN 5mg	ALN 10mg	ALN 5/0mg	ALN 10/0mg
No. of Subjects	56	56	61	59	59

PBO=Placebo

A total of 291 subjects entered into this study.

There were no significant differences between treatment groups with respect to continuous variables such as age, baseline lumbar spine BMD (by Lunar and non-Lunar machines), baseline serum osteocalcin, U/DPyr/Cr, BMI, estimated daily calcium intake,

height, weight, and number of months since menopause. Also, there were no significant differences between treatment groups in the baseline categorical variables.

The treatment groups were similar with regard to baseline BMD (measured by either Lunar or non-Lunar machines) of femoral neck, trochanter, intertrochanteric region, Ward's triangle, total hip, and total body.

There were no significant differences between treatment groups with respect to baseline biochemical indices of bone turnover, and serum calcium and phosphorus.

About 59% of the patients (N=291)who entered into this study, had at least one prestudy secondary diagnosis. There were no clinically significant secondary diagnosis that could significantly influence the outcome of the study. Among the secondary diagnoses, cardiovascular, musculoskeletal, digestive system, and urogenital system disorders were common.

Cardiovascular and CNS drugs were the common secondary medications that the subjects used within 14 days of the study drug.

Other than calcium carbonate, CNS, antiinflammatory, and anti-infective drugs were used concomitantly by about 43% of the subjects.

Subject accountability is presented in Table 16 (Sponsor's Table 15, vol.10, p. D-2624).

Table 15

Subject Accounting

	Total	PBO	ALN 5 mg	ALN 10 mg	ALN 5.0 mg	ALN 10.0 mg
ENTERED: Total(age range, years)	291 (40 to 69)	56 (40 to 69)	56 (40 to 59)	61 (40 to 69)	59 (40 to 69)	59 (40 to 59)
COMPLETED:	203	38	43	44	38	40
DISCONTINUED:	88	18	13	17	21	19
Clinical adverse experience	20	4	1	5	5	5
Laboratory adverse experience	1	0	0	0	1	0
Lost to follow-up	29	5	8	3	7	6
Withdrew consent	37	9	4	8	8	8
Other*	1	0	0	1	0	0

* Subject placed on hormone replacement therapy in violation of protocol
PBO = Placebo, ALN = Alendronate

Data Source: [4.4.1], [4.4.2], [4.4.3]

Not all subjects came in on the specified day of the Visit set in the protocol. Therefore, "relative day ranges" were established for the efficacy analysis. The relative day ranges for both efficacy and safety analyses are presented in Table 17 (Table 16, vol 12, p. D-2625).

Table 16

Relative Day Ranges for Efficacy and Safety Analyses

Time Point	Laboratory Efficacy Clinical and Laboratory Safety	BMD
Baseline	-100 to 1	-100 to 14
Month 3	2 to 134	--
Month 6	135 to 224	15 to 269
Month 9	225 to 314	--
Month 12	315 to 404	270 to 449
Month 15	405 to 494	--
Month 18	495 to 629	450 to 629
Month 24	630 to 850	630 to 850

Data Source: [3.3]

"If a subject had data for multiple visits within a day range for any given interval, then the valid data from the last visit were used in the analyses." For baseline mean value, the average of the values determined in the day range of -100 to 14 days for BMD and -100 to Day

1 for biochemical efficacy and clinical safety parameters were used.

A subject was not included in the ITT analysis, if there were no baseline data or at least one post-treatment measurement prior to that time point.

The sponsor has provided a list of reasons for excluding subjects in the ITT analysis. The stated reasons are appropriate and similar to those of the other controlled study.

8.2.4.2 **Efficacy Endpoint Outcomes**

a. **BMD**

i) Spine BMD-Lumbar spine BMD was the primary efficacy endpoint. The results are shown in Figure 2 and Tables 18-20 (Sponsor's Figure 1, vol.12, p.D-2631 and Tables 18-20, vol. 12, pp.D-2631-2634).

Figure 1

Lumbar Spine BMD
Mean Percent Change From Baseline ± SE of the Mean
(Intention-to-Treat Approach)

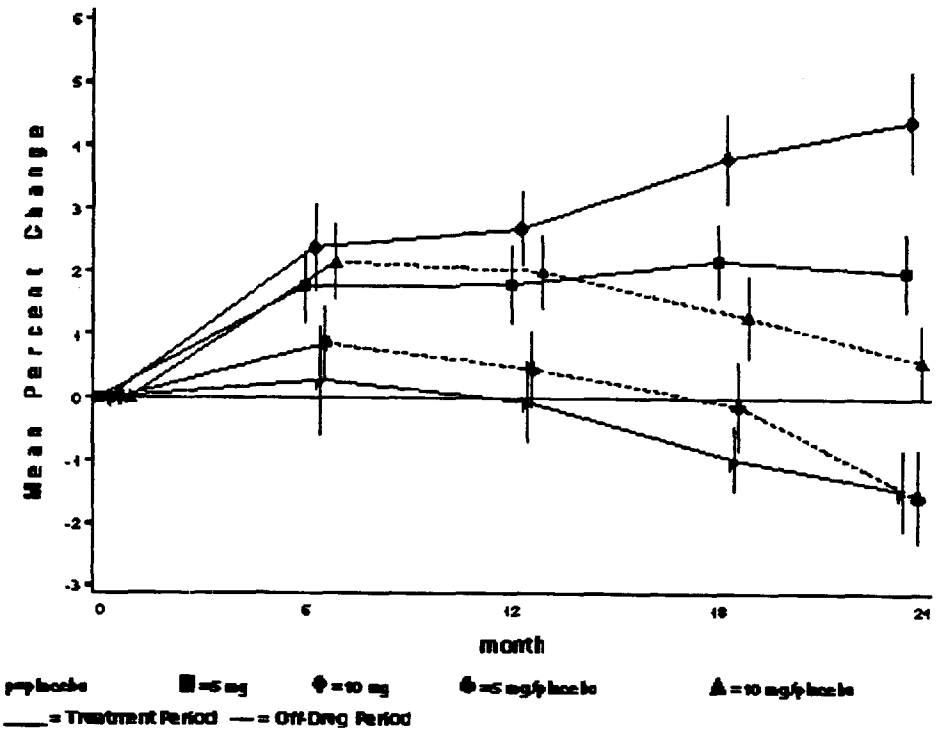


Table 18

Lumbar Spine BMD (g/cm^2)
Analysis of Percent Change From Baseline to Month 24
(Intention-to-Treat Approach)

Treatment	N	Means (Observed)		Percent Change From Baseline to Month 24			
		Baseline	Month 24	Mean	SD	Adjusted Mean	LSD Interval
Placebo	44	0.94	0.93	-1.47*	4.13	-1.47	(-2.45,-0.48)
5 mg	47	0.97	0.99	2.00**	4.31	2.06	(1.10, 3.01)
10 mg	52	0.97	1.01	4.40***	5.71	4.49	(3.58, 5.40)
5/0 mg	42	0.96	0.95	-1.57*	4.85	-1.45	(-2.46,-0.44)
10/0 mg	44	0.97	0.97	0.57	3.74	0.53	(-0.46, 1.51)

Within-treatment test of mean = 0 ***: $p \le 0.001$; **: $p \le 0.01$; *: $p \le 0.05$
Treatment-by-center interaction p-value: 0.166

Adjusted Trend Test		Overall		Pairwise Comparisons		Pooled
Doses Included	p-Value	p-Value	Treatment	Placebo	5 mg	SD
Placebo through 10 mg	<0.001	<0.001	5 mg	<0.001		4.66
Placebo through 5 mg	<0.001		10 mg	<0.001	0.010	

Data Source: [4.7]

Table 19

Lumbar Spine BMD (g/cm^2)
Analysis of Percent Change From Months 6 to Month 24
(Intention-to-Treat Approach)

Treatment	N	Mean (Observed)		Percent Change From Month 6 to Month 24			
		Month 6	Month 24	Mean	SD	Adjusted Mean	LSD Interval
Placebo	38	0.95	0.94	-1.58	4.80	-1.53	(-2.42,-0.64)
5 mg	48	0.99	0.99	0.39	3.60	0.56	(-0.23, 1.36)
10 mg	49	1.00	1.01	1.91***	3.48	1.90	(1.12, 2.69)
5/0 mg	43	0.96	0.94	-2.22***	4.06	-2.09	(-2.92,-1.25)
10/0 mg	48	0.99	0.97	-1.88***	3.70	-1.78	(-2.58,-0.99)

Within-treatment test of mean = 0 ***: $p \le 0.001$; **: $p \le 0.01$; *: $p \le 0.05$
Treatment-by-center interaction p-value: 0.134

Adjusted Trend-Test		Overall		Pairwise Comparisons				Pooled
Doses Included	p-Value	p-Value	Treatment	Placebo	5 mg	10 mg	5/0 mg	SD
Placebo through 10 mg	<0.001	<0.001	5 mg	0.014				3.90
Placebo through 5 mg	0.018		10 mg	<0.001	0.093			
			5/0 mg	0.524	0.001	<0.001		
			10/0 mg	0.765	0.004	<0.001	0.714	

Data Source: [4.7]

Table 20

Lumbar Spine BMD (g/cm^2)
Analysis of Percent Change From Month 12 to Month 24
(Intention-to-Treat Approach)

Treatment	N	Means (Observed)		Percent Change From Month 12 to Month 24			
		Month 12	Month 24	Mean	SD	Adjusted Mean	LSD Interval
Placebo	39	0.95	0.93	-1.53**	3.48	-1.39	(-2.16,-0.62)
5 mg	42	1.00	1.00	0.31	2.60	0.41	(-0.34, 1.15)
10 mg	45	0.99	1.01	1.86**	3.88	1.96	(1.24, 2.68)
5/0 mg	41	0.96	0.94	-2.11**	4.28	-1.92	(-2.69,-1.14)
10/0 mg	40	0.99	0.97	-1.70***	2.79	-1.62	(-2.37,-0.87)

Within-treatment test of mean = 0 ***: $p \le 0.001$; **: $p \le 0.01$; *: $p \le 0.05$
Treatment-by-center interaction p-value: 0.545

Adjusted Trend-Test		Overall	Treatment	Pairwise Comparisons				Pooled
Doses Included	p-Value	p-Value		Placebo	5 mg	10 mg	5/0 mg	SD
Placebo through 10 mg	<0.001	<0.001	5 mg	0.019				3.40
Placebo through 5 mg	0.017		10 mg	<0.001	0.035			
			5/0 mg	0.493	0.002	<0.001		
			10/0 mg	0.764	0.008	<0.001	0.700	

Data Source: [4.7]

In the placebo group, spine BMD decreased significantly (1.5%) from baseline at Month 24. Whereas, the ALN 5 and 10 mg (continuously) groups showed significant mean percent increases relative to both baseline and placebo, over 2 years. Increase in spine BMD in the ALN 10 mg group was significantly greater than 5 mg group. ALN 5 mg/day for 6 months only resulted in a significant mean decrease relative to baseline at Month 24. The 10mg for 6 month group showed a small nonsignificant mean increase at 24 months. There was no significant treatment-by-center interaction regarding treatment effect on spine BMD.

Analysis of BMD results by P-P approach showed similar outcome, but decrease at Month 24 at 5/0 mg group was not significant, relative

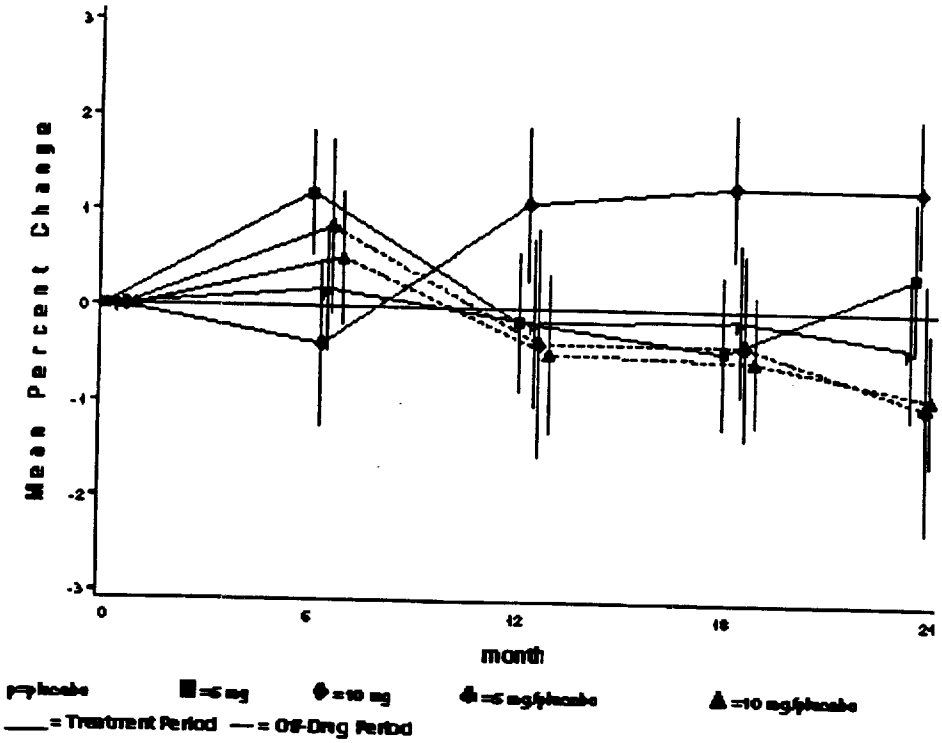
to baseline.

Both ALN 5/0 and 10/0 groups showed significant decreases from Month 6 to Month 24. Decreases were comparable to those of the placebo group. Consistently higher proportion of patients in the continuous ALN 5 and 10 mg groups attained a particular threshold (% change) of response at Month 24, relative to the placebo group.

ii) Femoral neck BMD- Changes in femoral neck BMD (a key secondary efficacy endpoint) to study drugs are shown in Figure 3 (Sponsor's Figure 3, vol. 12, p.D-2639).

Figure 3

Femoral Neck BMD
Mean Percent Change (±SE) From Baseline
(Intention-to-Treat Approach)



Data Source: [4.7]

The mean percent changes from baseline to Month 24 were 0.4,1.3,-1.0, and -0.9% at 5,10,5/0, and 10/0 mg doses, respectively. The placebo group lost about 0.4% (mean value) at Month 24. There were no significant differences between treatment groups with respect to mean percent changes in femoral neck BMD.

From Month 6 to Month 24, the mean percent changes were -1.2,-0.8, 1.3, and -1.7%,in the placebo, 5,10,5/0, and 10/0 mg groups, respectively. Only at the 10 mg ALN group the difference was significant compared to four other groups.

iii) Trochanter BMD- At doses of 5 and 10 mg for 2 years, mean increases in BMD from baseline were 2.6% and 2.9%, respectively at Month 24. The placebo group showed no significant change at Month 24 compared to baseline value. In groups with 6 months of treatment (5 or 10 mg/day) showed slight increase of 1.4 or 1.8%, respectively.

Treatment-by-center and treatment-by-machine (Lunar vs non-Lunar) analyses showed no significant differences in the outcome of the effect of ALN on trochanter BMD. The results are presented in Table 21(Sponsor's Table 25, vol. 12, p. D-2645).

Table 25

Trochanter BMD (g/cm^2)
Analysis of Percent Change From Baseline to Month 24
(Intention-to-Treat Approach)

Treatment	N	Means (Observed)		Percent Change From Baseline to Month 24			
		Baseline	Month 24	Mean	SD	Adjusted Mean	LSD Interval
Placebo	22	0.68	0.68	0.63	9.32	1.01	(-0.99, 3.01)
5 mg	28	0.68	0.70	2.64*	5.34	2.92	(1.16, 4.69)
10 mg	29	0.70	0.72	2.92*	6.11	2.82	(1.06, 4.57)
5/0 mg	23	0.68	0.69	1.37	7.23	1.56	(-0.39, 3.52)
10/0 mg	25	0.64	0.65	1.78	5.63	1.89	(0.02, 3.75)

Within-treatment test of mean = 0 ***: $p \leq 0.001$; **: $p \leq 0.01$; *: $p \leq 0.05$
Treatment-by-center interaction p-value: 0.126

Adjusted Trend-Test		Overall		Pairwise Comparisons		Pooled
Doses Included	p-Value	p-Value	Treatment	Placebo	5 mg	SD
Placebo through 10 mg	0.415	0.821	5 mg	--	--	6.63
Placebo through 5 mg	--		10 mg	--	--	

Data Source: [4.7]

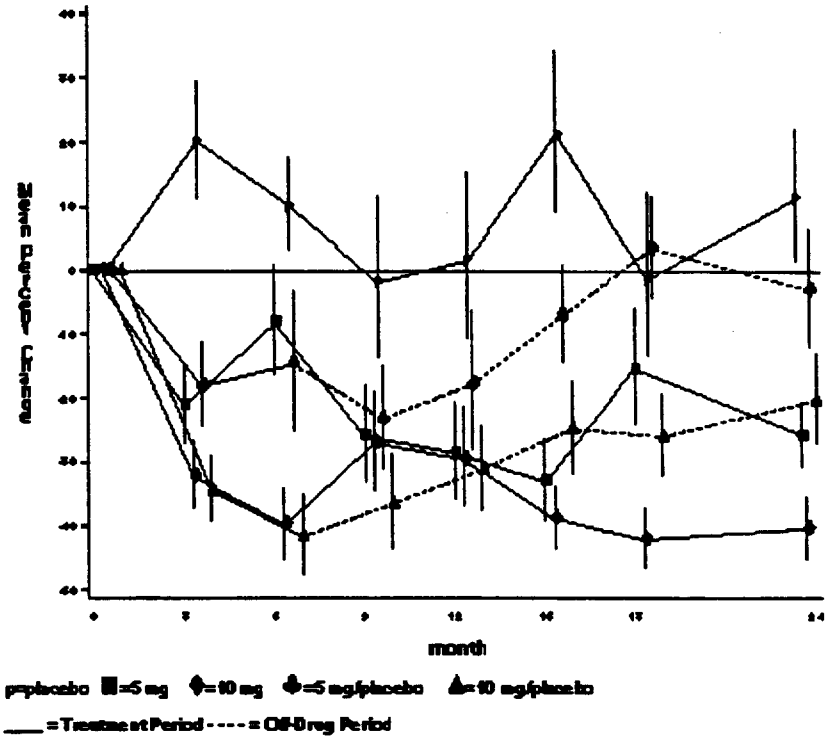
b. Biochemical Efficacy Endpoints

The purpose of evaluation of the biochemical endpoints was to elucidate the "mechanism of effect of alendronate on the key clinical efficacy endpoints, i.e., BMD results." Analyses were performed for Ln (fraction of baseline) at Month 24.

i) Urinary DPyr/Cr- The results are shown in Figure 4 (Sponsor's Figure 5, vol.12, p. D-2650).

Figure 5

Urinary Deoxypyridinoline/Creatinine (nmol/mmol)
Geometric Mean Percent Change ± SE of Mean
Transformed From Ln (Fraction of Baseline)
(Per-Protocol Approach)

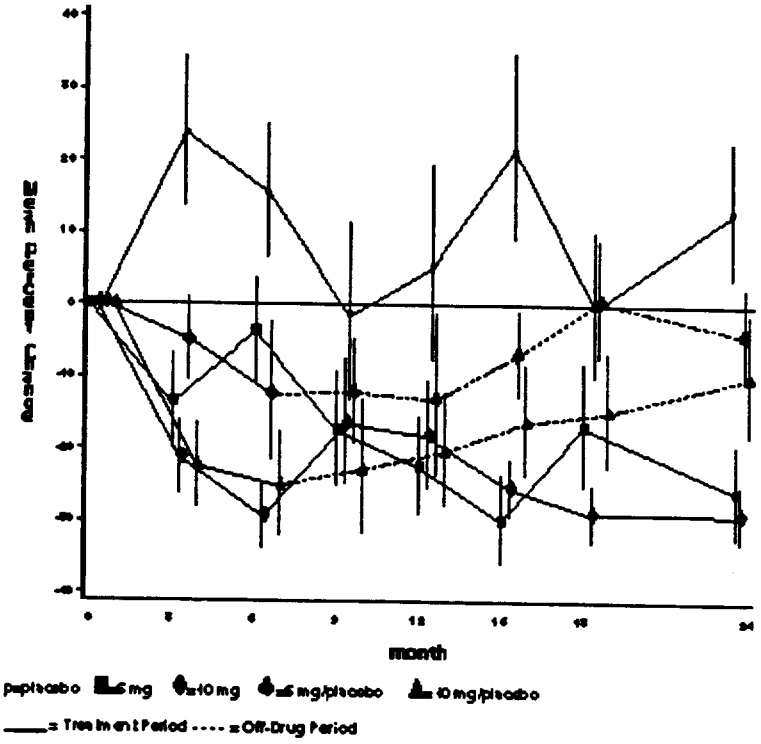


In both 5 and 10 mg ALN groups U/DPyr/Cr decreased significantly at Months 3 and 6 and remained suppressed throughout the course of the study. In the 5/0 and 10/0 mg doses groups, U/DPyr/Cr decreased maximally between 6 and 9 months and then tended to return toward baseline. At 5 and 10 mg doses decreases from baseline and compared to the placebo group,were statistically significant. There was no difference between two ALN treatment groups with respect to mean decreases in U/DPyr/Cr.

ii)Urinary pyridinoline/creatinine-The results are shown in Figure 5 (Sponsor's Figure 6, vol. 12, p.D-2653).

Figure 6

Urinary Pyridinoline/Creatinine (nmol/mmol)
Geometric Mean Percent Change ± SE
of Mean Transformed From Ln
(Fraction of Baseline)
(Per-Protocol Approach)



Data Source: [4.45]

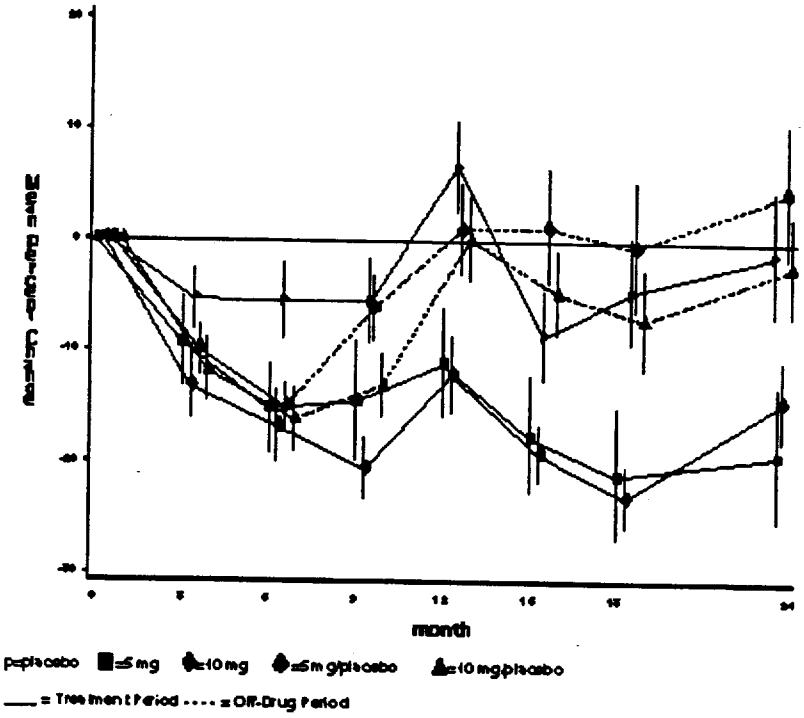
The placebo group showed no significant change in U/Pyr/Cr at Month 24. At 5 and 10 mg doses of ALN, 25% to 330% decreases were observed between months 6 and 15 and suppression was maintained during the rest of the study period. With 5/0 and 10/0 mg doses, initial decrease during months 3 to 9 were comparable to that observed with continuous administration at the same doses. After 6 to 9 months, the mean values tended to return toward baseline. At the end of the treatment period (Month 24), decreases in 5 and 10 mg groups were significant relative to baseline and placebo. There was no

significant difference between two treatment groups with respect to decreases in U/Pyr/Cr.

iii) Serum alk. phosphatase (SAP)- The results are shown in Figure 6 (Sponsor's Figure 7, vol.12, p.D-2656).

Figure 7

Serum Alkaline Phosphatase (U/L)
Geometric Mean Percent Change ± SE of Mean
Transformed From Ln (Fraction of Baseline)
(Per-Protocol Approach)



Data Source: [4.46]

At Month 6, in both 5 and 10 mg groups SAP decreased by 15 to 20% and decreases were maintained during the rest of the study period. The placebo group showed some small increase or decrease between months 3 and 15 and thereafter returned toward baseline at Month 24.

iv) Serum osteocalcin- In all treatment groups (including

placebo) serum osteocalcin decreased (-14.7 to -38.2%) during months 3 to 9. The placebo and ALN 5/0 mg groups showed some tendency to increase after 9 months, but for all groups osteocalcin levels were below baseline means at Month 24.

v) Urinary calcium, serum phosphate, and urinary calcium/creatinine- There were initial small decreases during Months 3 to 6, but returned toward baseline or above baseline between Months 9 and 24.

Serum phosphate decreased in all treatment groups after initiation of treatment and remained decreased from baseline at Month 24.

There were no significant changes from baseline in urinary calcium/creatinine values during the course of the study.

Correlation between selected clinical, biochemical, and demographic parameters- Baseline lumbar spine BMD showed a positive correlation with subject's body mass index (BMI, kg/m^2) and body weight. Baseline biochemical markers of bone turnover showed no consistent correlation with changes in spine BMD from baseline to Month 24 of the study.

There were no significant differences in treatment-by-subgroup interaction for variables such as age, smoking, oophorectomy, renal function, number of months since menopause, height, weight, baseline spine BMD, and baseline U/Dpyr/Cr.

8.2.4.3 **Safety Outcomes**

One hundred seventy-five of the 291 subjects (60%) who completed the

study, experienced at least one clinical AE. Clinical AE summary is presented in Table 22.

Table 22. Summary of clinical AE.

No. Of Subjects	Placebo N=56	ALN 5 mg N=56	ALN 10 mg N=61	ALN 5/0mg N=59	ALN 10/0mg N=59
With one or more AEs	33 (59%)	33 (59%)	40(56.6%)	30(50.8%)	39(66.1%)
With serious AEs	2(3.6%)	2(3.6%)	1(1.6%)	2 (3.4%)	2 (3.4%)

There were no patients with serious drug-related Aes. Two (3.6%), 3(4.9%), 2 (3.4%), and 3(5.1%) of patients were reported to withdraw from the study due to a drug-related AE in placebo, 10mg, 5/0 mg, and 10/0 mg groups, respectively.

There were no significant differences in clinical AEs by the body system between treatment groups.

The most common AEs (experienced by at least 5% of patients in any treatment group) were abdominal pain, influenza, and back pain.

Regarding drug-related (possibly, probably, or definitely) clinical Aes, abdominal pain was reported in 7.1%,6.6%,5.1%, and 10.2% of patients in placebo, ALN 10mg, 5/0 mg, and 10/0 mg groups, respectively. Drug-related gastrointestinal AEs are presented in Table 23 (Sponsor's Table 35, vol. 12, p.D-2674).

Table 35 (Cont.)

Clinical Adverse Experiences
Considered Possibly, Probably, or Definitely
Drug Related by Investigator--Subject Count (%)

	Placebo (N = 56)	ALN 5 mg (N = 56)	ALN 10 mg (N = 61)	ALN 5/0 mg (N = 59)	ALN 10/0 mg (N = 59)
Musculoskeletal Disorders					
Arthralgia	0	0	0	1 (1.7)	0
Pain, arm	0	0	0	1 (1.7)	0
Pain, back	0	1 (1.8)	0	0	0
Nervous System and Psychiatric Disorders					
Dizziness	0	0	0	1 (1.7)	0
Headache	0	0	1 (1.6)	0	0
Vertigo	0	0	0	0	1 (1.7)
Skin and Skin Appendage Disorders					
Erythema	0	0	1 (1.6)	1 (1.7)	0
Rash	0	0	1 (1.6)	0	0
Urogenital System Disorders					
Lesion, breast benign	1 (1.8)	0	0	0	0

This table contains counts of subjects. Although a subject may have two or more clinical adverse experiences, the subject will be counted only once in "Number (%) of subjects with any clinical adverse experience."

Data Source: [4.34]

Table 38

Upper GI Clinical Adverse Experience Summary--Summary Count (%)

	Placebo (N = 56)	ALN 5 mg (N = 56)	ALN 10 mg (N = 61)	ALN 5/0 mg (N = 59)	ALN 10/0 mg (N = 59)
Number (%) of subjects with one or more adverse experiences	10 (17.9)	8 (14.3)	8 (13.1)	11 (18.6)	13 (22.0)
with drug-related adverse experiences	5 (8.9)	1 (1.8)	4 (6.6)	5 (8.5)	9 (15.3)
with serious adverse experiences	0	0	0	0	0
with serious drug-related adverse experiences	0	0	0	0	0
withdrawn from therapy due to adverse experiences	1 (1.8)	1 (1.8)	1 (1.6)	3 (5.1)	2 (3.4)
withdrawn from therapy due to a serious adverse experience	0	0	0	0	0
withdrawn from therapy due to a drug-related adverse experience	1 (1.8)	0	1 (1.6)	2 (3.4)	2 (3.4)
withdrawn from therapy due to a serious drug-related adverse experience	0	0	0	0	0

Data Source: [4.31]

Nine subjects experienced serious AEs and these were vaginal neoplasm, varicose vein, venous insufficiency, manic depression, osteoarthritis of the hip, brain tumor (diplopia), cyst, leg pain, and nerve entrapment. None of these serious AEs were considered drug-related by the investigators.There was no death in this study.

A total of 20 subjects were reported to discontinue the study due to AEs. Of these 20 subjects, 10 were considered study drug-related by the investigator.

Discontinuations were due to: diarrhea (probable) in 1 placebo; nausea and abdomin. pain (possible) in 1 placebo; erythema (possible) in 1 ALN 5 mg; rash (possible) in 1 ALN 10 mg; abdominal pain (possible) in 1 ALN 10 mg; abd. pain (possible) in 2 ALN 5/0 mg; abdominal pain (possible) in 2 and glossitis in 1 ALN 10/0 mg group.

Review of summary of AEs for individual subjects who discontinued the study due to drug-elated Aes, revealed that severe erythema, moderate skin rash, moderate to severe abdominal pain, dizziness, asthenia/fatigue, abdominal distension, and glossitis occurred in some patients as possibly or probably ALN-related AEs.

Upper gastrointestinal AEs- Upper G-I AEs are summarized in Table 24 (Sponsor's Table 38, vol. 12, p.2685).

Table 24. Summary of upper G-I AEs.

Digestive System Disorders					
Acid regurgitation	1 (1.8)	0	0	0	2 (3.4)
Diarrhea	2 (3.6)	0	1 (1.6)	0	0
Dyspepsia	0	0	0	0	1 (1.7)
Gastritis	0	1 (1.8)	0	0	0
Gastroenteritis	0	0	0	1 (1.7)	0
Glossitis	0	0	0	0	1 (1.7)
Nausea	1 (1.8)	0	0	1 (1.7)	0
Metabolic, Nutritional, Immune Disorders					
Weight gain	0	0	0	1 (1.7)	0

Fractures as adverse events- Five subjects experienced fractures (all nonvertebral) during the study.

In 4 subjects, fractures were associated with trauma and in the remaining subject etiology of fracture was not verified. No subject discontinued the study due to fracture episode.

Laboratory AEs- Of the total 291 subjects, 273 subjects experienced at least one laboratory AE post-baseline. Of the 273 subjects, 161 subjects had at least one or more laboratory AEs. About 18% of patients in the placebo and about 19.3% to 31% in the ALN groups experienced drug-related laboratory AEs. Only one subject in the ALN 10 mg group was reported to experience serious laboratory AEs. One patient in the ALN 5/0 mg group discontinued the study due to AEs.

Hypocalcemia occurred consistently (up to 13% of treated patients) in the ALN groups compared to none in the placebo group. However, all episodes of hypocalcemia were asymptomatic and none required withdrawal from treatment.

Few subjects (3 to 6) experienced decreased hemoglobin or decreased hematocrit during the study. The report showed that in most cases abnormal hematologic episodes occurred during placebo phase (5/0 or 10/0 group), or during the period when the subject was off the drug. (**Comments**: The numbers are too few to draw any conclusion on the causality of these laboratory AEs).

Review of the drug-related laboratory AEs revealed no significant AEs that could be attributable to ALN therapy. In one site, there were three cases (one in the placebo and 1 each in 5 and 10 mg of ALN)of drug-related eosinophilia, but laboratory data

could not be verified by the sponsor.

One patient in the ALN 10 mg group was reported to develop hyperkalemia (serum potassium of 6.8 mEq/L (normal range 3.5-5.3 mEq/L). This adverse event was due to overdose of potassium supplement (self-prescribed). One patient in the ALN 5 mg group was reported to develop monoclonal gammopathy (immunoglobulin G positive).

The different treatment groups were similar with respect to changes in **body weight, systolic blood pressure, and pulse rate** of the patients.

Changes in predefined limits of laboratory measurements- Relative to the placebo group, a lower proportion of subjects in the 10/0 mg group and a higher proportion of subjects in 10 mg group exceeded the predefined limits for neutrophils and serum creatinine, respectively. (**Comments**: It is difficult to explain the clinical significance of this observation).

Review of the summary statistics for change from baseline at 3,6,9, 12,15,18,and 24 months revealed no consistent results.

Changes from baseline in serum chemistry parameters (e.g., albumin, creatinine, potassium, sodium, glucose, BUN, AST, and ALT were not clinically significant. Between-group differences were also not significant.

Sponsor's discussion:

The objective of this placebo controlled study was to examine the effects of ALN (5 or 10 mg/day for 24 months) on BMD of the lumbar

spine, proximal femur, and total body in early menopausal women.

At 24 months, ALN at both doses caused significant increase in lumbar spine BMD relative to both baseline and placebo. The placebo treated subjects showed significant decreases in BMD despite adequate daily calcium supplementation. Groups of subjects who received ALN at doses of 5 or 10 mg/day for 6 months(followed by 18 months of placebo)also showed small increase in BMD at Month 6 followed by loss of BMD (after stoppage of ALN therapy) at a rate similar to that of the placebo group. The increases in BMD at ALN 10 mg/day were greater than that observed at 5 mg/day. At 5mg/day dose, ALN produced no increase in BMD during the second year of treatment, but prevented bone loss. Compared to the placebo group, the difference was +0.3% in the ALN vs -1.5% decrease in the placebo.

The effect of ALN therapy on femoral neck BMD was not clear (with ITT analysis). However, per protocol analysis of the data showed a significant 2% increase. These results were different from those previously reported in early menopausal and postmenopausal women with established osteoporosis. (Comments: Sponsor states that poor precision of the hip BMD measurements,"less than optimal BMD quality control procedure and/or densitometer operator training" may be the contributing factors for lack of significant effect of ALN on femoral neck BMD). ALN therapy resulted in significant increase from baseline in trochanter BMD, but not to the placebo group.

ALN therapy resulted in decreased markers of bone resorption (urinary DPyr and Pyr) and bone formation (SAP and serum osteocalcin).The placebo group showed no significant changes in these markers during the study except for osteocalcin which decreased). The effects of ALN treatment on markers of bone turnover tend to indicate a partial inhibition of bone turnover. There was no evidence of cumulative or progressive inhibition of bone turnover as a result of 24 months of ALN treatment. Discontinuation of ALN therapy resulted in gradual return toward baseline values. These data seem to indicate that "continued dosing with alendronate is necessary to achieve persistent suppression of bone turnover."

From a safety point of view, the results of this study showed no significant differences between the treatment groups with regard to frequency of clinical (including upper G-I) and laboratory AEs.

In conclusion, ALN treatment at doses of 5 or 10 mg/day for 24 months caused significant increase in lumbar spine BMD relative to baseline and placebo. Discontinuation of treatment resulted in a return of suppressed markers of bone resorption toward baseline and resumption of loss of BMD at a rate similar to that observed in the placebo group.

Continuous administration of ALN is necessary to obtain sustained increases in spine BMD.

The overall safety profile of ALN was comparable to that of the placebo.

Reviewer's Comments: The overall design of this controlled study was

similar to that of the previous prevention study (Protocol # 029).

The objectives were also to evaluate the safety, and effect of ALN therapy (relative to placebo) on BMD of spine, hip, and total body in early postmenopausal women. This study differed from the other study with regard to the duration of treatment; at 5 and 10 mg/day doses ALN was administered for 6 months to 2 years as opposed to 3 years in other study. This study was also different from Protocol 029, with respect to monitoring of study sites (not all sites were monitored by MRL), densitometers used (from four different manufacturers), and quality assurance procedure. Additionally, in this study baseline hip scans were not performed routinely in all subjects.

In both studies, subjects were recruited based on their time since menopause, age (between 40 and 60 years),and baseline BMD of spine (similar mean values as of Study # 029). None of these subjects had a history of osteoporotic fractures.

Subjects with active upper G-I disorders were excluded from the study.

The results showed increases from baseline in spine BMD at both doses (5 mg and 10 mg/day). Increase at 10 mg/day was greater than that observed at 5 mg dose. At 5 mg dose, increase in spine BMD at Month 24 was comparable (2.65% vs 2.0%) between the two studies (Protocols 029 and 038).

Increase in spine BMD in the ALN group at a dose of 5 mg/day is approximately 3.5% relative to placebo. Increase in the BMD of

spine is likely to decrease the long-term risk of vertebral fractures. This assumption is based on the relationship between bone mass and fracture reported in the literature.

In contrast to Protocol 029, the results of ALN therapy on BMD of hip (femoral neck, trochanter, and intertrochanteric regions) and total body were not consistent, but appear to indicate similar trends.

The effects of ALN on biochemical markers of bone turnover indicate its primary mechanism of action (i.e., inhibition of bone resorption). **There is no evidence that ALN therapy for 24 months leads to "complete" inhibition of bone turnover, nor its effect is cumulative or progressive.**

Stoppage of ALN therapy after 6 months resulted in return of suppressed biochemical markers of bone turnover (U/DPyr and SAP) toward baseline values. **This finding seems to suggest continuous treatment with ALN in this study population, in order to achieve the expected therapeutic effect.**

The safety profile of ALN at doses of 5 and 10 mg/day for 6 months to 24 months is similar to that reported in Protocol 029.

8.3 Reviewer's Trial #-3 Sponsor's Protocol # 055

This multicenter (4-investigator sites) study was carried out in the U.S., U.K., and Denmark.

Title: A population-based, randomized, double-blind, placebo-controlled study of ALN for early intervention in bone loss in postmenopausal women. The study has an open randomized estrogen/progestin (E/P) comparison group.

8.3.1 **Objective/Rationale**

Primary objective- a)To determine the safety, tolerability, and efficacy of ALN (2.5 and 5 mg/day for 24 months) in early postmenopausal women. b) To compare the tolerability and efficacy of each of the doses of ALN with that of the combined E/P.

Secondary objectives- a) To examine the value of biochemical markers in selecting subjects with rapid bone loss in monitoring the response to ALN therapy, b) to examine the relationship between dietary calcium intake and rate of bone mass loss in either treatment group, c) to determine the *in vivo* coefficient of variation of the DXA measurements, and d) to determine utility of X-ray, and single X-ray absorptiometry (of calcaneus) in measuring bone mineral density, and monitoring response to treatment.

The rationale for use of ALN and estrogen therapy is well documented in the literature. Both treatment regimens are approved for the management of postmenopausal osteoporosis.

8.3.2 **Design**

Randomized, double-blind, placebo-controlled study with an open-labeled randomized E/P group.

Study consists of two strata:

Startum 1: Included subjects randomized to receive open-label E/P and blinded placebo, ALN 2.5 or 5 mg).

Startum 2: Included subjects to receive blinded ALN (2.5 or 5 mg) or placebo therapy for 24 months.

8.3.3 **Protocol**

8.3.3.1 Population, procedure

Postmenopausal subjects aged 45 to 59 years were recruited for this study.

The criteria for selection of subjects were similar to those of Protocols 029 and 038.

The exclusion criteria were also similar to those of other controlled studies. In this study hysterectomized subjects were also excluded.

The study was designed as a 2-year study with a 4-year double-blind extension.

A total of 1609 subjects were enrolled in this study across four centers. Treatment groups are presented in Table 25 (Sponsor's Table 1., vol. 14, p. D-3860).

Table 1

Treatment Groups

Group	Treatment	Stratum 1 N	Stratum 2 N	Total
A	PBO	109	393	502
B	ALN 2.5 mg	109	390	499
C	ALN 5 mg	107	391	498
D	E/P	110	--	110
Total		435	1174	1609

PBO = placebo; ALN = alendronate; E/P = estrogen/progestin

Data Source: [3.2]

Treatment regimens-

E/P regimen:

U.S. Study- Premarin (conj. estrogens) 0.625 mg/day and Provera (medroxyprogesterone acetate) 5mg/day continuously.

European sites- 17beta-estradiol 2 mg/day for 12 days, then 17beta-E_2 2mg/day + norethisterone acetate (NETA) 1mg/day for 10 days, and 17beta-E_2 1mg/day for 6 days, repeated in 28-day cycles. The regimen is termed as TRISEQUEN. E/P was taken by the subjects following the labeling instructions.

ALN dose selection for prevention- The chosen ALN dose was expected to cause statistically and clinically significant increases in spine, total hip, and total body BMD relative to placebo. The target proportions of postmenopausal women with apparent bone loss were shown in Table 26 (Sponsor's Table 5, vol., 14, p. D-3871).

Table 5

Guidelines for Choosing a Prevention Dose

	Target Proportion of Subjects With Apparent Bone Loss at Different Skeletal Sites: Acceptable (Ideal)	
	≤3 Years Postmenopausal	>3 Years Postmenopausal
Lumbar spine BMD	<30% (≅25%)	<20% (≅15%)
Total hip BMD	<40% (≅30%)	<30% (≅20%)
Total body BMD	<40% (≅30%)	<30% (≅20%)

Data Source: [3.8.1]

ALN treatment: One ALN or placebo tablet was self administered with 6 to 8 ounces of water in the morning. (Dosing instructions were the same as for the approved treatment schedule).

Clinical observations and laboratory procedures were similar to those of other controlled studies.

Bone mineral density was measured by using Hologic 2000 densitometer at all sites. Sponsor has assured adequate quality controls for bone density measurements. BMD measurements at spine, hip (total hip and subregions such as the femoral neck, trochanter, and Ward's triangle), forearm, and total body were repeated every year.

Follow-up visits were at 6-month intervals postrandomization.

Log fractions of the baseline values of biochemical markers of bone turnover were determined at 6,12, 18, and 24 months.

Table 27 (Sponsor's Table 2, vol. 14, p. D-3862) presents spine BMD criteria for

identification of "fast bone losers."

Table 2

Threshold Bone Loss for Fast Bone Losers

Year	Percent Loss of Spine BMD From Baseline	
	Current BMD* ≥ 0.8 g/cm^2	Current BMD* <0.8 g/cm^2
1	8	6
2	11	8
* Spine BMD at most recent measurement		

Data Source: [3.2]

Fast bone losers were eligible to receive open-label treatment with 5 mg of ALN daily or to discontinue the study.

In this study subjects with too low ($\leq$ 0.87 g/cm^2 by Lunar, or 0.75 g/cm^2 by non-Lunar) or too high (as specified in Protocols 029 and 038) spine BMD.

The first subject was recruited on 9/9/92, and the last subject completed 2-year study on 8/10/95.

Other clinical efficacy evaluations- Change in **stature** from baseline at each time point and the rate of change at Month 24 was assessed. Change in **pain score** (based on the Brief Pain Inventory questionnaire) from baseline to Month 12 and Month 24 was evaluated. Also, the proportion of subjects who lost tooth ($\leq$ 1 tooth vs $\geq$ 2 teeth) was compared across treatment groups.

Routine clinical and laboratory safety data were derived at clinic visits and from case report forms.

8.3.3.2 **Endpoints:**

Bone mineral density was the primary efficacy endpoint to evaluate the rate of bone mass loss. Percent change from baseline BMD was calculated (100 x[on-treatment value -

baseline value]/baseline value) at Months 12 and 24 for each of the sites.

For biochemical markers of bone turnover, criteria were similar to those used in other controlled clinical trials.

Clinical and laboratory safety variables were evaluated using same criteria as used in other controlled clinical trials. Attempts were made to assess a dose-response relationship to clinical and laboratory AEs.

8.3.3.3 Statistical considerations: Hypotheses tested were similar to those of other controlled clinical trials.

Power calculation was performed considering a dropout rates of about 5 or 10%/year at significance levels of 0.01, or 0.05. With a power of 95%, small cumulative difference of 0.7 to 2.5% could be detected between the placebo and ALN groups after 24 months.

Other statistical considerations were similar to those of Protocols 029 and 038.

8.4.4 **RESULTS**

8.4.4.1 Patient disposition, comparability:

Of a total 1618 subjects randomized into the study, 9 discontinued the study prior to taking any study drug. Therefore, the clinical data for the 1609 subjects were evaluated.

There were no clinically significant differences between the treatment groups with respect to all continuous baseline characteristics (i.e., age, baseline spine BMD, serum osteocalcin, baseline U/N-telopeptide/Cr, BMI, daily estimated calcium intake, height, number of years since menopause, weight, oophorectomy status, lifestyle variables, family history of OP and/or fractures, race, renal

function, etc.).

Baseline BMDs of lumbar spine, total hip, and total body are summarized in Tables 27-30 (Sponsor's Tables 12-14, vol. 14, pp. D-3888-3889).

Table 12

Summary of Baseline Lumbar Spine BMD (g/cm^2)
(Intention-to-Treat Approach)

Treatment Group	Strata 1 and 2 Combined: PBO Comparison		Stratum 1: Cohorts E/P Comparison			
			U.S.		European	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
PBO	461	0.94 (0.12)	51	0.96 (0.09)	50	0.94 (0.14)
ALN 2.5 mg	452	0.93 (0.13)	44	0.97 (0.14)	50	0.93 (0.13)
ALN 5 mg	445	0.95 (0.14)	47	0.94 (0.11)	46	0.91 (0.13)
E/P	--	--	53	0.93 (0.12)	49	0.93 (0.12)

PBO = placebo; ALN = alendronate; E/P = estrogen/progestin

Data Source: [4.22.1], [4.23.1]

Table 13

Summary of Baseline Total Hip BMD (g/cm^2)
(Intention-to-Treat Approach)

Treatment Group	Strata 1 and 2 Combined: PBO Comparison		Stratum 1: Cohorts E/P Comparison			
			U.S.		European	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
PBO	461	0.85 (0.11)	51	0.84 (0.11)	50	0.86 (0.10)
ALN 2.5 mg	452	0.84 (0.12)	44	0.85 (0.15)	50	0.85 (0.10)
ALN 5 mg	445	0.85 (0.12)	47	0.84 (0.11)	46	0.85 (0.11)
E/P	--	--	53	0.83 (0.12)	49	0.85 (0.10)

PBO = placebo; ALN = alendronate; E/P = estrogen/progestin

Data Source: [4.22.3], [4.23.2]

Table 14

Summary of Baseline Total Body BMD (g/cm^2)
(Intention-to-Treat Analyses)

Treatment Group	Strata 1 and 2 Combined: PBO Comparison N	Strata 1 and 2 Combined: PBO Comparison Mean (SD)	Stratum 1: E/P Comparison U.S. N	Stratum 1: E/P Comparison U.S. Mean (SD)	Stratum 1: E/P Comparison European N	Stratum 1: E/P Comparison European Mean (SD)
PBO	454	1.037 (0.09)	49	1.042 (0.07)	50	1.029 (0.09)
ALN 2.5 mg	444	1.033 (0.09)	44	1.062 (0.11)	50	1.023 (0.09)
ALN 5 mg	439	1.035 (0.09)	47	1.039 (0.08)	46	1.029 (0.09)
E/P	--	--	52	1.044 (0.08)	49	1.025 (0.09)

PBO = placebo; ALN = alendronate; E/P = estrogen/progestin

Data Source: [4.22.5], [4.23.5]

Secondary diagnoses-Common secondary diagnoses for the combined strata and stratum 1 were hypertension, hypercholesterolemia, back pain, headache, and menopausal disorders and these disorders occurred at similar frequencies across the treatment groups within a stratum.

Concomitant therapies- The use of the common concomitant medications (e.g., ibuprofen, acetaminophen, aspirin, and vitamins/minerals) appears to be clinically insignificant.

Subject accounting and the number of subjects excluded from the efficacy analyses are presented in Tables 31 and 32 (Sponsor's Tables 18 and 19, vol. 14, pp.D-3899-3900).

Table 18

Subject Accounting
Strata 1 and 2 Combined

	Total	Treatment Groups			
		PBO	ALN 2.5 mg	ALN 5 mg	E/P
ENTERED (all females)	1609	502	499	498	110
Age in Years:					
40 to 49	272	92	78	85	17
50 to 59	1331	406	421	412	92
60 to 69	6	4	0	1	1
Completed 24 Months of Treatment:	1303	409	407	396	91
Discontinued Prior to 24 Months:					
Protocol deviation	30	9	12	9	0
Clinical adverse experience	109	27	26	41	15
Laboratory adverse experience	2	1	0	1	0
Lost to follow-up	26	10	8	8	0
Withdrew consent	139	46	46	43	4

PBO = placebo; ALN = alendronate; E/P = estrogen/progestin

Data Source: [4.5] and [4.11]

Table 19

Lumbar Spine BMD
Number of Subjects Included/Excluded From Analysis of
Percent Change From Baseline at Month 24 in Primary
BMD Efficacy Parameter

	PBO	ALN 2.5 mg	ALN 5 mg	E/P
Total Entered	502	499	498	110
Total Included in:				
Intention-to-treat analysis	461 (92%)	452 (91%)	445 (89%)	102 (93%)
Per-protocol analysis	386 (77%)	390 (78%)	376 (76%)	87 (79%)
Total Excluded From:				
Intention-to-treat analysis	41 (8%)	47 (9%)	53 (11%)	8 (7%)
Per-protocol analysis	116 (23%)	109 (22%)	122 (24%)	23 (21%)

PBO = placebo; ALN = alendronate; E/P = estrogen/progestin

Data Source: [4.12.1 to 4.12.3]

Review of the reasons for exclusion from the lumbar spine analysis at 24 months revealed no clinically significant information.

8.4.4.2 **Efficacy Endpoint Outcomes**

Lumbar spine BMD (primary endpoint) -

Percent changes in BMD from baseline by time point and at Months are presented in Tables 33-34. and Figure 6 (Sponsor's Tables 21-22 and Figure 1, vol. 14, pp. D-3905-3906).

Table 21

Lumbar Spine BMD (g/cm^2)
Analysis of Percent Change From Baseline by Time Point
(Intention-to-Treat Approach)
Strata 1 and 2 Combined

Time Point	Treatment	N	% Change From Baseline			
			Mean	SE	Median	Range
Month 12	PBO	461	-1.05	0.12	-0.99	
	ALN2.5 mg	451	1.98	0.13	1.98	
	ALN5 mg	445	2.74	0.12	2.56	
Month 24	PBO	461	-1.78	0.15	-1.80	
	ALN2.5 mg	452	2.28	0.16	2.43	
	ALN5 mg	445	3.46	0.16	3.57	

PBO = placebo; ALN = alendronate

Data Source: [4.7]

Table 22

Lumbar Spine BMD (g/cm^2)
Analysis of Percent Change From Baseline at Month 24
(Intention-to-Treat Approach)
Strata 1 and 2 Combined

Treatment	N	Means (Observed)		Percent Change From Baseline			
		Baseline	Month 24	Mean	SD	Adjusted Mean	LSD Interval
PBO	461	0.94	0.93	-1.78***	3.24	-1.87	(-2.10, -1.64)
ALN 2.5 mg	452	0.93	0.95	2.28***	3.41	2.19	(1.95, 2.42)
ALN 5 mg	445	0.95	0.98	3.46***	3.37	3.38	(3.14, 3.61)

PBO = placebo; ALN = alendronate
Within-group test of mean = 0
***: ≤ 0.001 **: p ≤ 0.01 *: p ≤ 0.05
Treatment-by-center interaction p-value: 0.529

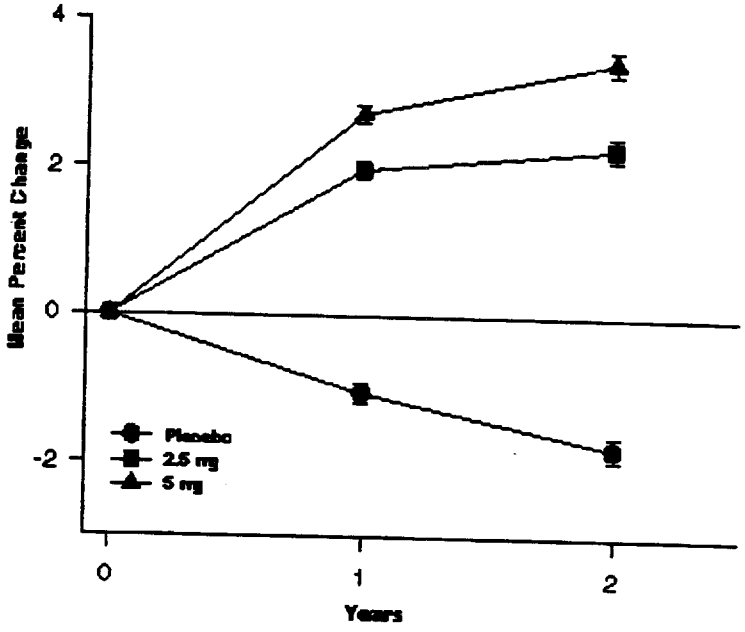
Adjusted Trend-Test		Overall		Comparison Between Doses		Pooled
Dose Included	p-Value	p-Value		PBO	2.5 mg	SD
PBO through 5 mg	<0.001	<0.001	2.5 mg	<0.001	.	3.34
PBO through 2.5 mg	<0.001		5 mg	<0.001	<0.001	

PBO = placebo

Data Source: [4.7]

Figure 1

Lumbar Spine BMD
Percent Change From Baseline at Month 24 (Mean ± SE)
(Intention-to-Treat Approach)
Strata 1 and 2 Combined



The placebo group lost bone mass from baseline at Month 12 and Month 24 by -1.05% and -1.78%, respectively. The ALN 2.5 mg/day group showed increases in BMD from baseline by 1.98% and 2.28% at corresponding time points, respectively. For all three treatment groups, differences from baseline to Month 24 were statistically significant. Maximum increases in BMD occurred during the first 12 months of treatment with ALN at both doses. At Month 12, percent changes from baseline for the two ALN groups were significantly different from placebo ($p < 0.001$). During the second year of ALN treatment BMD showed a further increase. The results of P-P analysis were similar.

The results of threshold analysis are shown in Tables 35 and 36 (Sponsor's Tables 23 and 24, vol. 14, D-3908).

Table 23

Lumbar Spine BMD
Proportion of Subjects With Percent Change
From Baseline Exceeding a Specified Threshold at Month 24
Strata 1 and 2 Combined

Treatment	N	-6%	-4%	-2%	0%	2%	4%	6%	8%
PBO	461	91.3	76.8	53.8	29.5	10.4	3.5	1.3	0.2
ALN 2.5 mg	452	99.1	96.0	90.5	75.9	53.1	31.4	12.4	5.1
ALN 5 mg	445	99.3	97.5	94.6	86.1	67.6	44.5	23.4	9.9

PBO = placebo; ALN = alendronate

Data Source: [4.7]

Table 24

Lumbar Spine BMD
Percent of Subjects Showing a Measured
Decrease or Increase at Month 24
Strata 1 and 2 Combined

Group	Percent Losers	Percent Gainers	Odds of Gain vs Loss	Odds Ratio for Gain vs PBO (95% CI)
PBO	70.5	29.5	0.4	--
ALN 2.5 mg/day	24.1	75.9	3.2	7.5 (5.7, 10.0)
ALN 5 mg/day	13.9	86.1	6.2	14.8 (10.9, 20.1)

PBO = placebo; ALN = alendronate

Data Source: [4.7]

At Month 24 about 44.5% of patients in the ALN 5 mg group showed 4% increase in BMD compared to 3.5% in the placebo group.

Only about 5.4% of subjects in ALN 5 mg group had a measured decrease in BMD in excess of 2% (i.e., ≥ 1% per year), compared to 46.2% in the placebo group. For subjects treated with ALN 5 mg, the odds are about 6 to 1 for showing a measured increase in BMD.

ALN, E/P, placebo comparison-

The results are summarized in Table 37 and Figure 7 (Sponsor's

Table 25 and Figure 3,vol. 14, pp. 3911 and 3914).

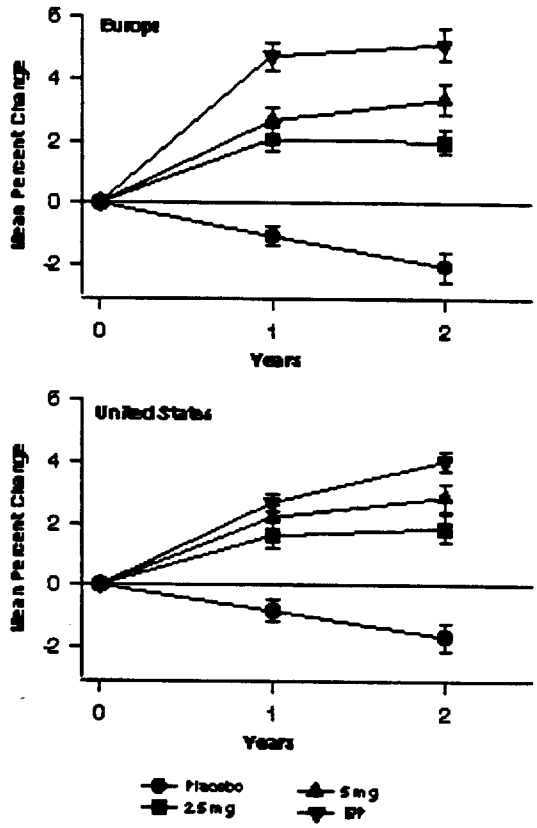
Table 25

Lumbar Spine BMD (g/cm^2)
Analysis of Percent Change From Baseline by Time Point
(Intention-to-Treat Approach)
Stratum 1 Cohorts

Time Point	Treatment	N	Percent Change From Baseline			
			Mean	SE	Median	Range
Stratum 1: European Cohort						
Month 12	PBO	50	-1.07	0.32	-1.00	
	ALN 2.5 mg	50	2.07	0.37	2.05	
	ALN 5 mg	46	2.67	0.40	2.85	
	E/P	49	4.75	0.44	4.99	
Month 24	PBO	50	-2.06	0.49	-2.04	
	ALN 2.5 mg	50	1.98	0.38	2.43	
	ALN 5 mg	46	3.34	0.48	3.82	
	E/P	49	5.14	0.54	5.26	
Stratum 1: U.S. Cohort						
Month 12	PBO	51	-0.84	0.36	-0.91	
	ALN 2.5 mg	44	1.61	0.40	1.74	
	ALN 5 mg	47	2.20	0.41	2.24	
	E/P	53	2.66	0.30	2.66	
Month 24	PBO	51	-1.68	0.45	-1.46	
	ALN 2.5 mg	44	1.85	0.47	1.76	
	ALN 5 mg	47	2.85	0.46	3.00	
	E/P	53	4.04	0.33	4.14	

PBO = placebo; ALN = alendronate; E/P = estrogen/progestin
Data Source: [4.7]

Lumbar Spine BMD
Percent Change From Baseline at Month 24 (Mean ± SE)
(Intention-to-Treat Approach)
Stratum 1–European and U.S. Cohorts

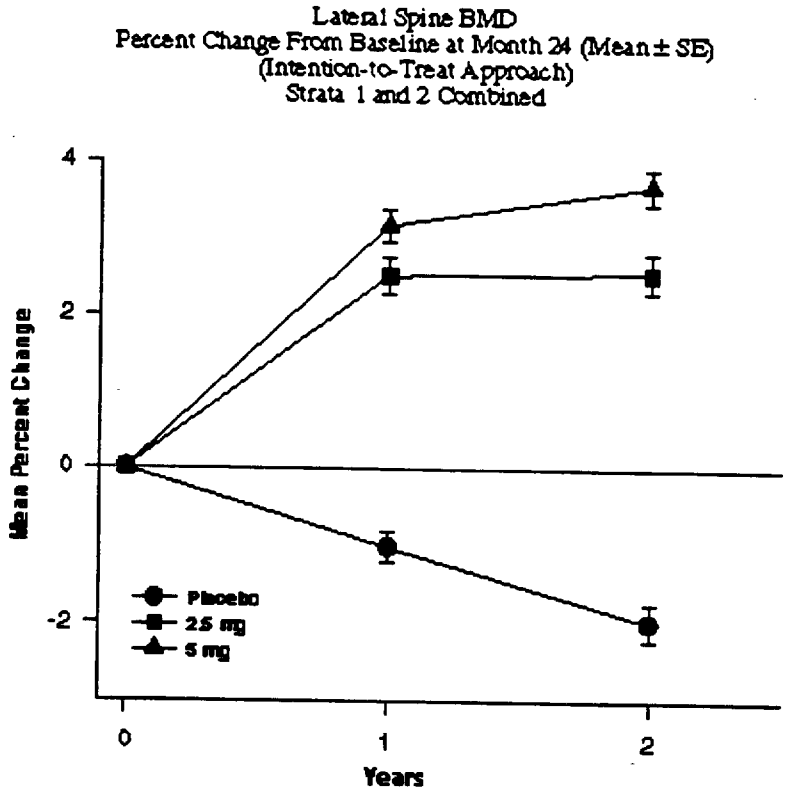


At Month 24 in the U.S. cohort, the mean percent increase from baseline BMD of spine in E/P group was significant (p=0.05) from that observed in the ALN 5 mg group. For the European cohort the difference at the same time point was highly significant (p=0.008). In the U.S. studies, the differences observed between two centers were not significant (p=0.70). Whereas, in European centers, the mean percentage change for the E/P group was higher in Denmark compared to corresponding change in the U.K. (6.63% vs 4.03%). (**Comments**: The formulation of E/P was identical in the U.K. and Danish sites. Sponsor has no explanation

for this difference).

The results for the lateral spine BMD at Month 24 were similar to those observed at the lumbar spine site (See figure 8 (Sponsor's Figure 4, vol. 14,p. D-3921).

Figure 4



Total hip BMD-

The results are presented in Tables 38 and 39 and Figure 9 (Sponsor's Tables 30-31, and Figure 6, vol. 14, pp.D-3920-21).

Table 30

Total Hip BMD (g/cm^2)
Analysis of Percent Change From Baseline by Time Point
(Intention-to-Treat Approach)
Strata 1 and 2 Combined

Time Point	Treatment	N	Percent Change From Baseline			
			Mean	SE	Median	Range
Month 12	PBO	460	-0.64	0.10	-0.61	
	ALN 2.5 mg	451	0.87	0.10	0.99	
	ALN 5 mg	445	1.48	0.10	1.39	
Month 24	PBO	461	-1.42	0.13	-1.36	
	ALN 2.5 mg	452	1.06	0.12	1.04	
	ALN 5 mg	445	1.85	0.12	2.01	

PBO = placebo; ALN = alendronate

Data Source: [4.7]

Table 31

Total Hip BMD (g/cm^2)
Analysis of Percent Change From Baseline at Month 24
(Intention-to-Treat Approach)
Strata 1 and 2 Combined

Treatment	N	Means (Observed)		Percent Change From Baseline			
		Baseline	Month 24	Mean	SD	Adjusted Mean	LSD Interval
PBO	461	0.85	0.84	-1.42***	2.86	-1.45	(-1.63, -1.27)
ALN 2.5 mg	452	0.84	0.85	1.06***	2.53	1.03	(0.84, 1.21)
ALN 5 mg	445	0.85	0.87	1.85***	2.53	1.81	(1.63, 2.00)

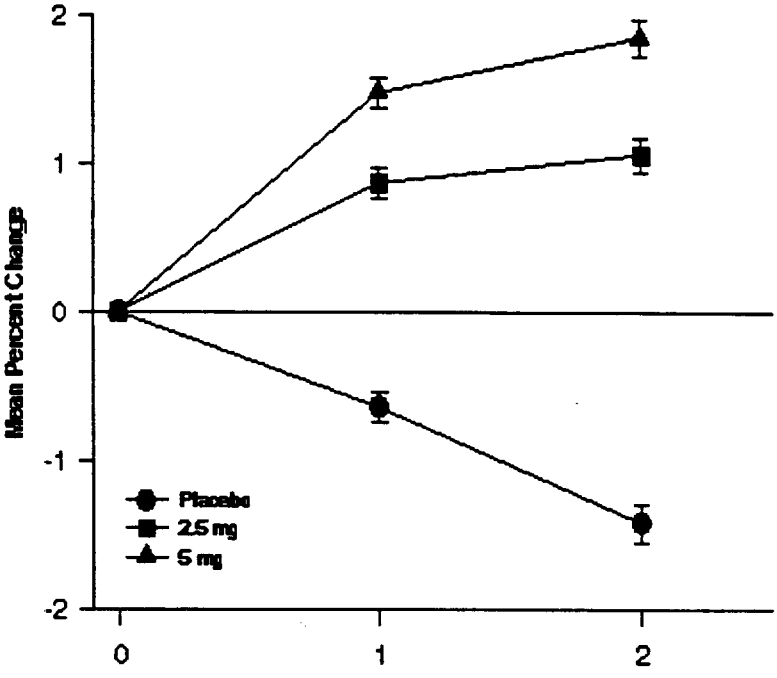
PBO = placebo; ALN = alendronate
Within-group test of mean = 0 ***: $p \leq 0.001$ **: $p \leq 0.01$ *: $p \leq 0.05$
Treatment-by-center interaction p-value: 0.077

Adjusted Trend Test		Overall p-Value		Comparison Between Doses		
Dose Included	p-Value			PBO	2.5 mg	Pooled SD
PBO through 5 mg	<0.001	<0.001	2.5 mg	<0.001	.	2.60
PBO through 2.5 mg	<0.001		5 mg	<0.001	<0.001	

Data Source: [4.7]

Figure 6

Total Hip BMD
Percent Change From Baseline at Month 24 (Mean ± SE)
(Intention-to-Treat Approach)
Strata 1 and 2 Combined



At Month 24, ALN at doses 2.5 and 5 mg showed BMD increases from baseline by 1.06% and 1.85%, respectively. Whereas, the placebo group showed a decrease in BMD by 1.42% at Month 24. In both ALN groups during the second year of treatment BMD continued to increase. The placebo group during the second year of the study progressively lost bone mass.

The results of threshold analysis showed 67 to 78% of patients in the ALN 2.5 and 5 mg groups achieved a measured bone gain as opposed to 31% of patients in the placebo group. The odds ratio between the ALN 5 mg and placebo groups in terms of increased total hip BMD

was about 8.

Femoral neck, trochanter, and Ward's triangle BMD- The results are summarized in Table 40 (Sponsor's Table 36 ,vol. 14, p. D-3928).

Table 36

Summary of Percent Change From Baseline BMD at Month 24
Strata 1 and 2 Combined
(Intention-to Treat Approach)

Treatment Group	Subregion Site					
	Femoral Neck		Trochanter		Ward's Triangle	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
PBO	461	-1.57 (0.17)	461	-0.90 (0.16)	461	-2.40 (0.28)
ALN 2.5 mg	452	0.81 (0.16)	452	1.74 (0.16)	452	0.97 (0.29)
ALN 5 mg	445	1.27 (0.16)	445	2.98 (0.10)	445	1.75 (0.29)

PBO = placebo; ALN = alendronate

Data Source: [4.7]

At all subregions of hip, ALN groups showed significant increases from baseline both at Months 12 and 24.See Figures 10-12 (Sponsor's Figures 9-11, vol. 14, pp. D-3929-3931).

Figure 9

Femoral Neck BMD
Percent Change From Baseline at Month 24 (Mean ± SE)
(Intention-to-Treat Approach)
Strata 1 and 2 Combined

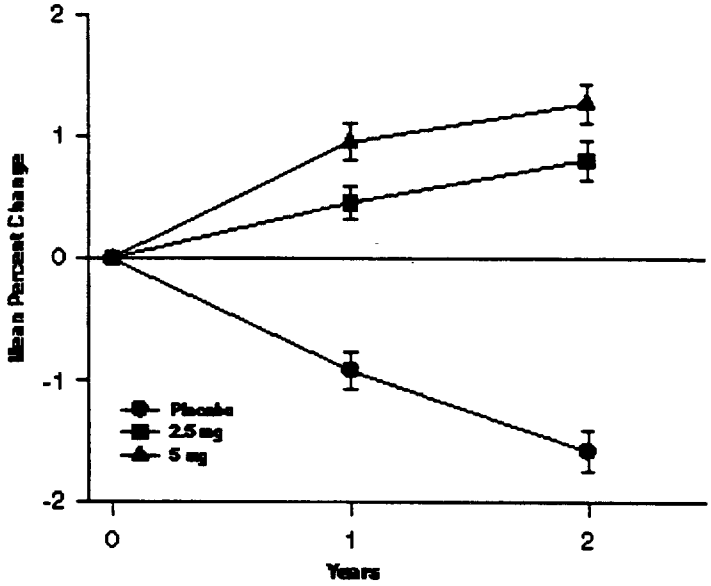


Figure 10

Trochanter BMD
Percent Change From Baseline at Month 24 (Mean ± SE)
(Intention-to-Treat Approach)
Strata 1 and 2 Combined

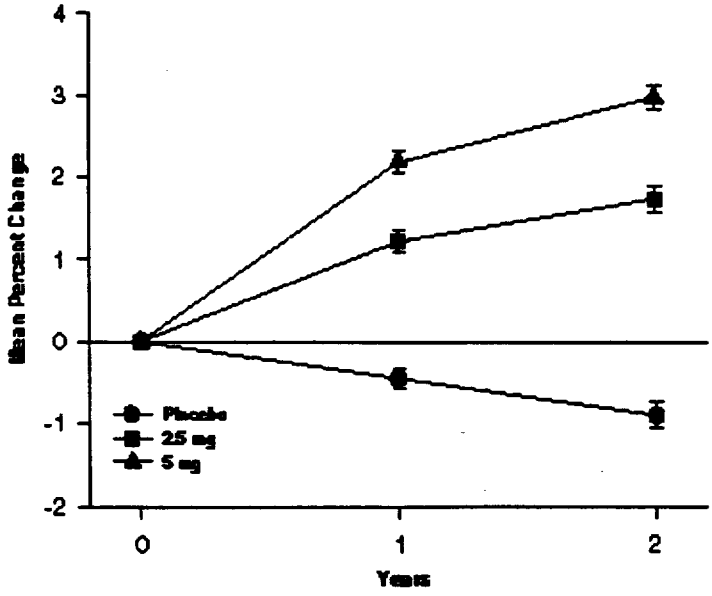
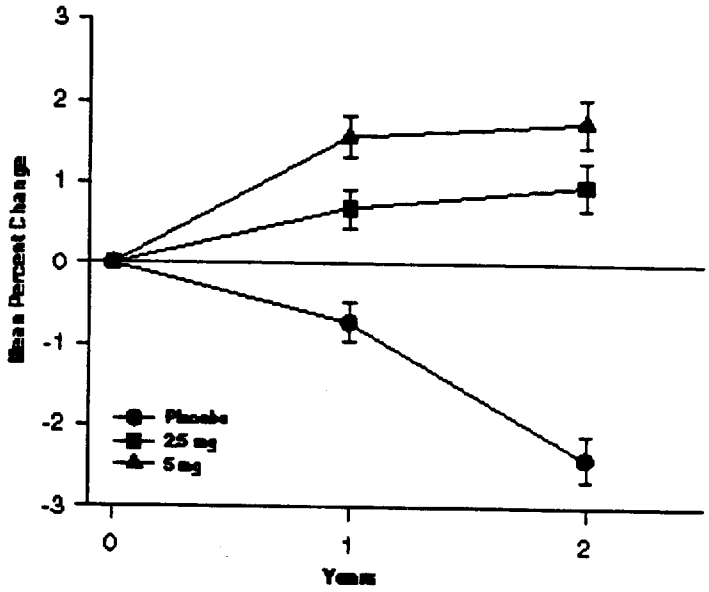


Figure 11

Ward's Triangle BMD
Percent Change From Baseline at Month 24 (Mean ± SE)
(Intention-to-Treat Approach)
Strata 1 and 2 Combined



The placebo group at all of these subregions showed bone loss "0.90 to 2.40%" at Month 24.

ALN, E/P, and placebo comparison-

Both in the U.S. and European cohorts, ALN (two doses) and E/P groups showed increases from baseline at Month 24. The placebo group showed decreases from baseline. Tables 41-42 (Sponsor's Tables 37-38, vol. 14, pp.D-3932-33).

Table 37

Femoral Neck, Trochanter and Ward's Triangle BMD
Summary of Percent Change From Baseline BMD at Month 24
(Intention-to Treat Approach)
Stratum 1: European Cohort

Treatment Group	Subregion Site: Femoral Neck N	Femoral Neck Mean (SE)	Trochanter N	Trochanter Mean (SE)	Ward's Triangle N	Ward's Triangle Mean (SE)
PBO	50	-1.49 (0.58)	50	-1.24 (0.54)	50	-2.14 (0.82)
ALN 2.5 mg	50	1.08 (0.46)	50	1.33 (0.39)	50	0.44 (0.78)
ALN 5 mg	46	1.35 (0.47)	46	2.84 (0.41)	46	1.81 (0.83)
E/P	49	2.41 (0.46)	49	4.77 (0.44)	49	5.05 (0.81)

PBO = placebo; ALN = alendronate; E/P = estrogen/progestin

Data Source: [4.7]

Table 38

Femoral Neck, Trochanter, and Ward's Triangle BMD
Summary of Percent Change From Baseline BMD at Month 24
(Intention-to-Treat Approach)
Stratum 1: U.S. Cohort

Treatment Group	Subregion Site: Femoral Neck N	Femoral Neck Mean (SE)	Trochanter N	Trochanter Mean (SE)	Ward's Triangle N	Ward's Triangle Mean (SE)
PBO	51	-0.91 (0.49)	51	-0.84 (0.47)	51	-1.64 (0.82)
ALN 2.5 mg	44	0.43 (0.50)	44	1.87 (0.56)	44	0.86 (1.03)
ALN 5 mg	47	0.13 (0.49)	47	2.15 (0.40)	47	1.97 (0.99)
E/P	53	1.45 (0.46)	53	3.00 (0.49)	53	2.03 (0.77)

PBO = placebo; ALN = alendronate; E/P = estrogen/progestin

Data Source: [4.7]

In the E/P group, increases in all of these subregions at Month 24 were greater than those seen with ALN 2.5 and 5 mg groups.

Total body BMD-
The results are presented in Table 43 and Figure 13 (Sponsor's Table 39 and Figure 15, vol. 14. pp. D-3938-3939).

Table 39

Total Body BMD (g/cm^2)
Analysis of Percent Change From Baseline at Month 24
(Intention-to-Treat Approach)
Strata 1 and 2 Combined

Treatment	N	Means (Observed)		Percent Change From Baseline			
		Baseline	Month 24	Mean	SD	Adjusted Mean	LSD Interval
PBO	454	1.04	1.02	-1.76***	2.13	-1.82	(-2.02,-1.62)
ALN 2.5 mg	444	1.03	1.03	-0.03	4.01	-0.09	(-0.30, 0.11)
ALN 5 mg	439	1.03	1.04	0.67***	2.02	0.61	(0.40, 0.81)

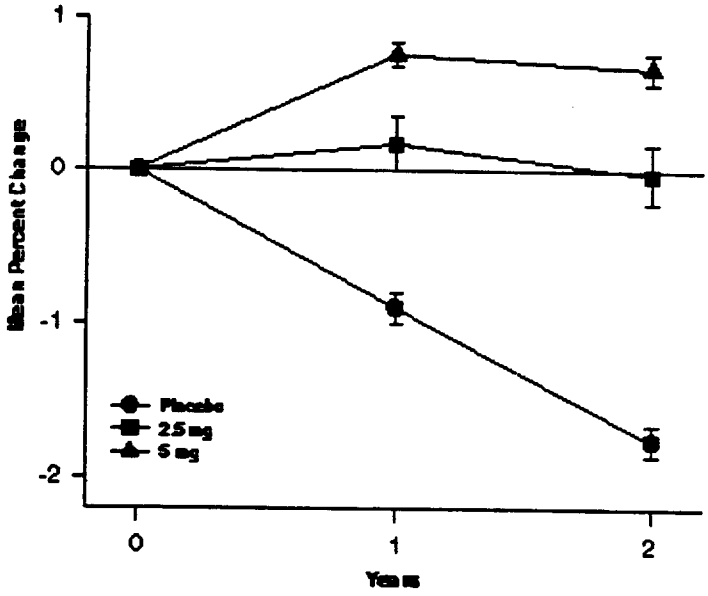
PBO = placebo; ALN = alendronate
Within-group test of mean = 0 ***: $p \leq 0.001$ **: $p \leq 0.01$ *: $p \leq 0.05$
Treatment-by-center interaction p-value: 0.654

Adjusted Trend-Test		Overall p-Value		Comparison Between Doses		Pooled SD
Dose Included	p-Value			PBO	2.5 mg	
PBO through 5 mg	<0.001	<0.001	2.5 mg	<0.001		2.87
PBO through 2.5 mg	<0.001		5 mg	<0.001	<0.001	

Data Source: [4.7]

Figure 15

Total Body BMD
Percent Change From Baseline at Month 24 (Mean ± SE)
(Intention-to-Treat Approach)
Strata 1 and 2 Combined



At Month 24, the placebo group lost BMD from baseline by about 1.76%, compared to mean percent changes of -0.03 and 0.67% in the ALN 2.5 and

5 mg groups, respectively.

The results of threshold analysis showed odds ratio between ALN and placebo groups in terms of a measured increase in total body BMD of 8.

ALN, E/P, and placebo comparison-

At Month 24, mean changes from baseline were 0.64 and 2.59 for the ALN 5 mg and E/P groups, respectively ($p< 0.001$). In the U.S. cohort, the difference between ALN 5 mg and E/P groups was not significant ($p= 0.28$).

Implication for dose selection- The same guidelines (as of other controlled studies) were used for choosing a prevention dose for ALN. The results are shown in Figures 14-15 (Sponsor's Figures 18-19, vol. 14, pp. D-3946-3947).

Figure 18

Lumbar Spine
Proportion of Subjects With Apparent Bone Loss
≤3 Years Postmenopausal

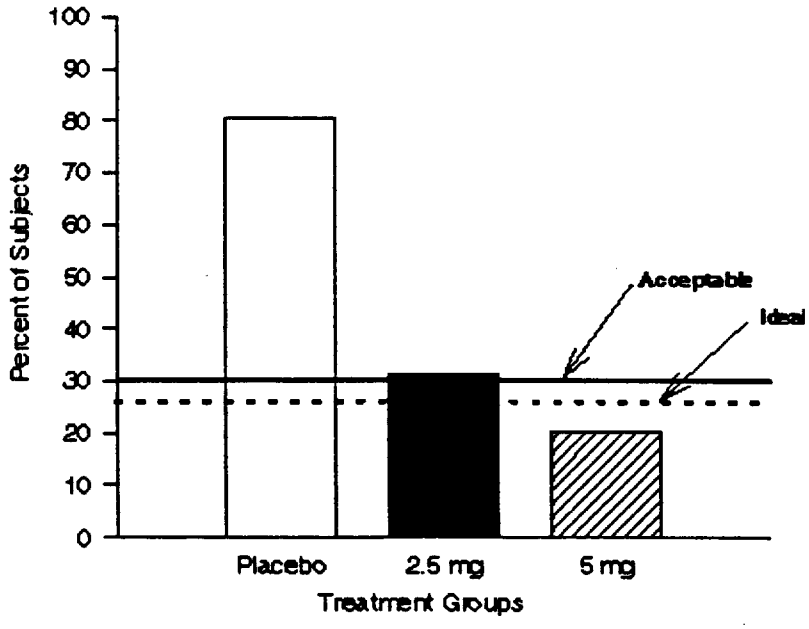
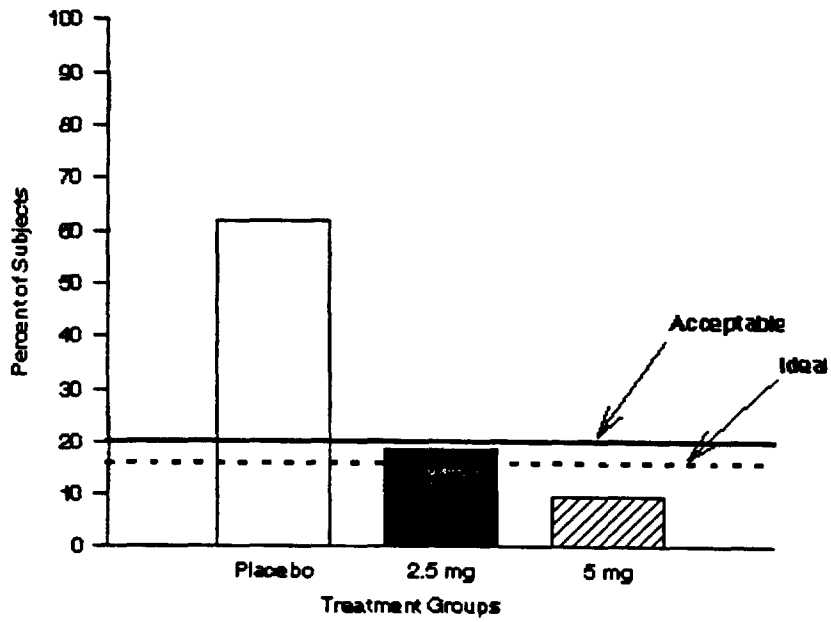


Figure 19

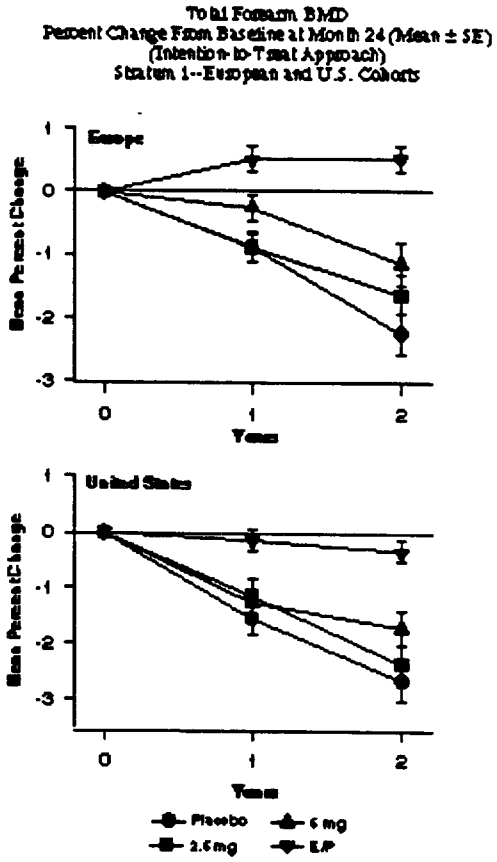
Lumbar Spine
Proportion of Subjects With Apparent Bone Loss
>3 Years Postmenopausal



For both groups of postmenopausal (≤ and > 3 years) women, subjects who received ALN 5 mg daily achieved the target for the lumbar spine. Similar result was observed for the total hip. For the total body BMD, acceptable target was archived only for subjects postmenopausal > 3 years.

Total forearm BMD- All three treatment groups showed decreases in forearm BMD at Month 24. See Figure 16 (Sponsor's Figure 25, vol. 14, p. D-3957).

Figure 25

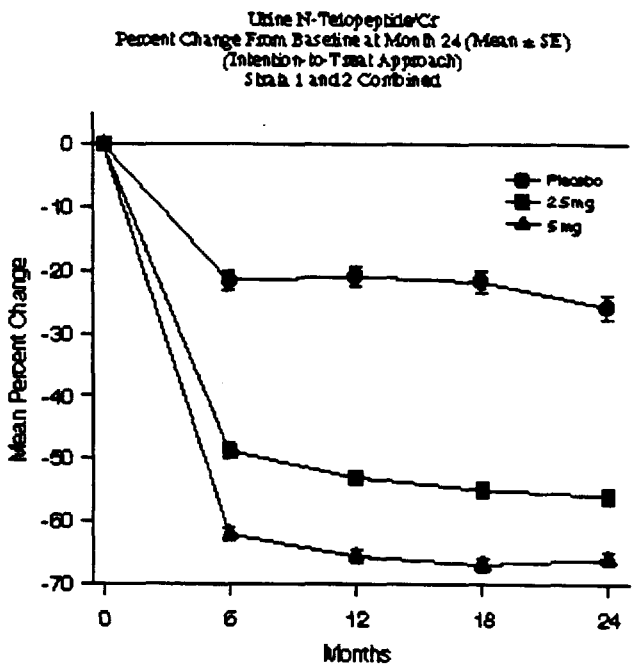


Phalanges and calcaneus BMD- Both phalanges and calcaneus BMD measurements are not in our Osteo-Guidelines for monitoring the drug effects on BMD. These measurements were performed only by some centers.

Biochemical markers

Urine N-telopeptide/Cr-
The results are shown in Figure 17 (Sponsor's Figure 32, vol. 14,(Sponsor's Figure 32, vol. 14, p. D-3971).

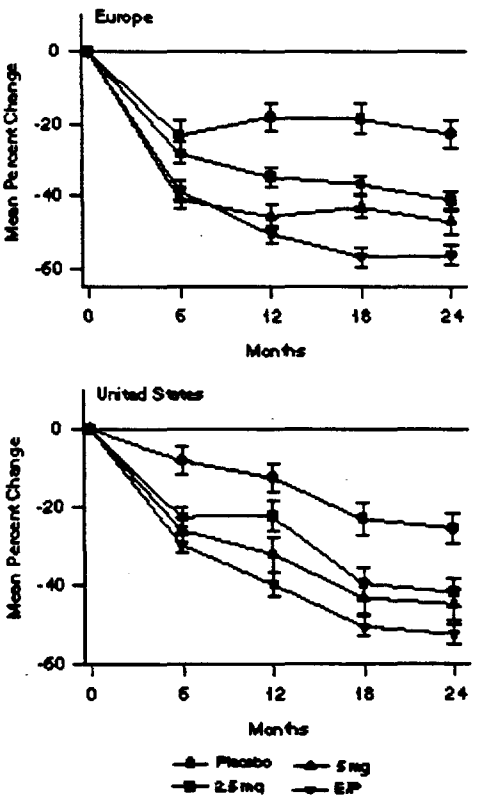
Figure 32



All three treatment groups showed decreases in baseline NTX at 4 time points (6,12,18, and 24 months). The reason for the decrease in the placebo group is not clear. Decreases in the ALN 2.5 mg group were 48.6% at Month 6 to 55.83% at 24 months. For the ALN 5 mg group, the corresponding reductions were -62% at Month 6 to -66% at Months 24. At Month 24, the differences in mean percent changes from baseline between ALN and placebo groups were significant ($p < 0.001$).

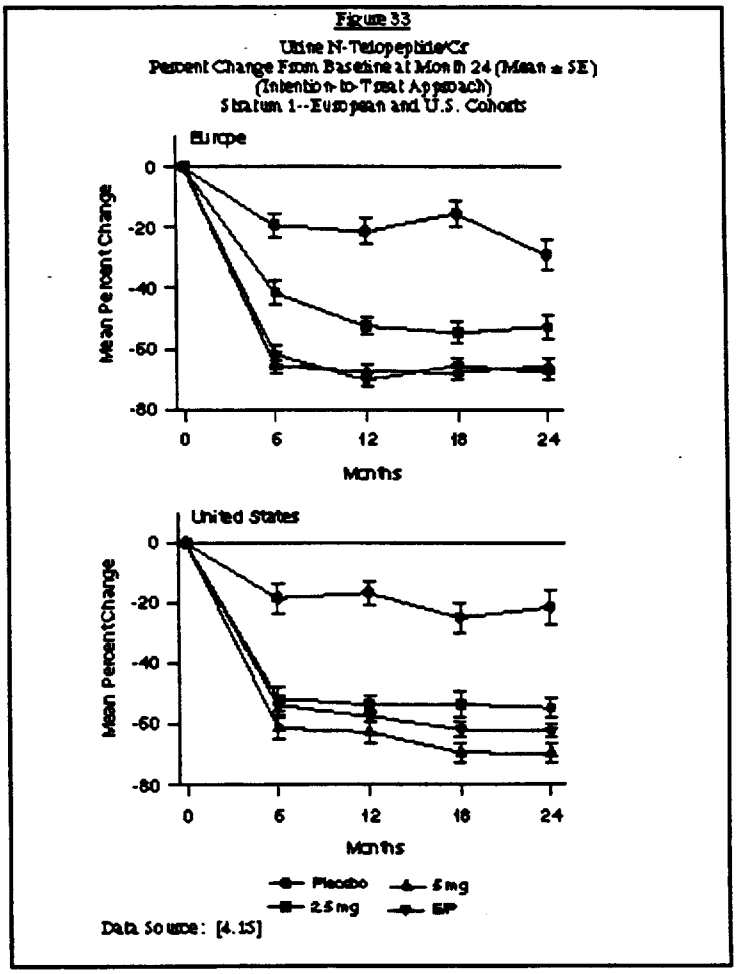
Figure 35

Serum Osteocalcin
Percent Change From Baseline at Month 24 (Mean ± SE)
(Intention-to-Treat Approach)
Stratum 1--European and U.S. Cohorts



ALN, E/P, and placebo comparison- In both European and U.S. cohorts, ALN 5 mg and E/P groups showed similar suppression of NTX between

6 and 24 months (See Figure 18/Sponsor's Figure 33,vol.14,p. D-3974).



Osteocalcin-

The results are shown in figure 19 (Sponsor's Figure 35, vol. 14, p. D-3980).

All three treatment groups showed decreases from baseline in serum osteocalcin at 4 time points. The percent decreases in the ALN 5 mg group were lower than those of the ALN 2.5 group, and the maximum decrease was -45.5% at Month 24.

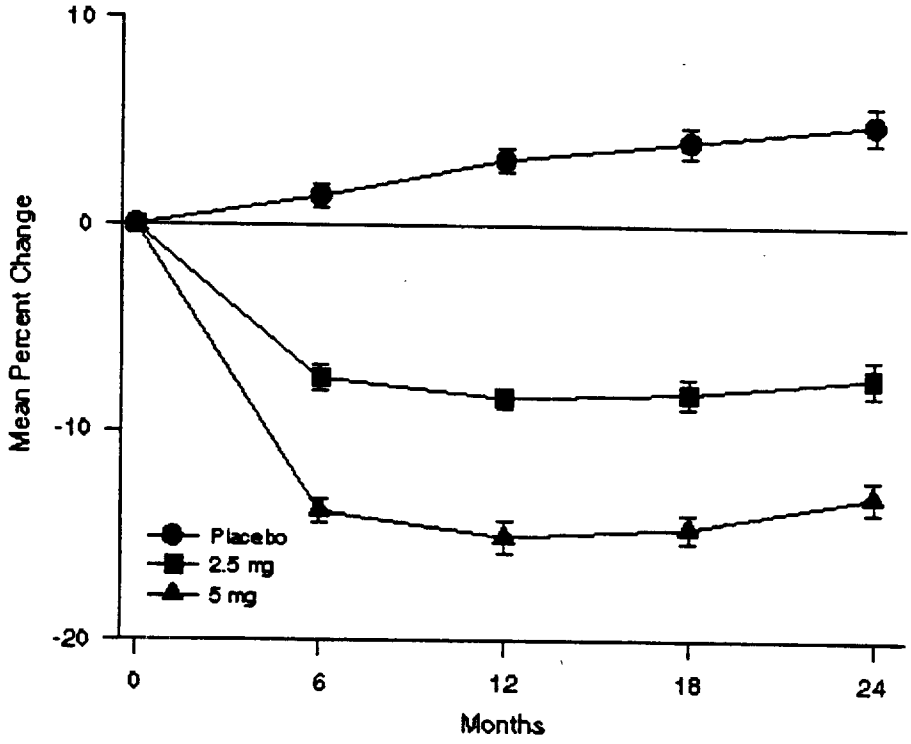
Decrease from baseline in the E/P group was larger at both cohorts (European and U.S.)compared to ALN 5 mg group.

Serum alkaline phosphatase-

The results are shown in Figure 20 (Sponsor's Figure 36, vol. 14, p. D-3983).

Figure 36

Serum Alkaline Phosphatase
Percent Change From Baseline at Month 24 (Mean ± SE)
(Intention-to-Treat Approach)
Strata 1 and 2 Combined



ALN at both doses decreased SAP. At 5 mg dose, decreases were between -13.09 to -15.08% at Month 24. At the later time point, there were significant differences in the in the degree of suppression of SAP between treatment groups.

E/P therapy also resulted in decrease in SAP at 4 time points. The degree of suppression of SAP was
greater than that observed in ALN 5 mg group.

Serum calcium-

Al three treatment groups showed small decreases in serum calcium and at Month 24, there was no difference between the placebo and ALN groups. In the E/P group (European and U.S. cohorts), decrease in serum calcium was greater than that observed in ALN 5 mg group.

Serum phosphorus-

Serum phosphorus levels decreased by 2 to 3% at Month 24. In the placebo group, there was an initial decrease (between 6 to 18 months), but at Month 24 serum phosphorus level returned to baseline. E/P therapy in the cohort studies showed 11 to 18% decrease in serum phosphorus levels.

Subgroups

Subgroup analyses were performed for both categorical and continuous characteristics. For each of the continuous characteristics, subgroups were defined by tertile (low, middle, and high).

The overall results showed greater increase in spinal BMD in the following subgroups:

- subjects who were more than 2 years postmenopausal.

- subjects with lower baseline spine BMD.

- subjects with higher baseline

serum osteocalcin levels (to E/P treatment).

Changes in BMD were not related to baseline calcium intake in any treatment group.

Stature

At Month 24, the placebo and ALN 5 mg groups showed decreases of -0.4 and -0.6 mm, compared to a slight gain of 0.1 mm in the ALN 5 group (p=0.078).

Pain- All three treatment groups were reported to experience a "small increase" in the level of pain. Sponsor states that these changes were not clinically meaningful and not affected by ALN treatment.

Tooth counts-
The results are inconclusive.

8.4.4.3 **Safety comparisons**

Clinical and laboratory AEs were evaluated. AEs that occurred during the placebo run-in period were not reported.

Clinical AEs

The clinical AEs (subject count and percentage) in the combined strata and stratum 1 are summarized in Table 44 (Sponsor's Table 62, vol. 14, p. D-4004).

Table 62

Clinical Adverse Experiences
Summary - Subject Count (%)

	Strata 1 and 2 Combined			Stratum 1	
	PBO (N = 502)	ALN 2.5 mg (N = 499)	ALN 5.0 mg (N = 496)	E/P (N = 110)	PBO* (N = 109)
Number (%) of subjects with one or more adverse experiences	468 (93.2)	476 (95.4)	474 (95.2)	109 (99.1)	103 (94.5)
with drug-related adverse experiences	56 (11.2)	59 (11.8)	58 (11.6)	96 (87.3)	16 (14.7)
with serious adverse experiences	30 (6.0)	41 (8.2)	36 (7.2)	5 (4.5)	7 (6.4)
with serious drug-related adverse experiences	0	0	0	0	0
withdrawn from therapy due to adverse experiences	27 (5.4)	26 (5.2)	41 (8.2)	15 (13.6)	5 (4.6)
withdrawn from therapy due to a serious adverse experience	3 (0.6)	3 (0.6)	5 (1.0)	0	2 (1.8)
withdrawn from therapy due to a drug-related adverse experience	11 (2.2)	6 (1.2)	10 (2.0)	13 (11.8)	2 (1.8)
withdrawn from therapy due to a serious drug-related adverse experience	0	0	0	0	0
Deaths	0	1 (0.2)	1 (0.2)	0	0

PBO = placebo; ALN = alendronate; E/P = estrogen/progestin.
This table does not include those adverse experiences that occurred during the placebo run-in period.
* Stratum 1 placebo-treated subjects are a subset of the placebo group noted for Strata 1 and 2 combined.

Data Source: [4.26]

There were 11.2,11.8, 11.6, and 87.3% of subjects experienced drug-related AEs in the placebo, ALN 2.5 mg, ALN 5 mg, and E/P groups, respectively. No subject withdrew from the subject due to a serious drug-related AEs. In the E/P group (stratum 1), the drug-related AEs were significantly higher than in the placebo group.

Evaluation of AEs by body system revealed no significant difference between the placebo and ALN groups in the combined strata. There was significantly higher proportion of patients in stratum 1 experienced urogenital system disorders compared to placebo and ALN groups (Table 45/Sponsor's Table 64, vol. 14, pp. D-4008-4012).

The most common AEs in the placebo

and ALN groups included back pain, upper respiratory infection, and headache. In Stratum 1 group (E/P), the common AEs were upper respiratory infection and urogenital disorders.

	PBO (N.= 502)	ALN 2.5 mg (N= 499)	ALN 5.0 mg (N = 498)	E/P (N = 110)
Urogenital System Disorders (Cont.)				
Discharge, vaginal	2 (0.4)	5 (1.0)	6 (1.2)	2 (1.8)
Dryness, vaginal	8 (1.6)	8 (1.6)	9 (1.8)	0
Hemorrhage, uterine	12 (2.4)	15 (3.0)	15 (3.0)	33 (30.0)
Hemorrhage, vaginal	7 (1.4)	4 (0.8)	7 (1.4)	2 (1.8)
Hot flashes	14 (2.8)	15 (3.0)	9 (1.8)	1 (0.9)
Infection, urinary tract	24 (4.8)	24 (4.8)	34 (6.8)	4 (3.6)
Mass, adnexal	0	1 (0.2)	0	2 (1.8)
Mass, breast	5 (1.0)	13 (2.6)	8 (1.6)	5 (4.5)
Menopausal disorder	64 (12.7)	60 (12.0)	53 (10.6)	54 (49.1)
Menstruation	1 (0.2)	2 (0.4)	0	4 (3.6)
Menstruation disorder	1 (0.2)	4 (0.8)	1 (0.2)	33 (30.0)
Neoplasm, cervical, benign	4 (0.8)	1 (0.2)	2 (0.4)	7 (6.4)
Pain, breast	9 (1.8)	8 (1.6)	7 (1.4)	26 (23.6)
Pap test abnormal	1 (0.2)	3 (0.6)	1 (0.2)	2 (1.8)
Premenstrual syndrome	0	0	0	3 (2.7)
Pruritus, vaginal	0	2 (0.4)	1 (0.2)	2 (1.8)
Urinary frequency	6 (1.2)	2 (0.4)	4 (0.8)	0
Uterine disorder	1 (0.2)	0	2 (0.4)	2 (1.8)
Vaginitis	4 (0.8)	6 (1.2)	11 (2.2)	7 (6.4)

PBO = placebo; ALN = alendronate; E/P = estrogen/progestin.

This table contains counts of subjects. Although a subject may have two or more clinical adverse experiences, the subject will be counted only once in 'Number (%) of subjects with any clinical adverse experience."

This table does not include those adverse experiences that occurred during the placebo run-in period.

Data Source [4.28]

Urogenital System Disorders				
Cervical disorder	1 (0.2)	0	0	3 (2.7)
Cervicitis	1 (0.2)	0	0	2 (1.8)
Cyst, breast	3 (0.6)	3 (0.6)	0	3 (2.7)
Cystitis	23 (4.6)	29 (5.8)	22 (4.4)	4 (3.6)

Digestive system disorders with incidence ≥ 1% in combined strata and in Stratum 1 are presented in Table 46 (Sponsor's Table 64

contd.,vol. 14, p. D-4009).

Table 64 (Cont.)

Most Common Clinical Adverse Experiences - Subject Count (%)
(Subject Incidence ≥ 1% in at Least One Treatment Group)
Strata 1 and 2 Combined

	PBO (N = 502)	ALN 2.5 mg (N = 499)	ALN 5.0 mg (N = 498)	E/P (N = 110)
Digestive System Disorders				
Acid regurgitation	22 (4.4)	23 (4.6)	24 (4.8)	0
Appetite increase	0	0	0	2 (1.8)
Broken tooth	28 (5.6)	38 (7.6)	31 (6.2)	6 (5.5)
Cholelithiasis	2 (0.4)	3 (0.6)	6 (1.2)	1 (0.9)
Constipation	17 (3.4)	13 (2.6)	21 (4.2)	4 (3.6)
Dental caries	58 (11.6)	49 (9.8)	52 (10.4)	9 (8.2)
Dental procedure complication	1 (0.2)	1 (0.2)	2 (0.4)	3 (2.7)
Diarrhea	51 (10.2)	40 (8.0)	53 (10.6)	11 (10.0)
Dyspepsia	49 (9.8)	46 (9.2)	46 (9.2)	6 (5.5)
Flatulence	10 (2.0)	10 (2.0)	13 (2.6)	3 (2.7)
Gastroenteritis	7 (1.4)	10 (2.0)	9 (1.8)	0
Gastroenteritis, infectious	35 (7.0)	18 (3.6)	28 (5.6)	5 (4.5)
Gingival/periodontal disorder	7 (1.4)	3 (0.6)	5 (1.0)	0
Gingivitis	4 (0.8)	7 (1.4)	3 (0.6)	2 (1.8)
Hematochezia	0	1 (0.2)	6 (1.2)	0
Hemorrhoids	6 (1.2)	6 (1.2)	6 (1.2)	2 (1.8)
Infection, dental process	35 (7.0)	30 (6.0)	24 (4.8)	8 (7.3)
Nausea	37 (7.4)	38 (7.6)	38 (7.6)	8 (7.3)
Gastrointestinal, polyp, benign	0	0	4 (0.8)	3 (2.7)
Pain, dental	38 (7.6)	44 (8.8)	41 (8.2)	8 (7.3)
Tooth disorder	9 (1.8)	12 (2.4)	6 (1.2)	2 (1.8)
Vomiting	17 (3.4)	17 (3.4)	24 (4.8)	3 (2.7)

Six subjects in the ALN 5 mg group experienced hematochezia compared to none in the placebo and to 1 in the ALN 2.5 mg groups. Also, 4 subjects in the ALN 5 mg group had benign intestinal polyp compared to none in the placebo and ALN 2.5 mg groups.

Clinical AEs that increased significantly in stratum 1 (of E/P group) were shown in Table 47 (Sponsor's Table 66, vol. 14, p. D-4016).

Table 66

Clinical Adverse Experiences in Stratum 1 Significantly Increased or Decreased in Estrogen/Progestin Relative to Placebo

	Subject Count (%)		p-Value
	PBO	E/P	
Adverse Experiences Occurring With Significantly Greater Incidence in Estrogen/Progestin Than With Placebo			
Hemorrhage, uterine	4 (3.7)	33 (30.0)	<0.001
Menopausal disorder*	14 (12.8)	54 (49.1)	<0.001
Menstruation disorder	0	33 (30.0)	<0.001
Neoplasm, cervical, benign	0	7 (6.4)	0.014
Pain, breast	1 (0.9)	26 (23.6)	<0.001

Review of drug-related clinical AEs showed no significant differences between placebo and ALN groups. Neither was there any dose-response trend with respect to the incidence of AEs.

With regard to the incidence of serious AEs, there were no significant differences between three treatment groups in the combined strata and in stratum 1 (placebo vs E/P).

There were two deaths in ALN groups. One subject (Study # 055002) on Day 344 of ALN 2.5 mg/day, showed a WBC count of 6.1 with normal CBC count. Five days later the subject died in her bed (cause of death was uncertain). The other subject (Study #055003), a 54-year-old woman on Day 713 of ALN 5 mg/day treatment developed nausea, vomiting, and diarrhea. Next day, subject suffered a myocardial infarction and died. The cause of death in both cases was not directly related to the study drug.

Upper G-I AEs

The upper G-I AEs are summarized in Table 48 (Sponsor's Table 72

(Sponsor's Table 72, vol. 14, p. D-4042).

Table 72

Upper Gastrointestinal Clinical Adverse Experiences Summary - Subject Count (%)

	Strata 1 and 2 Combined			Stratum 1	
	PBO (N = 508)	ALN 2.5 mg (N = 499)	ALN 5.0mg (N = 498)	E/P (N = 110)	PBO* (N = 109)
Number (%) of subjects with one or more adverse experiences	148 (29.5)	152 (30.5)	148 (29.7)	31 (28.2)	25 (22.9)
with drug-related adverse experiences	34 (6.8)	33 (6.6)	35 (7.0)	11 (10.0)	6 (5.5)
with serious adverse experiences	2 (0.4)	1 (0.2)	2 (0.4)	0	0
with serious drug-related adverse experiences	0	0	0	0	0
withdrawn from therapy due to adverse experiences	8 (1.6)	6 (1.2)	7 (1.4)	2 (1.8)	1 (0.9)
withdrawn from therapy due to serious adverse experience	1 (0.2)	0	0	0	0
withdrawn from therapy due to drug-related adverse experience	7 (1.4)	5 (1.0)	6 (1.2)	2 (1.8)	1 (0.9)
withdrawn from therapy due to serious drug-related adverse experience	0	0	0	0	0
Deaths	0	0	0	0	0

PBO = placebo; ALN = alendronate; E/P = estrogen/progestin.
This table does not include those adverse experiences that occurred during the placebo run-in period.
* Stratum 1 placebo-treated subjects are a subset of the placebo group noted for the combined Strata 1 and 2.

In the placebo, ALN 2.5, and 5 mg, and E/P groups, 6.8%, 6.6%,7.0%,and 10% of subjects experienced drug-related upper G-I AEs. Twenty-three subjects were reported to discontinue the study due to an upper G-I AE: 8 in the placebo, 6 in ALN 2.5 mg, 7 in the 5 mg , and 2 in the E/P groups, respectively. Five upper G-I AEs (2 in placebo, 1 in ALN 2.5 mg, and 2 in 5 mg group) were considered serious.

Patient # AN8197- Subject on placebo developed chest pain. Subject was diagnosed to have hiatal hernia, but Study drug was continued.

Patient # 8477- Subject developed vomiting, and it was attributed to

her preexisting diaphragmatic hernia, and presumed gastric ulcer. Subject underwent surgery and she was discontinued from the study.

Patient # AN 8159- Developed abdominal pain on Day 124 of ALN (2.5 mg/day) therapy. Patient was hospitalized and endoscopy was performed. No abnormalities were found and subject continued ALN therapy.

Patient # 9114- On Day 67 of ALN (5 mg/day)therapy, subject was hospitalized due to a "spastic sphincter of Oddi attack." Treatment was continued for some time while various G-I investigations were performed. Subsequently, she was diagnosed to have pancreatitis and continued to experience abdominal pain. Subject was restarted on study medication on Day 458. G-I AEs were considered not related to study drug by the investigator.

Patient# AN 7206- On Day 112 of ALN (5 mg/day) therapy, developed gall-bladder colic. Subject was hospitalized for surgery, and on the same day she developed bleeding ulcer (considered as a complication of surgery). Subject recovered from bleeding ulcer. ALN therapy was interrupted from Day 136 to 139.

Fractures

A total of 61 subjects suffered fractures during the study. There were no significant differences between treatment groups with respect to the incidence of fractures. All fractures were nonvertebral and were reported as a result of significant trauma with one exception. This patient on placebo experienced a rib fracture without trauma.

Rash

The overall results showed no significant differences or increasing trend between the 4 treatment groups for rash. However, in the ALN 5 mg group, more patients experienced rash. These rashes were not considered drug-related and "all resolved without interruption of therapy."

Laboratory AEs

Laboratory AEs are summarized in Table 48 (Sponsor's Table 79 vol. 14, p. D-4058).

Table 79

Laboratory Adverse Experiences Summary - Subject Count (%)

	Strata 1 and 2 Combined			Stratum 1	
	PBO (N = 502)	ALN 2.5 mg (N = 459)	ALN 5.0 mg (N = 496)	E/P (N = 119)	PBO[a] N = 109
Number of subjects with at least one laboratory test during treatment	477	449	468	105	104
Number (%) of subjects with one or more adverse experiences	82 (17.2)	82 (17.5)	76 (15.8)	18 (17.1)	15 (14.4)
with drug-related adverse experiences	1 (0.2)	4 (0.9)	2 (0.4)	1 (1.0)	0
with serious adverse experiences	0	0	0	0	0
with serious drug-related adverse experiences	0	0	0	0	0
withdrawn from therapy due to an adverse experience	1 (0.2)	0	1 (0.2)	0	0
withdrawn from therapy due to a serious adverse experience	0	0	0	0	0
withdrawn from therapy due to a drug-related adverse experience	0	0	0	0	0
withdrawn from therapy due to a serious drug-related adverse experience	0	0	0	0	0
Deaths	0	0	0	0	0

PBO = placebo; ALN = alendronate; E/P = estrogen/progestin.
[a] Stratum 1 placebo-treated subjects are a subset of the placebo group noted for Strata 1 and 2 combined.
This table does not include those adverse experiences that occurred during the placebo run-in period.

In either the combined strata or Stratum 1, there were no significant differences between

treatment groups with respect to the proportion of patients with laboratory AEs.

In the 5 mg ALN group, decreased PTH, increased urine RBCs and WBCs, and increased platelet count occurred with significantly greater incidence than placebo in a subset of subjects. But in 2.5 mg ALN group, the incidence of these AEs were not significantly different from the placebo group. None of these laboratory AEs was associated with clinical AEs.

There were no significant differences between treatment groups with respect to laboratory AEs (e.g., increased SAP, ALT, AST, GGT and decreased serum calcium)that were considered possibly, probably, or definitely drug related by the investigator.

There were no deaths associated with laboratory AEs.

One subject in the placebo group and one in the ALN 5 mg group discontinued the study due to non-serious laboratory AEs. The placebo treated patient experienced leukopenia (probably preexisting) and the ALN treated subject experienced persistently increased platelet count.

There were no clinically significant changes occurred in body weight, blood pressure, and pulse rate in various treatment groups.

The ALN groups showed no significant dose-response trends in percentage of patients who exceeded the predefined limits of change in laboratory parameters. In the E/P-treated subjects, significantly higher (compared to Stratum 1 placebo group) proportion of

patients experienced decrease (< 8.5 mg/dL) in serum calcium. Also, both E/P and Stratum 1 placebo groups experienced decrease in serum phosphate, but the proportion of patients in the E/P group was higher than that of the placebo group.

Sponsor's Discussion:

Epidemiological studies have shown increased incidence of osteoporotic fractures in women past 50 years of age. Subjects with osteoporosis generally lose about 30% to 50% of their peak bone mass before they are diagnosed as having osteoporosis.

Earlier interventions to prevent the progressive loss of bone mass appear to be the most reasonable approach to decrease the risk of osteoporotic fracture.

The results from controlled clinical trials have previously shown progressive increases in BMD of spine,hip,and total body and an associated decrease in the incidence of vertebral fractures as a result of ALN therapy.

In postmenopausal women with established osteoporosis, ALN therapy at doses of 5,10,and 20 mg/day for 24 months resulted in increased spine BMD.The 10 mg dose was as effective as 20 mg dose. Increase in BMD at 5 mg dose was less compared to the other two doses. For prevention of postmenopausal osteoporosis, most likely the 5 mg dose would be optimum for both efficacy and safety standpoints.

The objective of this study was to prevent bone loss in women aged 45 to 59 years with normal bone mass

(in most cases) at baseline. This large multicenter study was carried out to establish the efficacy and safety of the test drugs in the target population of "middle-aged" postmenopausal women.

The results of this study showed loss of BMD at spine, total hip, and total body at Month 24 in about 76% of subjects in the placebo group.Treatment with ALN (2.5 mg or 5 mg/day) resulted in significant increases in spine and total hip BMD. **The Mean increases in the 5 mg group were greater than those observed at 2.5 mg group**. The total body BMD showed an increase only at 5 mg dose with no significant change at the lower dose. The total body BMD increase reflects the overall effect of the treatment on the mineral balance of the skeleton as a whole.

Alendronate 5 mg/day was not completely effective (BMD decrease about 50% less than that in the placebo group) in preventing bone loss at the forearm.

The target proportion of patients with apparent bone loss at spine, total hip, and total body were predetermined prior to the unblinding of the study. These targets were estimated based on the number of years since menopause (≤ 3 years of postmenopausal or > 3 years postmenopausal). About 30% of subjects within 3 years of menopause were considered acceptable with apparent loss of spine bone mass. For subjects ≤ 3 years postmenopausal, 80.5% of patients in the placebo group experienced loss in BMD at the lumbar spine bone. Whereas, in the ALN 2.5 mg and 5 mg doses, 31.4% and 20.3% of patients showed a measured loss, respectively. At the

5 mg dose of ALN, the observed percentages of patients with apparent bone loss at lumbar spine, total hip, and total body (for subjects > 3 years postmenop.), were all within the acceptable targets for a preventive dose. The acceptable target was not achieved for subjects ≤ 3 years postmenopausal at the 5 mg dose.

Estrogen therapy, with or without an added progestin resulted in increases in the spine and hip BMD. The mean increases in BMD were larger than those observed with ALN 5 mg dose. The largest increases in BMD were seen in Danish subjects treated with TRISEQUENS.

ALN 5 mg daily caused marked inhibition of bone resorption, as evaluated by urinary excretion of N-telopeptide (NTX). Response to ALN 2.5 mg dose was less than that of the 5 mg dose. The degree to which ALN and E/P suppressed NTX, reflected their antiresorptive effects on bone turnover, and both ALN 5 mg dose and E/P appeared to be equiactive in the suppression of NTX.

There were small decreases in serum calcium and phosphorus due to ALN therapy. This effect is attributable to net uptake of these elements into bone. In the estrogen group, decreases in serum calcium and phosphorus were more pronounced due to concurrent decrease in serum albumin. A corrected value for serum calcium (or ionized calcium) would be similar to that observed with ALN treatment. Marked decrease in serum phosphorus due to estrogen therapy was probably due to inhibition of renal tubular-reabsorption of phosphate.

The safety and tolerability of ALN therapy at doses of 2.5 and 5 mg

daily were similar to those of the placebo with respect to a wide variety of safety variables. Abdominal pain occurred with similar frequency in ALN 5 mg and the placebo groups.

In the E/P group, 87.3% of patients experienced at least one drug-related AE and 11.8% of patents discontinued the study due to drug-related AE. In the ALN 5 mg group, the corresponding percentages of patients were 11.6 and 2.0%, respectively.

In conclusion, ALN 5 mg daily substantially meets the predefined guidelines for targeted treatment effects (increased bone mass at the spine, hip, and total body) and "is the most appropriate for clinical use in prevention of osteoporosis."

Premarin/Provera therapy caused greater increases (significantly greater with Trisequens) in BMD of spine, hip, and total body.

The changes in biochemical markers of bone turnover were indicative of their antiresorptive action.The changes in biochemical markers of bone formation and resorption,"do not predict the degree of loss of bone mass, or the response to alendronate, in this population."

The safety and tolerability of the recommended ALN dose (5 mg daily) were similar to those of the placebo group.

Reviewer's Comments and Conclusion:

In addition to accrue data on the safety, tolerability, and efficacy of ALN 2.5 and 5 mg daily (p.o.),given for 2 years in early postmenopausal women, the tolerability and efficacy of ALN

were compared to those of open-label E/P treatment.

The study design was appropriate for obtaining additional data on safety and efficacy of ALN therapy from another randomized controlled study.

The rationale for selecting the doses of ALN (2.5 and 5 mg daily) for this controlled study was similar to that used in other controlled studies. For the E/P treatment, both Premarin and Provera are approved (at doses used in this study) for the prevention of PMO. The estrogen component (Trisequens) of Danish study site is not approved for PMO in the U.S.

The study population was somewhat similar to those of other controlled studies, but subjects were not defined by BMD values during enrollment. Attempts were made to identify subjects as "fast bone losers" at Years 1 and 2 and they were given options to either receive open-label ALN 5 mg daily or to leave the study.

The evaluation criteria for efficacy and safety were similar to those of other controlled studies.

The study had a 95% power (with sample sizes of 450 per ALN and the placebo treatment groups) to detect a 0.94% difference in mean percent change from baseline in lumbar spine BMD between ALN 5 mg and placebo.

The results of 2-year study demonstrated the efficacy of ALN 5 mg daily in preventing the bone loss at the lumbar spine, total hip, and total body in early postmenopausal women. **Over the same treatment period, E/P therapy was**

more effective in increasing BMD of lumbar spine and total hip than ALN 5 mg/day. This two-year study also provides adequate safety considerations for the ALN 5 mg/day.

In conclusion, this controlled study provides adequate evidence in support of the efficacy and safety of ALN 5 mg/day for 2 years for prevention of bone mass loss in early postmenopausal women.

9 **Reviewer's Overview of Efficacy and Safety**

Osteoporosis in postmenopausal women is a major health problem because of the significant morbidity and mortality, associated with its complications due to fractures. Numerous reports have indicated that the most preventable cause for osteoporotic fractures is low bone mass. During their lifetimes, women lose about 50% of their cancellous bone (concentrated in the spine and at the ends of long bones) and about 30% of their cortical bone.

The pathogenesis of postmenopausal osteoporosis and various factors that contribute to osteoporosis fractures are well documented in the literature. Bone density measurement seems to provide a mean to asses the fracture risk with high specificity. It is generally accepted that a woman with a bone mineral density or bone mineral content that lies between 1 and 2.5 SD below the adult peak mean value is at risk of developing osteoporotic fracture.

Studies have shown that bisposphonates after preferential localization in the skeletal tissue inhibit bone resorption. Alendronate (Fosamax), a bisphosphonate is currently approved for the treatment of postmenopausal women with established osteoporosis. The original NDA for Fosamax provided substantial data from two 3-year controlled trials in support of its efficacy and safety for the treatment of PMO. The primary efficacy endpoint of these studies was percent increases in BMD of spine, femoral neck, trochanter, and total body relative to placebo. Approximately 85% of patients in two primary Phase III studies achieved $\geq$ 3% increase in spine BMD at Month 36 as a result of ALN therapy at a dose of 10 mg/day.

The results of these and other controlled treatment studies with alendronate provided the rationale for its use in the prevention of osteoporosis in postmenopausal women, who are deemed to be at increased risk for osteoporosis.

The design of three Phase III clinical trials which provided the efficacy and safety data for the prevention was basically similar, (i.e., **multicenter, double-blind, randomized, and placebo-controlled)**.

Duration of treatment of the three studies varied from 24 to 36 months. FDA Osteo-Guidelines recommend that for establishing the efficacy (based on preservation of BMD or increase in BMD of spine, hip, and total body) of an antiresorptive agent for the prevention of PMO, Phase III controlled study should last for at least 24 months. Studies 029 and 055 are currently ongoing, and they are likely to accrue additional information on the efficacy and safety of ALN beyond 2 years of treatment. Study 055 also provided data to compare the tolerability and efficacy of ALN 5 mg/day for 24 months with that of estrogen/progesterone treatment.

Studies 029 and 038 enrolled almost identical populations with respect to age, months/years since menopause, and lumbar spine BMD. Study 055 enrolled early menopausal subjects, but did not require any cutoff point for the spine BMD.

A total of 2347 subjects entered into these studies. All three studies had approximately 90% to 95% power to detect small differences in percent change from baseline in spine BMD at Month 24 (Studies 038 and 055) or Month 36 (Study 029).

The primary efficacy endpoint for all three studies was to evaluate the changes in BMD over duration of the study and at the end of the study. This was in agreement with the FDA Osteo-guidelines for establishing the efficacy for prevention of PMO indication. The safety endpoints were routine clinical and laboratory parameters similar to those of the controlled trials for the approved PMO treatment indication.

ALN 5 or 10 mg/day for 24 to 36 months in Studies 029 and 038 increased BMD of spine. Study 029 also showed increased BMD of femoral neck, trochanter, and total body at the ALN doses tried. In this study, ALN 1 mg/day for 36 months caused significant loss (from

baseline) in lumbar spine and femoral neck BMD (approx. 75% cortical bone) after 36 months of treatment. Thus, ALN 1 mg/day is not the appropriate dosage regimen for the proposed prevention indication. Study 055 used an intermediate dose of ALN (2.5 mg/day), in addition to a 5 mg/day dose for 24 months. In this study, ALN in both 2.5 and 5 mg/day doses caused **significant increases** (from placebo) in BMD of spine and total hip at Month 24. Total body BMD though not increased, nevertheless showed significantly less loss relative to placebo at Month 24. This study is a relatively large study involving about 445 to 461 subjects in each treatment group. The European and U.S. cohorts of this study also showed increased BMD of the lumbar spine and total hip at ALN doses of 2.5 and 5 mg/day (for 24 months), relative to the placebo.

Under the proposed Indications and Usage (revised by the sponsor dated November 12, 1996), the sponsor states that "*...For the prevention of osteoporosis, Fosamax should be considered in postmenopausal women.... and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of future fracture.*" In Study 055, ALN 2.5 mg/ day for 24 months significantly increased (as 5 mg dose did) BMD of lumbar spine and total hip, and significantly attenuated loss in total body BMD relative to placebo. **Thus, for the prevention of osteoporosis in early postmenopausal women ALN 2.5 mg/day could be a clinically meaningful dosage regimen.** This could also reduce the incidence and severity of various observed and perceived clinical and laboratory AEs associated long-term use of ALN therapy.

The overall safety profile of sponsor's proposed dose for ALN (5 mg/day) for the prevention of PMO is similar to that of the placebo in these controlled studies. The proposed ALN 5 mg/day dosage regimen for the prevention of PMO appeared to be well tolerated.

In conclusion, The results from three controlled clinical trials provide adequate evidence in support of its use for the prevention of osteoporosis in early postmenopausal women. This reviewer feels that for the prevention of osteoporosis indication, the ALN dosage of 2.5 mg/day may be clinically as effective as 5 mg/day. At this lower dose, clinical and laboratory AEs of long-term use of ALN in this target population may be minimized.

10 **Draft Labeling**

Both Fosamax Package Circular and Patient Package Insert have been recently revised (and changes being effected-dated October 24,1996). The draft labeling for supplements S-003 and S-006 will be reviewed after the EMD Advisory Committee meeting.

11 **Conclusion and Recommendation:** The NDA (20-560) supplement (S-003), which provides substantial evidence of efficacy and safety of Fosamax (at sponsor's recommended dosage of (5 mg/day) for the prevention of osteoporosis in postmenopausal women (with low bone mass) is approvable (See also Statistical Review and Evaluation). The Indications and Usage, Precautions, Warnings, Adverse Reactions sections of the draft labeling and sponsor's recommended dosage regimen for the proposed indication need further discussions at the forthcoming EMD Advisory Committee meeting on February 20, 1997.

S.N.Dutta, M.D.

Gloria T. Troendle

CC: Orig NDA (20-560/S-003)
HFD-340
HFD-510/SND/2/5/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-560/S03/S06

CHEMISTRY REVIEW(S)

FEB 5 1997

CHEMIST'S REVIEW	1. ORGANIZATION DMEDP, HFD-510	2. NDA NUMBER 20-560

3. NAME AND ADDRESS OF APPLICANT

Merck & Co. Inc.
BLA-30
West Point, PA

4. SUPPLEMENT NUMBER, DATE
Supplement
SE1-003
4/29/96

5. NAME OF THE DRUG
Fosamax

6. NONPROPRIETARY NAME
Alendronate Sodium
Tablets

8. AMENDMENT DATE
6/12/96
11/12/96

7. SUPPLEMENT PROVIDES FOR:
A new dosage strength (5 mg/tablet) of Fosamax to be used For the prevention of osteoporosis in postmenopausal women.

9. PHARMACOLOGICAL CATEGORY
Treatment of Osteoporosis

10. HOW DISPENSED
RX

RELATED IND/NDA/DMF

12. DOSAGE FORM
Tablet

13. POTENCY
5 mg

14. CHEMICAL NAME AND STRUCTURE
See Chem. Rev. # 1

15. COMMENTS

(A). Originally, the NDA was approved for the use of Fosamax (10 mg and 40 mg/tablet) for treatment of postmenopausal osteoporosis and Paget's disease of bone. The 4/29/96 supplement provides clinical and safety documentation supporting the use of Fosamax (5 mg/tablet) for the prevention of osteoporosis in postmenopausal women.

16. CONCLUSIONS AND RECOMMENDATIONS

The sponsor has provided sufficient CMC information in the 4/29/96 supplement (SE1-003) and the update status of manufacturing facilities for the drug substance and drug product is acceptable by the Office of Compliance. The supplement can be approved from chemistry viewpoint.

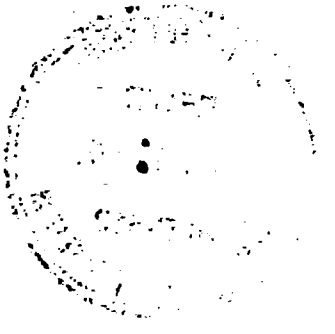
17. NAME	REVIEWER SIGNATURE	DATE COMPLETED
Chien-Hua Niu, Ph.D.	Chien Hua Niu	11/20/96

DISTRIBUTION: ORIGINAL JACKET REVIEWER DIVISION FILE

R/D initialed by:

Disc Supplement #3: NDA20560.S03

Stephen Moore
2/5/97



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-560/S03/S06

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

FOSAMAX

(alendronate sodium)

TABLETS

NDA 20-560/SEI-003

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF METABOLISM and ENDOCRINE DRUG PRODUCTS (HFD-510)

FINDING OF NO SIGNIFICANT IMPACT
NDA 20-560/SEI-003
FOSAMAX[alendronate sodium tablet]

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their efficacy supplement to the previously approved new drug application for **FOSAMAX [alendronate sodium tablets], Merck Research Laboratories** prepared an environmental assessment update in accordance with 21 CFR 25.31a(attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Alendronate sodium is a synthetic drug which is administered as an oral tablet in the prevention of osteoporosis in postmenopausal women. The drug substance is manufactured by **Merck Sharp & Dohme, County Tipperary, Ireland.** The drug product is manufactured at **Merck Sharp & Dohme, Barceloneta, Puerto Rico,** and packaged at **Merck & Co., Inc., Wilson, NC and Merck Sharp & Dohme, Barceloneta, Puerto Rico.** Alternate contract packaging facilities are also indicated in the confidential portion of the EA. The finished drug product could be used in hospitals, clinics and by patients in their homes.

Alendronate sodium may enter the environment from excretion by patients, as emissions from manufacturing sites or from disposal of pharmaceutical wastes. Chemical and physical test results indicate that the majority of the drug substance will most likely be restricted to the aquatic environment. The available data indicates that there is no rapid degradation mechanism for substance in the environment.

As alendronate sodium is expected to persist in the aquatic environment for some time, the toxicity of the material to organisms was characterized. Acute static toxicity studies in water fleas (*Daphnia Magna*), rainbow trout (*Oncorhynchus mykiss*) and fathead minnows (*Pimephales primulas*), testing of green algae (*S. Capricornutum*) and microbial inhibition studies indicate that the drug substance is not toxic to organisms at the expected environmental concentrations.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or

partly used product and packaging. Waste drug substance and drug product will be disposed of at a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

2/5/97
DATE

PREPARED
Chien-Hua Niu, Ph.D.
Review Chemist
Division of New Drug Chemistry II
Center for Drug Evaluation and Research

2/5/97
DATE

CONCURRED
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Division of New Drug Chemistry II
Center for Drug Evaluation and Research

2/9/97
DATE

CONCURRED
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

Attachment Environmental Assessment

cc:. Original NDA 20-560/SEI-003 /Thomas/ RHedin/HFD-510
HFD-510/Division file
HFD-510/SMoore/RHedin
HFD-004/FONSI File NDA #20-560
HFD-004/Docket File
HFD-019/FOI COPY

FDA Note: Detailed fate and effects information was provided in the original EA submitted for NDA 20-560.

1. Date

April 1, 1996

2. Name of Applicant

Merck Research Laboratories
Merck & Co., Inc.

3. Address

Sumneytown Pike
West Point, PA. 19486

4. Description of the Proposed Action

a. Requested Action

Merck Research Laboratories, Division of Merck & Co., Inc. has filed a supplemental New Drug Application for Tablets FOSAMAX® (alendronate sodium MSD). Alendronate sodium is a potent inhibitor of bone resorption and is approved for the treatment of diseases involving excessive bone resorption such as osteoporosis in postmenopausal women and Paget's disease of bone. This supplement requests the approval of a 5 mg strength for prevention of osteoporosis. Chemically,

alendronate sodium is a bisphosphonate and is structurally related to pyrophosphate, an endogenous regulator of calcium metabolism.

b. Need For Action

Alendronate sodium offers patients effective therapy for a broad range of bone resorption disorders. In light of the therapeutic benefits associated with its availability and use, approval of the requested action is justified and preferable to non-approval (no-action). Alendronate sodium is supplied primarily as a 10 mg tablet. The recommended dosage for the treatment of osteoporosis is 10 mg once a day. A 40 mg strength is also marketed for the treatment of Paget's disease. This supplement requests the approval of a third strength, 5 mg, for the prevention of osteoporosis. FOSAMAX® Tablets (5 mg) will be packaged in high density polyethylene (HDPE) bottles, 75 ml and 14 oz., with child-resistant and metal non-child resistant caps, respectively, and clear PVC peelable blister packages (unit dose).

The total quantity to be manufactured in the 5th year of production to support the U. S. market for both the prevention and treatment claims is given in Confidential Appendix III, Part 1.

c. Locations Where the Product will be Produced and the Types of Environments Adjacent to Those Locations

The bulk drug substance (alendronate sodium) will be manufactured in the Merck Manufacturing Division facility in Ballydine, Ireland for the U.S. market.

The drug product will be formulated at the Merck Manufacturing Division facility in Arecibo, Puerto Rico. The drug product will be packaged at the Merck Manufacturing Division facilities located in Arecibo, Puerto Rico and Wilson, North Carolina. The drug product may also be packaged at PACO, Pharmaceutical Services, Inc. locations in Lakewood, New Jersey and Canovanas, Puerto Rico. Returned and outdated drug-related materials will be disposed of at the Merck West Point, Pennsylvania, facility.

Environments present at the locations mentioned above, specific to the vicinity of product manufacture and formulation, are described in the following sections. Environments specific to alternate packaging facilities are described in Appendix II.

1) Ballydine, Ireland

Merck Sharp & Dohme
Ballydine Plant
Ballydine, Kilsheelan
Clonmel, County Tipperary, Ireland

a) Geographic Conditions

The Merck Sharp and Dohme (Ireland) Ltd. manufacturing facility is located in Ballydine, Kilsheelan, County Tipperary. The facility occupies a 180 acre site situated on the north side of the River Suir, midway between Clonmel and Carrick-on-Suir. The population of Clonmel is approximately 14,000 people. The coordinates of the location are latitude 52° N and longitude 7° W. The area around the plant is predominantly agricultural with dairy farming and tillage being the main activities. The Ballydine area has a population of approximately 100. The village of Kilsheelan, which is approximately 3 miles west of the plant, has a population of approximately 1000.

b) Weather/Air Resources

While the plant is surrounded by sparsely populated farm-land, four (4) sources of air pollution exist within a radius of ten (10) miles of the plant. These are a creamery, a crystal glass manufacturing plant,

a medium-density fiber board processing plant and a soft drink and cider processing facility.

c) Water Resources

All water used on the site is pumped from the adjacent River Suir (dry weather flow is approximately 180 million gallons per day). All river water is treated to potable grade. The treatment process consists of flocculation, pH adjustment, sand filtration and chlorination. Approximately 158 million gallons of potable water are processed annually. This water is used for fire, cooling and drinking water.

Approximately 27 million gallons of potable water are demineralized annually to serve as process and boiler feed water.

There are no wells in the vicinity of the plant and the neighborhood drinking water supply is provided by the local authority. Livestock drink from the river and tributaries as well as troughs fed from public supply.

d) Land Resources

The site is located approximately 29 meters above sea level. Terrain in the area consists of gently rolling hills. Soil in the area can

generally be described as an acid brown earth of glacial till origin of mixed old red sandstone and carboniferous limestone. The soil has a sandy loam texture and is free draining with good structure.

2) Wilson, North Carolina

Merck & Co., Inc.
I-95 and Highway 264
4633 Merck Road
Wilson, North Carolina

a) Geographic Conditions

Wilson is located 45 miles east of Raleigh, North Carolina. The plant is located 4.5 miles west of Wilson on a 225-acre plot, near the intersection of Interstate Highway 95 and Highway US 264, at latitude 35° 45' north and longitude 78° 00' west. Land use surrounding the plant is primarily residential and agricultural.

b) Air Resources

Air quality in the region meets the National Ambient Air Quality Standards (NAAQS) for sulfur oxides, nitrogen oxides, total suspended particulates and ozone. The annual rainfall is approximately 42 inches, and the average annual temperature is 59°F. Prevailing winds are from the southwest at an average annual speed of 7.7 mph.

c) Water Resources

Potable water is obtained from the local public water supply for the city of Wilson. The city of Wilson supplies water to the site. The plant potable water quality meets or exceeds all requirements of the Federal Safe Drinking Water Act. Compliance with these standards are also required in applicable Good Manufacturing Practices. Wastewater from the facility is routed to the city of Wilson treatment facility. In the developed area of the property, there are six natural drainage tributaries exiting the plant property and one entering the property. There is an established stormwater monitoring point for monitoring all stormwater releases from the plant site.

d) Land Resources

The plant site consists mainly of gently sloping terrain with forest and open farmland underlain by the Coastal Plain Providence to the east and the geologic Piedmont Geologic Providence to the west. The coastal plain soils are marine deposits and the piedmont soils are residual, formed from the chemical decomposition of the underlying bedrock. Both soils are interbedded sands, silts, and clays with the typical depth to bedrock 20-40 feet. The plant site elevation is about 160 feet above mean sea level.

3) Arecibo, Puerto Rico

Merck Sharp & Dohme
Quimica de Puerto Rico, Arecibo
Road #2, Kilometer 60.3
Barceloneta, Puerto Rico

a) Geographic Conditions

The Merck Sharp & Dohme Quimica de Puerto Rico Inc. (MSDQ) Arecibo facility is located on an 18.45 acre site in the Sabana Hoyos Ward of the Municipality of Arecibo. The 60 kilometer marker of the DeDiego Expressway (PR-2) lies to the south.

The coordinates of the facility location are latitude 14° N and longitude 66.45° W. Approximately 500 people live within a half mile radius of the facility.

b) Air Resources

Annual rainfall is approximately 60 inches and the mean ambient temperature varies between 76 and 82°F. An easterly trade wind is the predominant wind pattern.

The MSDQ Arecibo facility is located in the Barceloneta air basin which is in attainment with the National Ambient Air Quality Standards (NAAQS) for all criteria pollutants. The commonwealth

requires both new source permits and operating permits for all point sources. Puerto Rico is part of USEPA Region II and has been delegated authority over the National Emissions Standards for Hazardous Air Pollutants Program (NESHAPS). Meteorological data for the area is collected at the Isla Verde Airport in San Juan (about 50 miles east of the MSDQ-Arecibo facility).

c) Water Resources

All water used for consumption, process and sanitary equipment is supplied by an on-site artesian well. The Department of Natural Resources of Puerto Rico issued a permit on December 11, 1990 (Permit No. PPA-121-90) which allowed for the construction of a well which is capable of extracting 1,000,000 gallons per day (GPD) of water from the artesian aquifer. The depth of this aquifer varies from 800 to 1,700 feet depending on the topography of the area. The facility has a deep well franchise agreement issued on September 13, 1995 (Franchise No. RF-110-94) from the Department of Natural Resources which allows the extraction of 140,000 GPD.

The plant potable water quality meets or exceeds all requirements of the Federal Safe Drinking Water Act. Compliance with these standards are also required in applicable Good Manufacturing Practices.

Separate sewer systems exist for sanitary, process, and storm water runoff. The domestic/sanitary waste is discharged to the south of the site, into the Puerto Rico Aqueduct and Sewer Authority (PRASA) sewage system. The process sewer line joins with the sanitary sewer at the metering pit prior to discharge to the PRASA sewage system. The wastewater treatment plant is the Barceloneta Regional Wastewater Treatment Plant (BRWTP) located in Barceloneta, approximately 5 miles from the plant (NPDES Permit Number PR0021237). The final discharge (combined process and sanitary sewage) is subject to conditions specified in an industrial discharge permit with PRASA, effective November 21, 1995.

Storm water from the plant is collected in an independent sewer system. Surface water runoff from portions of the plant discharge to the drainage basin on the south side of the site.

There is one injection well on the plant property. It is located in the drainage pit on the south side of the site. It is only used for stormwater when the stormwater influx into the drainage pit exceeds the volume of the drainage basin.

There are no surface water bodies in the vicinity of the area. Due to geologic conditions of the Zone, the drainage is mainly

underground. The Atlantic Ocean is approximately 3 miles to the north of the site.

d) Land Resources

Land use surrounding the plant is mixed. Adjacent to the south side of the site, is another pharmaceutical company. Surrounding the site to the east and west is a motel and pineapple farm, respectively.

The MSDQ-Arecibo plant is located 91-95 meters above mean sea level, which is well above the 100-year floodplain.

d. Locations where the Product will be Used and the Types of Environments Present at and Adjacent to those Locations

The product is intended for use throughout the United States for management of diseases involving excessive bone resorption such as osteoporosis, Paget's disease, neoplastic invasion of bone and resorptive hypercalcemia and prevention of osteoporosis. Consumption will be on an in-patient and out-patient basis.

e. Locations where the Product will be Disposed of and the Types of Environments Present at and Adjacent to those Locations

Merck & Co., Inc. has a domestic return goods policy which involves the return of any unused market packages to the West Point, Pennsylvania location for evaluation and disposal. The product is disposed of at the West Point facility by incineration or an approved off-site facility, and any ash generated is landfilled at a permitted off-site facility. This essentially results in a single location for control of product disposal. The types of environments present at the disposal plant site are described below.

1) West Point, Pennsylvania

a) Geographic Conditions

The West Point plant is located on a site (~450 acres) in Upper Gwynedd Township, Montgomery County, which is approximately 30 miles northwest of Philadelphia. The center of the West Point plant is located near latitude 40° 12' 54" N and longitude 75° 17' 59" W. Land use surrounding the plant is primarily residential and agricultural with other industrial sites approximately one-half mile away.

b) Air Resources

Air quality in this area is in compliance with the Environmental Protection Agency's (EPA) National Ambient Air Quality Standards (NAAQS) of the Clean Air Act for total suspended particulates, sulfur oxides, and nitrogen oxides. This compliance is based on monitoring and reporting by the Pennsylvania Department of Environmental Protection (PA DEP) under the requirements of the State Implementation Plan. At this time, Montgomery County does not meet the ozone standard set forth by the NAAQS. The West Point plant lies within the outer zone of the Southeast Pennsylvania air basin. Pennsylvania is part of the EPA Region III and PA DEP is responsible for implementing the State Implementation Plan which includes new stationary source permits for manufacturing. Meteorological data for the region is collected at the Philadelphia International Airport. Annual rainfall is approximately 42 inches (107 cm) and the mean ambient monthly temperature varies between 33 and 77°F (0.5-25°C). Predominant winds are from west to southeast.

c) Water Resources

Potable water is supplied to the plant operations via an on-site storage tank which is supplied by on-site wells and a public water supplier, North Wales Water Authority. The plant potable water

quality meets all requirements of the Federal and State Safe Drinking Water Act. Compliance with these standards are also required in applicable Good Manufacturing Practices.

Stormwater drainage is controlled using detention basins which maintain site runoff at levels estimated for undeveloped property and to minimize erosion. This runoff is discharged into either the Towamencin Creek or the Wissahicken Creek.

Wastewaters generated as a result of the incineration of alendronate will be discharged to the Upper Gwynedd Township Wastewater Treatment Plant (UGTA WWTP). The UGTA discharges treated effluent to the Wissahicken Creek

The location of the discharge from the UGTA is downstream from the West Point site. Pennsylvania DEP limits the wasteload allocation and water pollutant limits (established by the Pennsylvania Water Toxics Management) from the UGTA by means of the National Pollutant Discharge Elimination System discharge permit. This wasteload allocation and water pollutant limit are used to determine the allowable contribution limits from the West Point site. The treated wastewater is also regulated by the UGTA under permit and local ordinance.

d) Land Resources

The plant is underlain by Triassic age sedimentary rocks, mapped as the Brunswick and Lockatong formations. These formations occur as layered beds of red and very dark gray shale with occasional layers of sandstone. Although these rocks generally have low primary porosities, permeability is maintained and improved by the presence of fractures and joint sets.

5. Identification of Chemical Substances that are the Subject of the Proposed Action

Information concerning the chemical structure, empirical formula, molecular weight, chemical names, laboratory codes, generic name, trade name and CAS (Chemical Abstracts Service Registry) number for alendronate sodium can be found in Appendix I. For convenience a summary of environmental fate and effects data for alendronate sodium is also included in Appendix I. There are no impurities in the drug substance at quantities that are significant with respect to the environment. Other than excipients listed in Appendix III Part 3, there are no additives used.

6. Introduction of Substances Into the Environment

a. Substances expected to be emitted and estimated releases

1) Bulk drug synthesis

Appendix III (Part 3) summarizes the chemical substances which may reasonably be expected to enter various environmental compartments (atmospheric, aquatic and terrestrial) as a result of bulk drug production. Appendix III also contains a simplified flowchart indicating emissions and a tabular summary of the control devices employed, their critical operating parameters and, where appropriate, permitted limits for emissions. Production of alendronate sodium will take place at the Merck Ballydine, Kilsheelan, Ireland facility to supply the U. S. market.

2) Dosage Form Production

Substances which may reasonably be expected to enter the various environmental compartments as a result of drug product manufacture, filling and packaging at the sites are identified in Appendix III. Appendix III also contains a simplified flowchart indicating emissions and a tabular summary of the control devices employed, their critical operating parameters and, where appropriate, permitted limits for emissions. Packaging activities

will not contribute emissions to the air, water, or land which would impact the environment.

3) Use Sites

Administered dosage form will normally enter the environment in highly diluted aqueous domestic sewage which will be subject to further local treatment. The maximum expected emitted concentration (MEEC) resulting from the use of alendronate sodium has been estimated (see Expected Introduction Concentration - Use in Confidential Appendix III, Part 1) based on the projected fifth year average production level for the U. S. market. This estimate assumes excretion of 100% of the drug activity and no environmental depletion. Use of the drug is not expected to result in emissions to the atmospheric or terrestrial environmental compartments.

4) Disposal Site

The Merck West Point, Pennsylvania incineration facilities will be used to treat returned product. On-site incineration facilities will handle the majority of this waste with resulting combustion efficiency of at least 99.9% on an hourly basis. In the event that the West Point facility is unable to accept such waste, the wastes will

be disposed of at an alternate permitted off-site facility. Expected emissions are described in the following sections.

(1) Air Emissions - Typical combustion products are expected to be emitted into the atmosphere from the incineration of returned goods. The on-site West Point facility incineration operation is in compliance with all applicable standards and permit limits. Any off-site incineration will be conducted at an equivalent, permitted facility.

(2) Liquid Emissions - Any wastewater generated from the incinerator operation will be discharged into the sanitary sewer which undergoes on-site equalization and is discharged for off-site biological wastewater treatment at the UGTA.

(3) Solid Emissions - All returned and outdated market packages and residual waste from operations at West Point will be incinerated at on-site or off-site facilities permitted to handle such waste streams.

b. Control Procedures and Citations of Compliance

1) Ballydine

a) Air Emissions Controls and Citations - Bulk Drug Substance

Air emissions from bulk manufacture of alendronate include the substances identified in Appendix III. These will be generated primarily from reaction operations and dry processing equipment. Emission control equipment and techniques are employed to reduce emissions to a minimum and include process condensers, scrubbers, and carbon adsorption. Control devices will be employed alone or in combination with each other so that the facility complies with applicable emission requirements.

Air emissions are subject to, and in compliance with the Irish Environmental Protection Agency Act, 1992 and the site's Integrated Pollution Control License (permit number 11, no expiration date). The purpose of the Integrated Pollution Control Permit is to have one permit for the entire site that encompasses all environmental media (air, water and waste). This permits limits emissions of HCl to less than 10 mg/m^3 and particulate emissions from rotoclones and dust collectors to less than 1 mg/m^3.

b) Liquid Emissions Controls and Citations- Bulk Drug Substance

Manufacture of alendronate drug substance generates liquid emissions from production operations and equipment clean-outs. Equipment clean-outs normally occur at the end of a batch campaign.

Aqueous waste streams are generated from production operations and equipment clean-outs. Aqueous waste streams are discharged to the chemical sewer and treated in an on-site biological wastewater treatment plant. The treatment plant consists of the following processes: equalization, flow control, neutralization, primary clarification, extended aeration, and secondary clarification. The treated effluent is discharged into River Suir.

Waste sludge is dewatered using a belt press or vacuum filter and disposed of in an approved solid waste management facility.

The waste treatment plant operation is operated in compliance with the Irish Environmental Protection Agency Act, 1992 and permitted by the Irish Environmental Protection Agency Integrated Pollution Control License (permit number 11, no expiration date). The permit limits the effluent to pH between 6.0 -9.0, temperature < 25°C, flow

<4500 m^3/day and BOD <100 mg/L (see additional limits in Table F-1).

The list of substances which may be discharged in the form of aqueous emissions is detailed in Appendix III.

c) Solid Emissions Controls and Citations- Bulk Drug Substance

Solid waste streams generated during alendronate drug substance manufacture at the site consist of wastes such as general trash, paper, and granular activated carbon and will be disposed of off-site in an approved solid waste management facility. The site has no specific limits or any other condition on solid waste generation. No new emission limits on solid waste generation are anticipated as a result of this proposed action.

Hazardous wastes are disposed of in a manner which fully conforms to local regulatory policy. Hazardous solid wastes are subject to, and in compliance with the Department of the Environment Waste Regulation (1979 and 1984) and the Transfrontier Shipment of the Hazardous Waste Regulations, 1985.

d) Employee Protection

Material Safety Data Sheets (MSDS's) are available on-site for all chemicals. Employees associated with the manufacture of drug substance have appropriate MSDS's available for their review. Employee protective clothing, such as gloves, uniforms, and safety glasses are used during the manufacturing process. Refer to Appendix IV for a copy of the MSDS for the drug substance.

2) Wilson, North Carolina

a) Air Emissions Controls and Citations - Drug Product Packaging

Specific ventilation systems for packaging provide for particulate removal consisting of filtration and collection. The fugitive material that is collected during the packaging process is transported to the Torit dust collector unit where the material is filtered (99.97% filter efficiency). The pulse cleaning mechanism in the filter causes the collected material to fall to a collection area where a screw device feeds the house vacuum system. The house vacuum system consists of a primary separator (cyclone) with a 95% by weight removal efficiency for particulates 10 microns or larger. The secondary separator (bag filter) consists of a bag filter with a 99.9% removal efficiency of particles 5 microns or larger. The house vacuum cleaning process is completed weekly and requires shaking of the

filters to release material. Collected material is either incinerated or disposed via landfilling at permitted waste management facilities. The particulate emissions are controlled to meet the requirements of the site permit, No. 4884R10, as amended, issued by the State of North Carolina Department of Natural Resources.

The operation of the Wilson manufacturing, packaging and power generating facilities is allowed and in compliance with Air Permit Number 4884R10, as amended, issued by the North Carolina Department of Natural Resources and Community Development in accordance with Article 21B, Chapter 143, General Statutes of North Carolina and "Other Laws, Rules and Regulations". Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements.

b) Liquid Emissions Controls and Citations - Drug Product Packaging

Aqueous liquid wastes will result from equipment cleaning. Prior to discharge to the City of Wilson collection system for processing in the Public Works Treatment Facility, the site measures the flow and periodically samples the effluent to verify compliance with the permit requirements. The treatment facility is subject to the permit limits established by Sewer Discharge Permit Number 8406. The results from 10 years of operation indicate the multiproduct

pharmaceutical facility's source control measures have satisfactorily met the discharge levels set forth in the permit.

The discharge of wastewater to the City of Wilson Wastewater Collection system is allowed under the site Sewer Connection and Discharge Permit Number 8406. The site discharge is limited to daily maximum discharges of BOD=582 lbs/day, COD=932 lbs/day, TSS=349 lbs/day, and pH 5-11. These permits are established under the city's "Rules and Regulations for the Discharge of Wastewaters into the Wastewater Treatment System of the City of Wilson, North Carolina". The City of Wilson Department of Public Works Wastewater Treatment Plant operates under National Pollutant Discharge Elimination System (NPDES) Permit Number NC0023906. No new permit limits are anticipated as a result of the proposed action.

c) Solid Waste Controls and Citations - Drug Product Packaging

Any solid waste resulting from packaging that contains pharmaceutical residuals will be collected for disposal at an off-site incineration or landfill facility, permitted by all Federal, State and local agencies. No hazardous solid waste will be generated by the packaging process.

The Wilson plant is in compliance with the North Carolina Solid Waste and Hazardous Waste Management Rules. No new permit limits are anticipated as a result of the proposed action. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements.

d) Employee Protection

Material Safety Data Sheets are available on-site for all chemicals required by the Occupational Safety Act of 1971, the Hazards Communication Act of 1985 and Title 29 Code of Federal Regulations Part 1910.1200. Employees associated with the manufacture of drug substance have appropriate MSDSs available for their review. Employee protective clothing, such as gloves, uniforms, and safety glasses are used during the manufacturing process to assure compliance with the Occupational Safety Act of 1971 and the Hazard Communication Act of 1985 and Title 29 Code of Federal Regulations, Subpart I. Refer to Appendix IV for a copy of the MSDS for the drug substance.

3) Arecibo, Puerto Rico

a) Air Emissions Controls and Citations - Drug Product Formulation

The air emissions resulting from the formulation and packaging operations will be controlled by dust collectors to ensure particulate emission control. Exhaust air from the formulation and packaging areas that may contain particulate material is filtered by a Torit dust collection unit (97% estimated efficiency). During normal operation, air enters the dust collector through the top inlet and passes through the filter elements. Dust is collected on the outside surfaces of the elements and clean air flows through the center of the elements. During filter element purge, the solid state control timer automatically selects the pair of elements to be cleaned. High pressure clean air pulses directly into the center of the selected elements blowing the collected dust off the filter elements. The dust is swept downward into the hopper by the prevailing air flow and gravity. The hopper discharges to drums where the material is collected and sent off-site for disposal.

Approval of the proposed action will not impact the facility's ability to comply with all applicable emission requirements.

b) Liquid Emissions Controls and Citations - Drug Product Formulation

Aqueous liquid wastes will result from equipment cleaning. Equipment will be vacuumed prior to water washing to remove residual drug product. Therefore, the quantity of residual drug product resulting in wastewater will be minimal.

The effluent from the Arecibo site is treated by the Barceloneta Regional Wastewater Treatment Plant (BRWTP), and this effluent is discharged from the BRWTP under NPDES Permit Number PR0021237. This permit is administered by the Puerto Rico Aqueduct and Sewer Authority (PRASA). The wastewater is subject to the pretreatment standards for existing sources of the Pharmaceutical Manufacturing Category under Title 40 of the Code of Federal Regulations Part 439 (Subcategory D). The site wastewater is regulated by an industrial permit #GDA-93-202-052 effective November 21, 1995 with an expiration date of November 21, 1997. This current agreement limits the site average daily wastewater discharge to a biological oxygen demand (BOD5) of 900 mg/L, total suspended solids (TSS) of 250 mg/L, and pH of 7.5 to 10.0. Chemical substances that may be discharged into the wastewater are listed in Appendix III.

Approval of the proposed action will not impact the facility's ability to comply with the conditions of the wastewater agreement.

c) Solid Waste Controls and Citations - Drug Product Formulation

Dry solid waste (e.g. paper, HEPA filters, dusts, tablets, etc.) from alendronate drug product formulation will be transported by a licensed carrier to a permitted incinerator for disposal. Currently, solid waste is incinerated off-site at the Commercial Incineration Corporation. This facility is governed by two permits: PFELC1603930305-III-O (expiration: 1/19/97) and SR0057 (expiration: 1/19/98). No hazardous solid waste will be generated by the packaging process.

Solid waste management at the Arecibo plant required conformance with conditions set forth by the Environmental Quality Board (EQB). The EQB has the authority to regulate solid waste management. Hazardous and non-hazardous wastes in Puerto Rico are regulated by the Public Policy Environmental Act (Act No. 9), and the Regulation for the Control of Hazardous and Non-Hazardous Wastes (Solid Waste Regulation). These requirements assure comprehensive control for the management of waste throughout the plant including returned market packages that are sent to West Point for disposal. These regulations are subject to the requirements of the Federal Resource Conservation and Recovery Act, the Federal Hazardous and Solid Waste Amendments. These regulations do not limit the quantity of solid waste generated.

However, recycling will be implemented to the fullest extent possible to minimize the amount of solid waste generated. Currently, the facility has no solid or hazardous waste permits and none are required for approval of the proposed action. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements.

d) Employee Protection

Material Safety Data Sheets are available on-site for all chemicals required by the Occupational Safety Act of 1971, the Hazards Communication Act of 1985 and Title 29 Code of Federal Regulations Part 1910.1200. Employees associated with the manufacture of drug substance have appropriate MSDSs available for their review. Employee protective clothing, such as gloves, uniforms, and safety glasses are used during the manufacturing process to assure compliance with the Occupational Safety Act of 1971 and the Hazard Communication Act of 1985 and Title 29 Code of Federal Regulations, Subpart I. Refer to Appendix IV for a copy of the MSDS for the drug substance.

4) West Point, Pennsylvania

a) Air Emission Controls and Citations - Drug Product Disposal

The on-site incineration facility employs necessary operating conditions as to ensure compliance with permitted emission levels in Plan Approval #46-301-267 (expiration: July 31, 1996) and Plan Approval #46-301-191C (expiration: June 19, 1999). As a contingency, off-site incineration will be conducted at a permitted facility.

The air emission controls for the disposal of this product meet the requirements of the Pennsylvania Air Pollution Control Regulations under Title 25 of the Pennsylvania Code, Part I - Department of Environmental Protection (PA DEP), Chapters 121-141.

Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements. No new permit limits are anticipated as a result of the proposed action.

b) Liquid Waste Controls and Citations - Drug Product Disposal

The liquid from incineration operation will be discharged into the site wastewater collection system and will undergo equalization along with other sanitary waste. This wastewater is discharged for

treatment to the UGTA. The treated effluent is discharged from the UGTA under NPDES Permit Number PA 0023256. This permit is administered by PA DEP.

The wastewater is subject to and in compliance with the pretreatment standards for existing sources of the Pharmaceutical Manufacturing Category under Title 40 of the Code of Federal Regulations Part 439. The wastewater is also regulated by the UGTA and is in compliance with the existing contract and the "Rules and Regulations Governing the Discharge of Sanitary and Industrial Wastewaters into the Public Sewers of Upper Gwynedd Township Authority". These regulations are based on the requirements of the Federal Clean Water Act and Pennsylvania Clean Streams Law. The current contract with UGTA limits plant effluent to a flow (calculated from a monthly average) of 1.225 million gal/day; BOD = 250 mg/L (daily maximum); TSS = 300 mg/L; and pH between 5.5 - 9.0. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements and no new permit limits are anticipated as a result of the proposed action.

c) Solid Waste Controls and Citations - Drug Product Disposal

Appropriate controls for the disposal of unused market packages are utilized as part of the site solid waste management program.

The waste is incinerated at permitted disposal facilities. Ash generated from the on-site incineration process is disposed of at a permitted facility and is monitored to confirm its acceptability with prevailing solid waste regulations. Currently, ash is disposed at the Grand Central Sanitary Landfill located in Pen Argyl, PA 18072 (PA Solid Waste permit #100265, no expiration date) or the Pine Grove Landfill located in Pine Grove, PA 17963 (PA Solid Waste permit #101427, expires 4/6/2000) or an equivalent facility that is permitted for solid waste disposal in the event an alternate facility is chosen through the competitive bid process.

Solid waste management at the West Point plant requires conformance with conditions set forth in Permits 400674 and 400459 (expiration: 1/25/2003 and 6/16/2005, respectively) issued by PA DEP and Permit PAD002387926 (expiration date: 3/19/2006) issued by both EPA and PA DEP. These requirements assure comprehensive control for management of waste throughout the plant including returned market packages. The requirements of the Pennsylvania Code, Title 25, Part I - Department of Environmental Protection, Chapter 75, are the primary regulations which impact solid waste management. The regulations are subject to the requirements of the Federal Resource Conservation and Recovery Act, the Federal Hazardous and Solid Waste Amendments, and the Pennsylvania Solid Waste Management Act.

Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements.

Incineration of returned goods may also take place off-site at Ogden Martin Systems of Lancaster, Inc. The facility is owned by the Lancaster County Solid Waste Management Authority and is located in Marietta, PA 17547. The facility is permitted under Solid Waste Permit #400592 and expires on 3/31/2009. An equivalent permitted solid waste facility may be used in the event an alternate waste disposal facility is chosen through the competitive bid process.

d) Employee Protection

Material Safety Data Sheets are available on-site for all chemicals required by the Occupational Safety Act of 1971, the Hazards Communication Act of 1985 and Title 29 Code of Federal Regulations Part 1910.1200. Employees associated with the manufacture of drug substance have appropriate MSDSs available for their review. Employee protective clothing, such as gloves, uniforms, and safety glasses are used during the manufacturing process to assure compliance with the Occupational Safety Act of 1971 and the Hazard Communication Act of 1985 and Title 29 Code of Federal Regulations, Subpart I. Refer to Appendix IV for a copy of the MSDS for the drug substance.

c. Effect of Application Approval on Compliance with Current Emissions Requirements

Merck & Co., Inc. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of alendronate sodium at its facility in Ballydine, Ireland; as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the formulation and packaging of alendronate sodium at its facilities in Wilson, North Carolina and Arecibo, Puerto Rico and incineration of returned goods at the West Point, Pennsylvania plant.

7. Fate of Emitted Substances to the Environment

Item 7 is not required since the expected environmental concentration due to entry into the environment is less than one (1) ppb from use and or disposal. (see Confidential Appendix III - Part I). In accordance with FDA Guidance Document (CDER, 1995), information for this section is not being provided.

For reference, a summary of the data provided in the original environmental assessment (NDA 20-560, approved September 29, 1995) is provided in Appendix I.

8. Environmental Effects of Released Substances

Item 8 is not required since the expected environmental concentration due to entry into the environment is less than one (1) ppb from use and or disposal. (see Confidential Appendix III - Part I). In accordance with FDA Guidance Document (CDER, 1995), information for this section is not being provided.

For reference, a summary of the data provided in the original environmental assessment (NDA 20-560, approved September 29, 1995) is provided in Appendix I.

9. Use of Resources and Energy

Item 9 is not required since the expected environmental concentration due to entry into the environment is less than one (1) ppb from use and or disposal. (see Confidential Appendix III - Part I). In accordance with FDA Guidance Document (CDER, 1995), information for this section is not being provided.

10. Mitigation Measures

Item 10 is not required since the expected environmental concentration due to entry into the environment is less than one (1) ppb from use and or disposal. (see Confidential Appendix III - Part I). In accordance with FDA Guidance Document (CDER, 1995), information for this section is not being provided.

11. Alternatives to the Proposed Action

FOSAMAX® (alendronate sodium, MSD) directly benefit patients by providing effective treatment for diseases involving excess bone resorption such as osteoporosis, Paget's disease, neoplastic invasion of bone and resorptive hypercalcemia and prevention of osteoporosis.

Approval of FOSAMAX® is justified from an environmental perspective and given its direct benefit to patients is preferable to non-approval which is the only alternative to the proposed action.

12. List of Preparers

Stuart Bacher

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M.S. - Chemical Engineering, 1964
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Steven C. Wittmer, P.E.

B.S. - Civil Engineering, 1975

University of Delaware, Newark, DE.

M.S. - Environmental Engineering, 1980

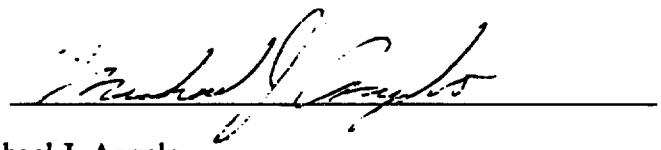
University of Delaware, Newark, DE.

Director, Environmental Affairs

Merck Manufacturing Division

13. Certification

The undersigned certify that the information presented is true, accurate and complete to the best of the knowledge of the firm responsible for the preparation of the environmental assessment.



4/1/96

Michael J. Angelo
Vice President, Safety & the Environment
Merck & Co., Inc.

Date

14. Literature Cited

Center for Drug Evaluation and Research (CDER), 1995, "Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements

APPENDICES

APPENDIX I

Drug Substance Information Summary

APPENDIX I

A. Drug Substance Information Summary

1. Nonmenclature

International Non-Proprietary Name:

Alendronate sodium

U. S. Adopted Name:

Alendronate sodium

Chemical Name:

4-amino-1-hydroxybutylidene bisphosphonic acid, monosodium salt, trihydrate

Laboratory Codes:

L-670,452

MK0217

Other Names:

FOSAMAX®

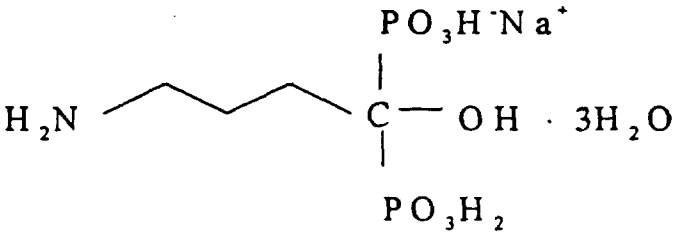
Chemical Abstracts Service (CAS) Registry No.:

121268-17-5

APPENDIX I (Con't)

2. Description

Structural Formula:



Molecular Formula:

$C_4H_{12}NNaO_7P_2 \cdot 3H_2O$

Molecular Weight:

325.1

3. Environmental Fate

a. Solubility, aqueous

40 mg/mL @25°C

APPENDIX I (Con't)

b. Dissociation Constant

pKa = 6.9

c. n-Octanol - Water Partitioning

log P = -2.6

d. Thermal Behavior

Dehydration occurs below 150°C, thermal degradation commences at ~200°C with charring evident at or above 400°C.

Vapor pressure

No evidence of sublimation up to 200°C.

e. UV - Vis Spectrum

No absorbance maxima are exhibited in the 210 - 440 nm wavelength region.

APPENDIX I (Con't)

4. Environmental Effects

a. Aquatic Toxicity

1) *Daphnia magna* (water flea)

48 hour LC_{50} = 21.7 mg/L

2) *Pimephales promelas* (Fathead Minnow)

48 hour LC_{50} = 1450 mg/L

3) *Oncorhynchus mykiss* (Rainbow trout)

96-hour LC_{50} > 1000 mg/L

NOEC > 1000 mg/L

APPENDIX I (Con't)

f. Biodegradation

Alendronate sodium is not readily biodegradable when exposed to a mixed microbial population of activated sludge origin.

g. Hydrolysis

Alendronate sodium is not susceptible to hydrolysis in aqueous solution.

@25°C

pH 5 (acetate buffer)	<10% (28 days)	t½ ~413 days
pH 7 (tris buffer)	<10% (28 days)	t½ ~375 days
pH 9 (borate buffer)	<10% (28 days)	t½ ~223

h. Photolysis

Alendronate sodium is not susceptible to photolysis under clear sky conditions.

APPENDIX I (Con't)

b. Microbial Inhibition

Azotobacter paspali	*MIC > 500 ≤ 1000 mg/L*
Scenedesmus quadricauda	*MIC > 1000 mg/L*
Trichodeme hamatum	*MIC > 1000 mg/L*
Aspergillus niger	*MIC > 1000 mg/L*
Pseudomones putida	*MIC > 1000 mg/L*
Selanastrum capricornutum	*MIC > 100 ≤ 500 mg/L*

Photobacterium phosphoreum (Microtox®)

EC_{50} (30 min, 15°C) = 385 mg/L

c. Maximum Non-Inhibitory Effect Concentration (Activated Sludge)

= 4320 mg/L

d. Algal Toxicity (14 day)

	Hardness	NOEL (mg/L)	MIC (mg/L)
S. capricornutum	~40 mg/L[1]	0.5	>0.5≤1.0
S. capricornutum	150-300 mg/L[2]	≥1.0	≥1.0≤10

[1]Unmodified algal media

[2]Hardness adjusted with $CaCO_3$

APPENDIX II

Confidential

Environmental Descriptions for

Manufacturers Other than Merck & Co., Inc.

APPENDIX III

Confidential

Chemicals Subject to Proposed Action

APPENDIX IV

Material Safety Data Sheet for Drug Substance

MATERIAL SAFETY DATA SHEET

PRODUCT NAME: SODIUM ALENDRONATE PURE DRY
PLANT MSDS CODE: BA-028

Date: 11/95

1. Chemical Product and Company Identification

Manufacturer---------- MERCK SHARP AND DOHME (IRELAND) LTD.
BALLYDINE, KILSHEELAN,
CLONMEL, COUNTY TIPPERARY,
IRELAND

Emergency Telephone Number------- 051-640411 (Ireland)
(908) 594-5555 (U.S.)

Chemical Name---------- (4-Amino-1-hydroxybutylidene) bisphosphonic acid, monosodium salt, trihydrate

Synonyms (Common)---------- Alendronate Sodium, MK-217, L-670,452
(Chemical)---------- None

Material Statistical Number------ 2-80987, 2-80988, 2-80989, 2-80990

Material Product Number---------- SP2239

Intended Use---------- Bone resorption inhibitor

2. Composition/Information on Ingredients

Component	Molecular Formula	Molecular Weight	CAS Number	Percent (%)
Sodium Alendronate	C4H18NNaO10P2	325.13	121268-17-5	100

EC Label---------- Xn, R22/34/37/41; N, R52/53

3. Hazards Identification

Appearance---------- Clean, white free-flowing crystalline powder.

Emergency Overview---------- WARNING!
Causes burns.
Risk of serious damage to eyes.
Irritating to respiratory system.
Harmful if swallowed.
Harmful to aquatic organisms.
May cause long-term adverse effects in the aquatic environment.

*** Continued on next page ***

Potential Health Effects:

Effects of Acute Exposure

Eye Contact----------	SEVERELY IRRITATING TO THE EYES. RISK OF SERIOUS DAMAGE TO EYES.
Skin Contact----------	CAUSES BURNS WHICH MAY BE DELAYED AND CAN RESULT IN PERMANENT SKIN CHANGES (E.G., DISCOLORATION).
Inhalation----------	Manufacturing experience indicates it may cause irritation.
Ingestion----------	Slightly toxic by the oral route.
Effects of Chronic Exposure------	Sodium alendronate is a bone resorption inhibitor used to treat osteoporosis. In clinical studies the no-effect level for effects on bone density is 1 mg/day. In preclinical studies, slight focal renal tubular degeneration (NOEL = 0.05 mg/kg/day), abnormal endochondral bone maturation (LOEL = 0.01 mg/kg/day) and focal gastritis (NOEL = 0.1 mg/kg/day) were noted in animals. No fetal changes were noted independent of maternal toxicity, but the pharmacologic activity of MK-217 inhibits Ca++ mobilization from bone necessary for normal parturition (birth). Based upon mutagenicity and genotoxicity assays, there is no risk of genotoxicity in man at therapeutic doses.
Carcinogen Designation----------	Not listed as a carcinogen by IARC, NTP or OSHA.

4. First-Aid Measures

Eye Contact----------	Immediately flush eyes with plenty of water for 15 minutes. Seek medical attention immediately.

*** Continued on next page ***

Skin Contact----------	In case of contact, immediately flush skin with plenty of water. Remove contaminated clothing. Wash clothing before reuse. Seek medical attention immediately. Skin burns may be delayed several days.
Inhalation----------	If inhaled, remove to fresh air. Seek medical attention immediately. If not breathing, give artificial respiration. If breathing is difficult, give oxygen.
Ingestion----------	Seek medical attention. Induce vomiting ONLY as directed by medical personnel. Never give anything by mouth to an unconscious person.
Notes to Physician----------	None

5. Fire-Fighting Measures

Flash Point (oC/oF)----------	Not applicable
Flash Point Test Method----------	Not applicable
Autoignition Temperature (oC/oF)-	Not available
Flammable Limits -LEL (%)--------	Not applicable
-UEL (%)--------	Not applicable
Combustibility Information-------	The match flame test created no reaction. The meker burner flame produced a light gray smoke, a slight red glowing, and a crusty brown char remained.
Dust Explosivity Information-----	An explosive cloud could not be developed.
Shock Sensitivity Information----	Not applicable
Extinguishing Media----------	Water, CO2, dry chemical
Special Fire Fighting Procedures-	Firefighters should wear SCBAs and protective clothing.
Fire/Explosion Hazards----------	None aside from five decomposition products.

*** Continued on next page ***

Hazardous Decomposition Products Resulting From A Fire- CO, CO2, and oxides of nitrogen and phosphorous may be released in a fire.

6. Accidental Release Measures

Steps to be taken in case materials released:

Contact emergency response personnel. Keep unnecessary persons away. If emergency response personnel are unavailable, vacuum or shovel up spilled material and place in an appropriate container for disposal. Use suitable protective equipment (Section 8). Follow all fire prevention procedures (Section 5).

For additional assistance in the U.S., CHEMTREC provides a toll-free Hotline for chemical emergencies regarding spills, leaks, exposure or accidents: 1-800-424-9300.

7. Handling and Storage

Special Precautions to be taken when:

Handling---------- Implement special handling procedures as necessary to control skin and eye contact.

Storing---------- Chelates metal ions - store in inert containers.

Other---------- None

8. Exposure Controls/Personal Protection

Exposure Guidelines

Component	OSHA Permissible Exposure Limit (PEL)	ACGIH Threshold Limit Value (TLV)	Merck Exposure Control Limit (ECL)
Sodium Alendronate	Not established	Not established	0.1 mg/m3 (8-hr TWA)

Personal Protective Equipment

*** Continued on next page ***

Respiratory----------	An approved and properly fitted, full-face, negative pressure, HEPA filtered respirator or respirator of equivalent or greater protection is recommended if handling powder form without engineering controls to reduce employee exposure below the exposure limit.
Hands/Arms----------	AVOID DERMAL CONTACT. Double latex gloves and disposable gauntlets or other protective clothing must be worn when handling powder. Gloves impervious to the solvent used should be worn when handling solutions of this compound.
Eye/Face----------	AVOID EYE CONTACT. Full-face protection required if potential exists for direct exposure to dust or aerosols.
Additional Protective Equipment--	Wear suitable disposable suit.
Ventilation----------	Use local exhaust ventilation.

9. Physical and Chemical Properties

Appearance----------	Clean, white free-flowing crystalline powder.
Odor/Threshold Level (ppm)-------	Not available
Boiling Point (oC/oF)----------	Not applicable
Freezing Point (oC/oF)----------	Not applicable
Melting Range (oC/oF)----------	Decomposes 250-280oC/482-536oF
pH ----------	4.3
Solubility in water----------	Freely soluble - 40 g/l @ 25oC
Specific Gravity (Water = 1)-----	Not applicable
Vapor Density (Air=1)----------	Not applicable
Vapor Pressure (mm Hg @ oC/oF)---	Not applicable
Volatile Components (% w/w)------	0%

*** Continued on next page ***

10. Stability and Reactivity

Stability (Normal Storage Conditions)- Stable

Storage Conditions to Avoid------ No special precautions needed.

Thermal Stability/Instability Information- Heat stable dry or in solution.

Incompatibilities (Chemical Entities)- Neutralization reaction with bases.

Incompatibilities (Materials of Construction)- Chelates metal ions - Store in inert containers.

Hazardous Polymerizations-------- None known

11. Toxicological Information

Quantitative Toxicity Data

TEST	SPECIES	ROUTE	RESULT
LD50	Mouse (F)	Oral	978 mg/kg
LD50	Rat (F)	Oral	552 mg/kg
Irritation	Rabbit	Dermal	Extremely irritating
Irritation	Rabbit	Ocular	Extremely irritating

12. Ecological Information

Environmental Fate---------- Alendronate sodium is freely soluble in water and has a low potential for bioaccumulation. It is stable in the aquatic environment and under natural light in aquatic media. Test studies indicate that alendronate sodium is not readily biodegradable and no biological inhibition of activated sludge was observed at concentrations of less than or equal to 4320 g/L.

Environmental Effects---------- 48 hr. LC50 (Daphnia magna) = 21.7 mg/L (slightly toxic to aquatic organisms)
96 hr. LC50 (Rainbow trout) = 1000 mg/L (practically non-toxic)
48 hr. LC50 (Fathead minnow) = 1450 mg/L (practically non-toxic)

*** Continued on next page ***

13. Disposal Considerations

Waste Disposal Information------- Avoid contact of spilled materials and runoff with soil and surface waterways. Dispose of or treat all spill residues including contaminated soils following all applicable regulations.

14. Transport Information

U.S. DOT------------------------- Not available

ICAO/IATA----------------------- Not available

IMO----------------------------- Not available

Hazardous Substance-Reportable Quantity (RQ)-- Not available

15. Regulatory Information

U.S. Federal Regulations--------- Not available

International Regulations-------- Not available

State Regulations---------------- Not available

16. Other Information

Date Prepared-------------------- December 7, 1992

Last Revision Date--------------- November 4, 1995

MSDS Coordinator----------------- 1-908-423-7926
Merck & Co, Inc.
One Merck Drive
P.O. Box 100, WS2F-48
Whitehouse Station, NJ 08889-0100
U.S.A.

While this information and recommendations set forth are believed to be accurate as of the date hereof, MERCK & CO., INC. makes no warranty with respect hereto and disclaims all liability from reliance thereon.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-560/S03/S06

PHARMACOLOGY REVIEW(S)

MAR 7 1997

NDA 20-560 March 3, 1997

Merck Research Laboratories
West Point, PA

Submission: April 29, 1996 and February 24, 1997

PHARMACOLOGY REVIEW OF NDA SUPLEMENT

DRUG: Fosamax (alendronate sodium tablets; MK-217)

CATEGORY: anti-osteolytic

STATUS:
NDA approved 9/95 for treatment of osteoporosis in postmenapausal women (10 mg/day)
New indication sought: prevention of osteoporosis in postmenapausal women (5 mg/day)

Elizabeth Barbehenn

Elizabeth Barbehenn, Ph.D.

Ronald W. Steigerwalt 3/7/97

cc: IND Arch
NDA Arch
HFD-510
HFD-510/Steigerwalt/Barbehenn/Dutta
Fosamax.#04

One study submitted:
Longterm effect of Alendronate treatment in fed/diet-restricted ovariectomized rats (vol 7)
#93-153-0. Merck and December 1993- December 1994.
Lot#:
TREATMENT: Three groups of Sprague-Dawley CD female rats (4 months-old; 12/g) underwent bilateral ovariectomy (ovx) and were treated orally for one year starting the day after surgery with **0, 0.1, and 0.5 mg/kg/day in d. water**. A fourth group had sham surgery and received only vehicle; a fifth group had neither surgery nor drug and were killed after drug week 2 (they were used only for biochemistry at drug week 2).

Rats were dosed *fed but diet restricted (17 g/day* Purina chow). Rats were bone-labeled prior to study completion with oxytetracycline. At necropsy, both tibia and 4th-6th lumbar vertebrae were fixed in 10% formalin. Subsequently, the 6th lumbar vertebrae were fixed in 70% ethanol, further dehydrated up to 100% ethanol, and embedded without prior decalcification. Sections of 5 um were cut and stained; 10 um sections were cut and left unstained for dynamic measurements. The femora and L1-3 were frozen for biomechanical analysis at (a non-GLP lab).

Longterm Effect of Alendronate Treatment in Ovariectomized Rats (0, 0.1, 0.5 mkd)

MORTALITY: "none drug-related" (one HD died DW 28 with decreased Pi of 3.3 mg/dl)

CLINICAL SIGNS: "none drug-related"

BW: Sham-ovx gained 14 g (vs 77, 93, and 65 g) for 0, 0.1 and 0.5 mkd ovx rats

BIOCHEMISTRY (DW 28 only for ovx rats). There was no baseline data except for the untreated control group (no surgery or drug) which was killed DW 2. No parameters were significant in ovx groups by trend test. ( ) = control data after 2 weeks [rest is DW 28]

	0;	0,	0, 0.1, 0.5 mkd
	(sham-ovx)		(ovx)
ALKP:	(54);	34,	67, 71, 70
T. Calcium:	(10.1);	10.3,	9.5, 9.5, 9.6
Ionized Ca:	(5.4);	5.4,	5.2, 5.3, 5.3
Pi (mg/dl):	(5.6);	4.5,	4.4, 4.5, 4.4

WHOLE FEMORAL BONE (Mean±SEM)

Parameter	Sham/Veh	Ovx/Veh	Ovx/0.1 mkd	Ovx/0.5 mkd
Total BMD ∇	0.25±0.005	0.22± 0.003*	0.22± 0.003*	0.23± 0.005*
Proximal BMD∇	0.26± 0.005	0.22± 0.002*	0.23± 0.003*	0.24± 0.005*
Distal BMD∇	0.26± 0.006	0.22 ±0.003*	0.22 ±0.004*	0.23 ±0.006*
Mid Fem BMD∇	0.24 ±0.005	0.23 ±0.004	0.23±0.003	0.24± 0.006
Ultimatd Load (N)	190± 9.7	182 ± 11	190± 4.4	190± 9.2
Stiffness (N/mm)	730± 45	650± 38	640 ±17	720 ±35

*p<0.05 from sham/vehicle (n=11-12/g)
∇= g/cm2

FEMORAL NECK (Mean±SEM)

Parameter	Sham/Veh	Ovx/Veh	Ovx/0.1 mkd	Ovx/0.5 mkd
Cortical Area (mm2)	2.5 ± 0.25	3.2 ± 0.29	3.1 ± 0.40	3.0 ± 0.16
Bone Area (%)	73 ±4.5	67 ±5.4	69 ±3.5	71 ± 4.1
Ultimate Load (N)	150± 9.6	160 ±6.0	130± 7.9*	130± 7.4*
Stiffness (N/mm)	960±71	1100± 46	840± 60*	970± 64

*p<0.05 from Ovx/Vehicle (n=5-9/g)

L3

Parameter	Sham/Veh	Ovx/Veh	Ovx/0.1 mkd	Ovx/0.5 mkd
Ash Wt (g)	0.051 ± 0.002	0.044 ± 0.001*	0.044 ± 0.001*	0.05 ± 0.002$^{\Delta}$
BMD (g/cm2)	0.14 ± 0.005	0.10 ± 0.003*	0.11 ± 0.003*	0.13 ± 0.004$^{\Delta}$
Ultimate Load (N)	380 ± 33	300 ± 18*	300 ± 22*	360 ± 20
Stiffness (N/mm)	960 ± 62	730 ± 96*	970 ± 47#	960 ± 42#

*p<0.05 from Sham/Vehicle(n=10-12/g)
Δp<0.05 from ovx/vehicle and 0.1 mkd
#p<0.05 from ovx/vehicle

SUMMARY AND EVALUATION: This is a supplement for a new indication for Fosamax: in addition to the *treatment* of osteoporosis in postmenopausal women (no upper limit on age; 10 mg/day), there will be an indication for *prevention* of osteoporosis in postmenopausal women (ages 40 to 60 years; 5 mg/day; 0.1 mg/kg/day).

Statistics for the biochemistry data were submitted by request; there were no statistically significant differences between the ovx rats in calcium, ionized calcium, ALKP, or phosphorous, control or drug-treated.

Non-GLP studies of bone quality:
Densitometric properties: Neither dose maintained the bone mineral density (BMD) of either the whole or proximal femora, but the high dose did maintain the BMD of the L3 vertebra.

Biomechanical properties: There were no significant effects of ovx or alendronate on either ultimate load or stiffness of the *whole femoral bone*. In the *femoral neck*, for some unexplained reason, there was no loss of strength or stiffness with ovariectomy alone, whereas rats that had ovx and drug treatment had significant decreases in ultimate load compared to sham/vehicle and ovx/vehicle. In *L3*, both doses prevented the loss of stiffness seen with ovx alone, although only the high dose prevented loss of strength.

The doses tested in these rats (0.1 and 0.5 mg/kg/day) were stated to "*correspond to approximately 0.04 and 0.2 mg/kg/day in humans*", presumably based on differential absorption (p. f87). Since the human dose is 0.1 mg/kg/day, Merck stated that they have tested alendronate at 0.4 and 2x the human doses. However, since rats were dosed fed (which lowers absorption), the true exposure and thus the multiples of the human dose, are even lower .

Given that the two low doses studied here were given to *fed* rats, it is amazing that any effects at all were seen. Unfortunately, higher exposures have never been tested; it would have been useful to at least have dosed these rats *fasted*, as humans are dosed, especially as there has been no attempt to measure plasma exposure.

RECOMMENDATION: Although the decreased load sustainable by the femoral neck in treated rats is disturbing, the efficacy seen in the clinical fracture data takes precedence in supporting this indication. Therefore, Pharmacology has no objection to approval for the indication of prevention.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-560/S03/S06

STATISTICAL REVIEW(S)

FEB 3 1997

STATISTICAL REVIEW AND EVALUATION

NDA#: 20-560/SE1-003

APPLICANT: Merck Research Laboratories

NAME OF DRUG: Fosamax (alendronate sodium tablets)

INDICATION: Prevention of Postmenopausal Osteoporosis

DOCUMENTS REVIEWED: Volumes 1 and 27-35 of NDA 20-560/SE1-003 dated April 29, 1996

MEDICAL REVIEWER: This review has been discussed with the clinical reviewer, Samarendra Dutta, M.D., HFD-510

RELEVANT ISSUES DISCUSSED IN THIS REVIEW

1. Studies 029, 038, and 055 demonstrated an alendronate treatment effect with regard to the prevention of lumbar spine BMD loss.

2. Each alendronate treatment group experienced a significantly more favorable BMD response than did the placebo group. Placebo patients experienced a significant reduction in lumbar spine BMD over the 2-3 year treatment period. However, patients who received alendronate 2.5 mg, 5 mg, and 10 mg daily experienced a significant increase in lumbar spine BMD over the same time period.

3. Study 038 demonstrated that the cessation of alendronate therapy after 6 months resulted in a reversal of the treatment effect.

4. Study 055 demonstrated that alendronate was not as effective as estrogen/progestin in increasing lumbar spine BMD.

5. Clinicians should assess the sponsor's recommendation of alendronate 5 mg given the positive BMD results experienced by patients who received alendronate 2.5 mg in Study 055.

BACKGROUND

The sponsor's current submission supplements the previously approved application for use of Fosamax in the treatment of postmenopausal osteoporosis and Paget's disease of bone, and provides clinical efficacy and safety documentation supporting the use of Fosamax for the prevention of osteoporosis in postmenopausal women.

KEY WORDS: calcium, dual-energy x-ray absorptiometry, estrogen, lumbar spine bone mineral density, postmenopausal osteoporosis prevention, progestin, resolution of effect.

BACKGROUND (Con t)

The sponsor has submitted the results of 3 double-blind, randomized, placebo-controlled studies (029, 038, 055) that involved the treatment of early postmenopausal women between the ages of 40 and 60 with oral alendronate at doses of 1, 2.5, 5, 10, or 20 mg daily with durations of treatment up to 3 years in support of their proposed prevention indication.

Subjects were excluded from these studies if they had either a history of osteoporotic fracture or radiologic evidence of a previous vertebral fracture. In addition, women with other diseases of bone metabolism, women receiving estrogen, or those previously treated with a bisphosphonate were excluded due to the possible confounding effects upon assessment of efficacy.

The primary efficacy endpoint in each of the studies was the percent change from baseline in PA lumbar spine bone mineral density (BMD) measured using dual-energy x-ray absorptiometry (DXA).

The primary focus of the sponsor's submission with regard to efficacy was to review the effects of continuous treatment for preventing bone loss with alendronate for 2 or 3 years versus placebo. Studies 029 and 055 provided the greatest amount of information in this regard as the primary objective of Study 038 was to examine the effect of treatment discontinuation on resolution of effects.

A statistical review and evaluation of each of these studies follows.

STUDY 029

This double-blind, randomized, placebo-controlled, multicenter (15 centers) study was conducted to evaluate the safety and efficacy of alendronate in the prevention of postmenopausal osteoporosis.

Subsequent to a 2-week single-blind, placebo run-in period, a total of 447 patients (90 placebo, 92 alendronate 1 mg, 88 alendronate 5 mg, 88 alendronate 10 mg, 89 alendronate 20 mg) were randomized to receive double-blind treatment once daily. In addition, all subjects received a daily dietary calcium supplement of 500 mg elemental calcium.

The original study protocol indicated that double-blind treatment would be administered for 2 years. However, during the first study year, the protocol was amended to extend the double-blind treatment period to 3 years in order to obtain longer-term data. Patients consenting to the third year of double-blind treatment continued to receive their randomized treatment with the exception of those patients who had received alendronate 20 mg for the first two years. These patients were blindly switched to receive placebo during the third year.

Patients were allowed not to continue double-blind treatment for a third year due to ethical considerations. In addition, patients who were identified as fast losers (experienced a decrease in spine bone mineral density greater than 6% after 18 and 24 months of double-blind treatment) were allowed to terminate the study or to receive open-label treatment with alendronate 5 mg during the third year. Only 8 patients (4 placebo, 4 alendronate 1 mg) were identified as fast losers . Seven of these patients received alendronate 5 mg during the third treatment year. One placebo patient did not elect to continue double-blind treatment.

The primary efficacy endpoint was the percent change in lumbar spine bone mineral density (BMD) subsequent to three years of double-blind treatment.

Patients who had a baseline and at least one post-treatment lumbar spine BMD measurement (which were taken every 6 months) were included in the sponsor's intent-to-treat-population (primary) analysis. The last observation carried forward (LOCF) procedure was utilized for patients who withdrew from the study.

STUDY 029 BMD RESULTS AND REVIEWER' S COMMENTS

A total of 311 patients (63 placebo, 66 alendronate 1 mg, 63 alendronate 5 mg, 62 alendronate 10 mg, 57 alendronate 20 mg) completed 3 years of double-blind treatment.

Thirty-three (6 placebo, 6 alendronate 1 mg, 6 alendronate 5 mg, 6 alendronate 10 mg, 9 alendronate 20 mg) of the 136 patients who failed to complete the study withdrew due to clinical adverse experiences. Acid regurgitation was the most common reason for such a withdrawal (1 placebo, 1 alendronate 1 mg, 2 alendronate 10 mg).

A total of 418 patients (82 placebo, 85 alendronate 1 mg, 81 alendronate 5 mg, 86 alendronate 10 mg, 84 alendronate 20 mg, p=.17) reported at least one clinical adverse experience during the 36-month treatment period.

Flatulence (1 placebo, 1 alendronate 1 mg, 1 alendronate 5 mg, 5 alendronate 10 mg, 5 alendronate 20 mg) was the only clinical adverse experience which was reported by at least 5% of the patients in at least one of the treatment groups for which a statistically significant positive trend (p=.026) was detected across the placebo, 1 mg, 5 mg, 10 mg alendronate dosage groups.

The results of the sponsor's primary efficacy analysis are displayed in Table 1. In examining this table, one notes the existence of a treatment effect ($p<.001$) in favor of each alendronate dosage regimen over placebo with respect to the change in lumbar spine BMD over 36 months of treatment. In addition a statistically significant positive trend ($p<.001$) was detected across the placebo, 1, 5, and 10 mg alendronate doses (the 20 mg dose was not analyzed using the trend test since patients did not receive 20 mg in the third treatment year).

The above mentioned favorable alendronate BMD results were consistent across center, age, race and densitometer (hologic and lunar).

The lumbar spine mean percent changes over the 36-month treatment period are illustrated in Figure 1 which follows Table 1 in this review. In examining this graph, one notes that the alendronate treatment groups showed most of their increases in lumbar spine BMD during the first year of treatment.

Table 2 which displays percentages of patients who achieved designated lumbar spine BMD changes may be utilized by the clinicians as an aid in interpreting the level of BMD response. For example, in examining Table 2, one notes that 44% percent of the alendronate 5 mg (sponsor's recommended dose) patients experienced at least a 4% increase in lumbar spine BMD. These results are also displayed graphically in Figure 2 which follows Table 2 in this review.

Patients in the placebo and alendronate 1 mg treatment groups experienced a significant (placebo: $p<.001$, alendronate 1 mg: $p<.01$) reduction in lumbar spine BMD over the 36 month double-blind treatment period whereas patients in the alendronate 5 mg, 10 mg, and 20 mg treatment groups experienced a significant ($p<.001$) increase in lumbar spine BMD over the same time period. These results and the previously mentioned dose response results, form the basis for the sponsor's recommended dose of alendronate 5 mg administered once daily for the prevention of osteoporosis in postmenopausal women.

STUDY 055

This double-blind, randomized, placebo-controlled, multicenter (4 centers) study was conducted to evaluate the safety and efficacy of alendronate in the prevention of postmenopausal osteoporosis.

This study was designed as a 2-year study with a planned 4-year double-blind extension. Two-year results have been submitted by the sponsor in the current submission.

Subsequent to a 2-week single-blind, placebo run-in period, patients were stratified into 2 stratums. Subjects in stratum 1 agreed to accept randomization to receive placebo, alendronate 2.5 mg, alendronate 5 mg, once daily , or open-label estrogen/progestin. Subjects who preferred to avoid possible estrogen/prosgestin treatment or in whom estrogen/progestin was contraindicated were placed in stratum 2 and randomized to receive placebo, alendronate 2.5 mg, or alendronate 5 mg once daily.

Each subject was responsible for the adequacy of their calcium intake as calcium supplements were not provided by the investigators. Calcium assessments were to be made twice at baseline and yearly thereafter. Subjects who were assessed to have a calcium intake of less than 500 mg per day were advised to increase their calcium intake either by diet or supplements to above this level.

Patients who had a baseline and at least one post-treatment lumbar spine BMD measurement (which were taken at 12 and 24 months) were included in the sponsor s intent-to-treat population (primary) analysis. The last observation carried forward (LOCF) procedure was utilized for patients who withdrew from the study.

The primary efficacy endpoint was the percent change in lumbar spine bone mineral density subsequent to two years of double-blind treatment.

STUDY 055 BMD RESULTS AND REVIEWER' S COMMENTS

A total of 1609 women were enrolled (435 stratum 1, 1174 stratum 2) across 2 U.S. and 2 European centers.

Patients randomized to estrogen/progestin therapy used Premarin (conjugated equine estrogens) and Provera (medroxyprogesterone acetate) in the United States and Trisequens (a product containing 17β-estradiol and norethisterone acetate) at the 2 European centers.

A total of 1303 patients (409 placebo, 407 alendronate 2.5 mg, 396 alendronate 5 mg, 91 estrogen/progestin) completed 24 months of double-blind treatment.

A total of 109 patients (27 placebo: 5.4%, 26 alendronate 2.5 mg: 5.2%, 41 alendronate 5 mg: 8.2%, 15 estrogen/progestin: 13.6%) withdrew due to clinical adverse experiences ($p<.01$ due to the higher estrogen/progestin adverse experience withdrawal rate). The most common reason for such a withdrawal was menopausal disorder (6 placebo: 1.2%, 10 alendronate 2.5mg: 2.0%, 9 alendronate 4mg: 1.8%, 5 estrogen/progestin: 4.5%).

Hematochezia (1 alendronate 2.5mg, 6 alendronate 5 mg), hematoma (1 alendronate 2.5 mg, 5 alendronate 5 mg), and intestinal polyps (4 alendronate 5 mg) were the only clinical adverse experiences which were reported by at least 1% of the patients in at least one of the treatment groups for which a statistically significant dose response (hematochezia: p=.005, hematoma:

p=.012, intestinal polyps: p=.014) was detected across the placebo, 2.5 mg, and 5 mg alendronate dosage groups.

The results of the sponsor's primary efficacy analyses in which alendronate 2.5 mg and alendronate 5 mg were compared to placebo with respect to the primary efficacy parameter are displayed in Table 3. In examining this table, one notes the existence of a treatment effect ($p<.001$) in favor of each alendronate dosage regimen over placebo with respect to the change in lumbar spine BMD over 24 months of treatment. In addition, a statistically significant ($p<.001$) positive trend was detected across the placebo, 2.5, and 5 mg alendronate doses. In fact, the alendronate 5 mg patients experienced a significantly greater ($p<.001$) percent increase in lumbar spine BMD than did their alendronate 2.5 mg counterparts.

The above mentioned favorable alendronate BMD results were consistent across center, age, race, and stratum (only 1 type of densitometer was used).

The lumbar spine mean percent changes over the 24-month treatment period are illustrated in Figure 3 which follows Table 3 in this review. In examining this graph, one notes that the alendronate treatment groups experienced most of their increases in lumbar spine BMD during the first year of treatment. In fact, the alendronate 2.5 and 5 mg treatment groups statistically outperformed the placebo group ($p<.001$) and the alendronate 5 mg treatment group statistically outperformed (Table 4) the alendronate 2.5 mg treatment group subsequent to 12 months of double-blind treatment.

Table 5 which displays percentages of patients who achieved designated lumbar spine BMD changes may be utilized by the clinicians as an aid in interpreting the level of BMD response. For example, in examining Table 5, one notes that 44.5% of the alendronate 5 mg (sponsor's recommended dose) patients compared to 3.5% of the placebo patients experienced at least a 4% increase in lumbar spine BMD. These results are displayed graphically in Figure 4 which follows Table 5 in this review.

The alendronate 5 mg versus placebo BMD results in this study are consistent with those of Study 029. This coupled with the enhanced treatment effect exhibited by alendronate 5 mg over, alendronate 2.5 mg may be used to support the sponsor's recommended dose of alendronate 5 mg administered once daily for the prevention of osteoporosis in postmenopausal women. However, one could utilize the results of this study to support a recommended dose of alendronate 2.5 mg since the objective of alendronate therapy is to maintain bone mass in the prevention patient population.

A secondary (as defined in the study protocol) hypothesis was that alendronate would prevent bone loss at the spine as well as or better than one or both forms of estrogen/progestin treatment. However, if one examines Tables 6 and 7 which display the results of the Stratum 1 alendronate-estrogen/progestin BMD comparisons, one notes that patients on estrogen/progestin statistically outperformed ($p<.001$) their alendronate 2.5 mg counterparts in the European and U.S. cohorts. Also, a statistically significant ($p<.01$) difference was detected in favor of estrogen/progestin over alendronate 5 mg in the European cohort and a strong statistical trend ($p=.055$) was detected in favor of estrogen/progestin over alendronate 5 mg in the U.S. cohort.

Consequently, based on these results, the sponsor's secondary hypothesis that alendronate would prevent bone loss at the spine as well as or better than one or both forms of estrogen/progestin treatment should be rejected.

STUDY 038

This double-blind, randomized, placebo-controlled multicenter (12 Italy, 1 U.K.) study was conducted to evaluate the safety and efficacy of alendronate in the prevention of osteoporosis in postmenopausal women.

Eligible patients were randomized to the following five treatment groups for 24 months of double-blind treatment.

	Treatment	
Group	Months 1-6	Months 7-24
A	Placebo	Placebo
B	Alendronate 5 mg	Placebo
C	Alendronate 5 mg	Alendronate 5 mg
D	Alendronate 10 mg	Placebo
E	Alendronate 10 mg	Alendronate 10 mg

Patients randomized to groups A, C, and E received placebo, alendronate 5 mg, and alendronate 10 mg respectively once daily for 24 months.

Patients randomized to group B (D) received alendronate 5 mg (10 mg) once daily for 6 months and placebo once daily for the remainder of the 24 month double-blind period.

All patients were instructed to take a daily dietary calcium supplement of 500 mg of elemental calcium.

Patients who had a baseline and at least one post-treatment lumbar spine BMD measurement were included in the sponsor's intent-to-treat (primary) analysis. The last observation carried forward (LOCF) procedure was utilized for patients who withdrew from the study. However, patients who were randomized to groups B and D did not have data carried forward from the active treatment phase to the placebo phase.

The primary efficacy endpoint was the percent change in lumbar spine bone mineral density over the 2-year treatment period. Subsequent to two years of double-blind treatment comparisons were made between Groups A, C, and E. In addition, the effect of cessation of alendronate treatment after six months was evaluated by comparing Groups B (D) and C (E).

STUDY 038 BMD RESULTS AND REVIEWER'S COMMENTS

A total of 291 caucasian women (56 placebo, 56 alendronate 5 mg, 61 alendronate 10 mg, 59 alendronate 5/0 mg, 59 alendronate 10/0 mg) entered the trial. Eighty-eight of these patients failed to compete the study. Twenty (4 placebo, 1 alendronate 5 mg, 5 alendronate 10 mg, 5 alendronate 5/0 mg, 5 alendronate 10/0 mg) of these patients withdrew due to clinical adverse experiences. The adverse experience profiles were similar across the treatment groups.

The results of the sponsor's efficacy analyses in which alendronate 5 mg and alendronate 10 mg were compared to placebo with respect to the primary efficacy parameter are displayed in Table 8. In examining this table, one notes the existence of a treatment effect ($p<.001$) in favor of each alendronate dosage regimen over placebo with respect to the change in lumbar spine BMD over

24 months of treatment. Furthermore, the alendronate 10 mg patients experienced a significantly greater (p=.01) percent increase in lumbar spine BMD than did their alendronate 5 mg counterparts.

These results were consistent across center, age, and type of densitometer (all women were caucasian).

The lumbar spine mean percent changes over the 24-month treatment period are illustrated in Figure 5 which follows Table 8 in the review. In examining this graph, one notes that the sponsor's recommended dosage (5 mg) group experienced most of their increase in lumbar spine BMD during the first 6 months of treatment.

The effect of cessation of alendronate treatment after 6 months is also apparent (Figure 5) as the lumbar spine BMD decreased for those patients who ceased alendronate therapy (Group B: alendronate 5/0 mg and Group D: alendronate 10/0 mg). In examining Table 9, one notes that these patients subsequent to stopping alendronate therapy were statistically outperformed by their alendronate 5 mg and alendronate 10 mg counterparts who did not cease alendronate therapy.

Consequently, the results of this study support those of Studies 029 and 055.

REVIEWER'S CONCLUDING COMMENTS (may be conveyed to the sponsor)

Studies 029, 038, and 055 taken together have demonstrated an alendronate treatment effect with regard to the prevention of lumbar spine BMD loss.

In examining Table 10, one notes that placebo patients experienced a significant decrease in lumbar spine BMD over a 2-3 year treatment period (see note 1, pg.18).

Each alendronate treatment group experienced a significantly ($p<.001$) more favorable BMD response than did the corresponding placebo group in each of the studies. Furthermore, each alendronate treatment group experienced a significant increase in BMD from baseline with the exception of the alendronate 1 mg dosage group in Study 029 (see note 2,pg.18).

Consequently, Studies 029, 038, and 055 demonstrated that the sponsor's recommended 5 mg dose of alendronate was successful not only in alleviating the bone loss experienced by placebo patients but in also significantly increasing BMD over a 2-3 year treatment period.

But the clinicians should assess the sponsor's recommendation of alendronate 5 mg given the positive BMD results experienced by patients who received alendronate 2.5 mg in Study 055.

It was demonstrated in Study 038 (Table 9) that cessation of alendronate therapy after 6 months resulted in a reversal of the treatment effect in that patients then experienced bone loss upon such cessation of therapy.

Also it was demonstrated (Tables 6 and 7) in Study 055 that alendronate 5 mg was not as effective as estrogen/progestin in increasing BMD.

Daniel N. Marticello
Mathematical Statistician

Concur: Dr. Nevius SEN 2/2/97

cc:
Archival NDA 20-560/SE1-003
HFD-510
HFD-510/SSobel,GTroendle,SDutta,RHedin
HFD-715/Division File, DMarticello, Chron

This review consists of 8 pages of text, 10 pages of tables, and 5 figures

TABLE 1

STUDY 029

LUMBAR SPINE BMD (g/cm^2)

INTENT-TO-TREAT 36 MONTH ANALYSIS

Treatment	*N*	*Baseline*	*Month 36*	*Mean Percent Change*
Placebo	82	.99	.95	-3.51
Alendronate 1 mg	88	.98	.97	-1.16*
Alendronate 5 mg	84	.96	.99	2.89*+
Alendronate 10 mg	84	.98	1.01	3.95*+a
Alendronate 20 mg#	78	.98	1.02	4.37*+a
				p<.001

Alendronate 20 mg patients received alendronate 20 mg for 2 years followed by placebo for 1 year.

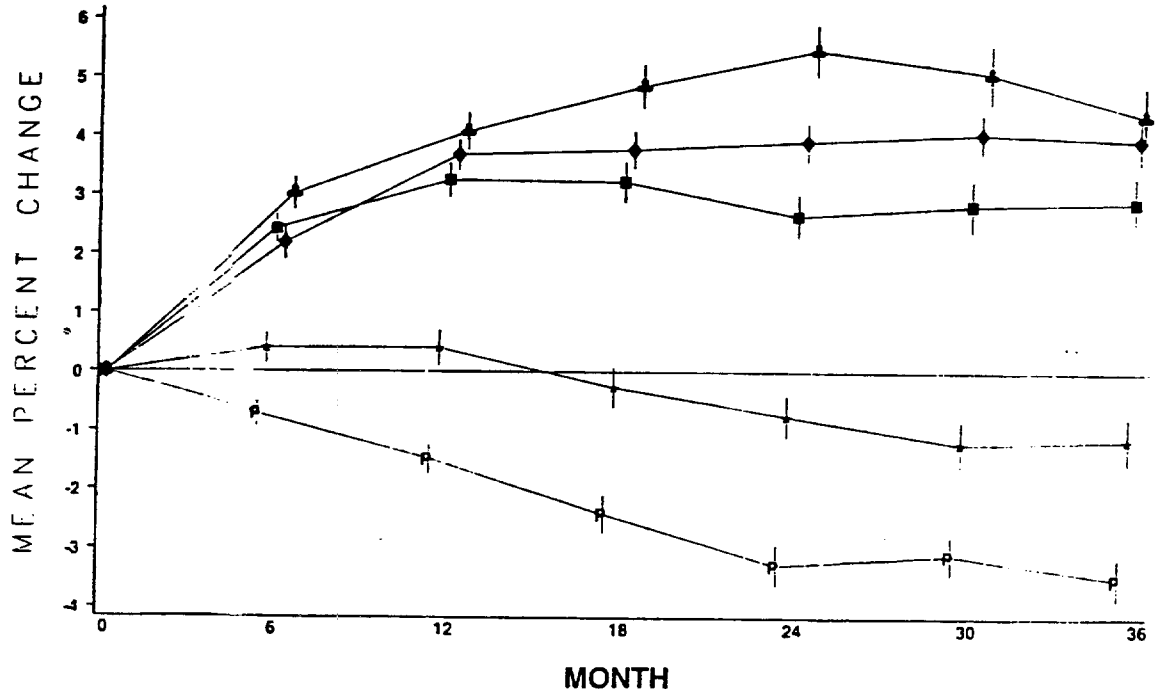
* p<.001 in favor of alendronate over placebo. Treatment-by-center interaction p=.26

+ p<.001 in favor of alendronate 5 mg, 10 mg, and 20 mg over alendronate 1 mg

a p<.05 in favor of alendronate 10 mg and 20 mg over alendronate 5 mg

Figure 1

Lumbar Spine BMD (g/cm^2)
Mean Percent Change ± SE of the Mean
(Intention-to-Treat Approach)



P=PLACEBO
★=1 MG
■=5 MG
◆=10 MG
✚=20/0 MG

TABLE 2

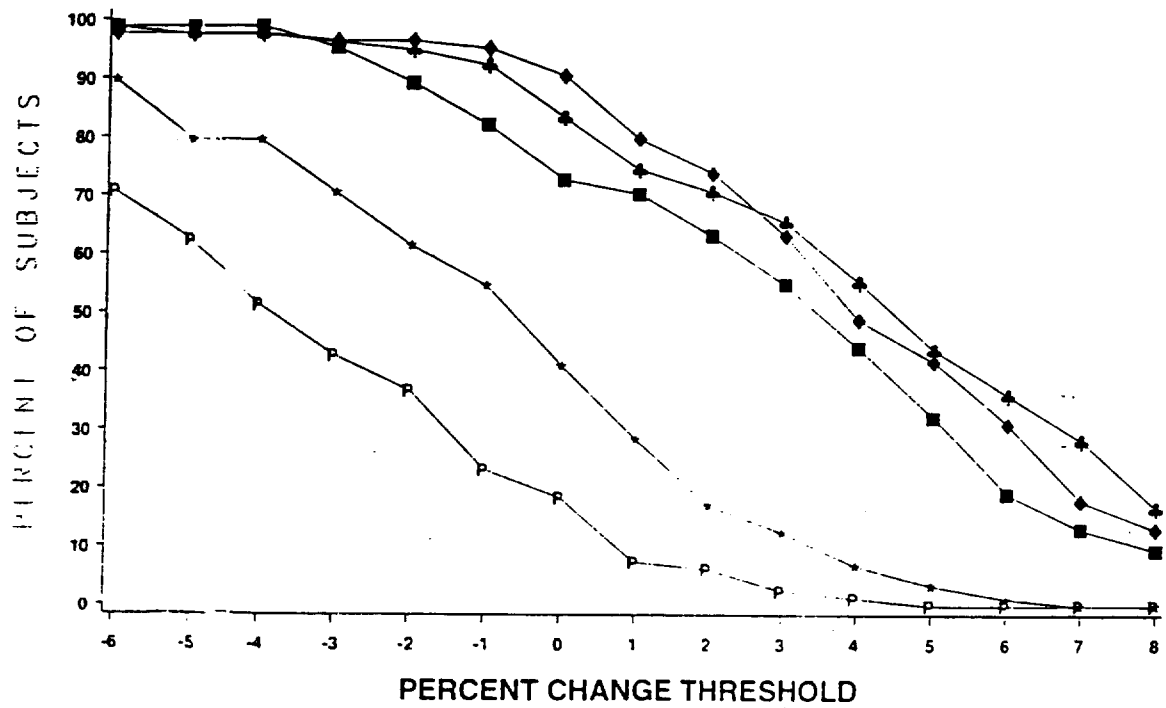
STUDY 029

PERCENT OF PATIENTS WITH 36 MONTH PERCENT CHANGE IN LUMBAR SPINE BMD EXCEEDING THRESHOLDS RANGING FROM -6% TO 8%

Threshold	*Placebo*	*1 mg*	*5 mg*	*10 mg*	*20 mg*
-6%	70.7%	89.8%	98.8%	97.6%	98.7%
-5%	62.2%	79.5%	98.8%	97.6%	97.4%
-4%	51.2%	79.5%	98.8%	97.6%	97.4%
-3%	42.7%	70.5%	95.2%	96.4%	96.2%
-2%	36.6%	61.4%	89.3%	96.4%	94.9%
-1%	23.2%	54.5%	82.1%	95.2%	92.3%
0%	18.3%	40.9%	72.6%	90.5%	83.3%
1%	7.3%	28.4%	70.2%	79.8%	74.4%
2%	6.1%	17.0%	63.1%	73.8%	70.5%
3%	2.4%	12.5%	54.8%	63.1%	65.4%
4%	1.2%	6.8%	44.0%	48.8%	55.1%
5%	0.0%	3.4%	32.1%	41.7%	43.6%
6%	0.0%	1.1%	19.0%	31.0%	35.9%
7%	0.0%	0.0%	13.1%	17.9%	28.2%
8%	0.0%	0.0%	9.5%	13.1%	16.7%

Figure 2

Percent of All Subjects With Change in Lumbar Spine BMD From Baseline at Month 36
Exceeding Thresholds Ranging From -6 to 8%
(Intention-to-Treat Approach)



P=PLACEBO
★=1 MG
■=5 MG
◆=10 MG
✚=20/0 MG

TABLE 3

STUDY 055

LUMBAR SPINE BMD (g/cm^2)

INTENT-TO-TREAT 24 MONTH ANALYSIS

Treatment	*N*	*Baseline*	*Month 24*	*Mean Percent Change*
Placebo	461	.94	.93	-1.78
Alendronate 2.5 mg	452	.93	.95	2.28*
Alendronate 5 mg	445	.95	.98	3.46*#
				p<.001

* p<.001 in favor of alendronate over placebo. Treatment-by-center interaction p=.53

\# p<.001 in favor of alendronate 5 mg over alendronate 2.5 mg

3. **Efficacy** (Cont.)

Figure 3

Lumbar Spine BMD
Percent Change From Baseline at Month 24 (Mean ± SE)
(Intention-to-Treat Approach)
Strata 1 and 2 Combined

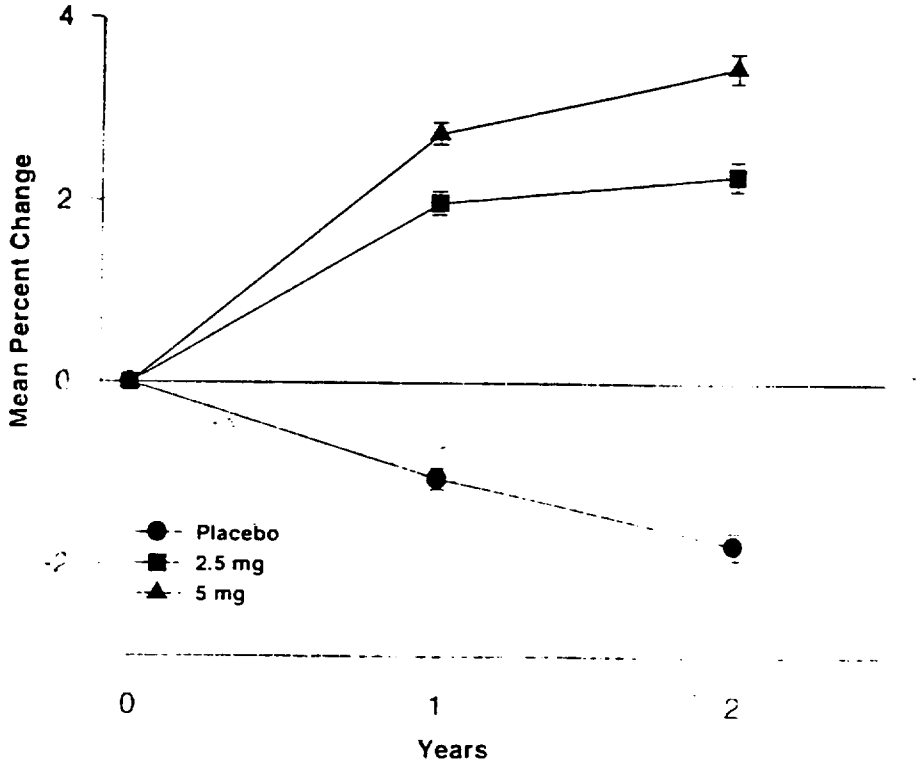


TABLE 4

STUDY 055

LUMBAR SPINE BMD (g/cm^2)

INTENT-TO-TREAT 12 MONTH ANALYSIS

Treatment	*N*	*Baseline*	*Month 12*	*Mean Percent Change*
Placebo	461	.94	.93	-1.05
Alendronate 2.5 mg	452	.93	.95	1.92*
Alendronate 5 mg	445	.95	.98	2.74*#
				p<.001

* p<.001 in favor of alendronate over placebo. Treatment-by-center interaction p=.58

# p<.001 in favor of alendronate 5 mg over alendronate 2.5 mg

TABLE 5

STUDY 055

PERCENT OF PATIENTS WITH 24 MONTH PERCENT CHANGE IN LUMBAR SPINE BMD EXCEEDING THRESHOLDS RANGING FROM -6% TO 8%

Threshold	*Placebo*	*Alendronate 2.5 mg*	*Alendronate 5.0 mg*
-6%	91.3%	99.1%	99.3%
-4%	76.8%	96.0%	97.5%
-2%	53.8%	90.5%	94.6%
0%	29.5%	75.9%	86.1%
2%	10.4%	53.1%	67.6%
4%	3.5%	31.4%	44.5%
6%	1.3%	12.4%	23.4%
8%	0.2%	5.1%	9.9%

3. Efficacy (Cont.)

Figure 4

Lumbar Spine BMD at Month 24 Exceeding Thresholds
(Intention-to-Treat Approach)
Strata 1 and 2 Combined

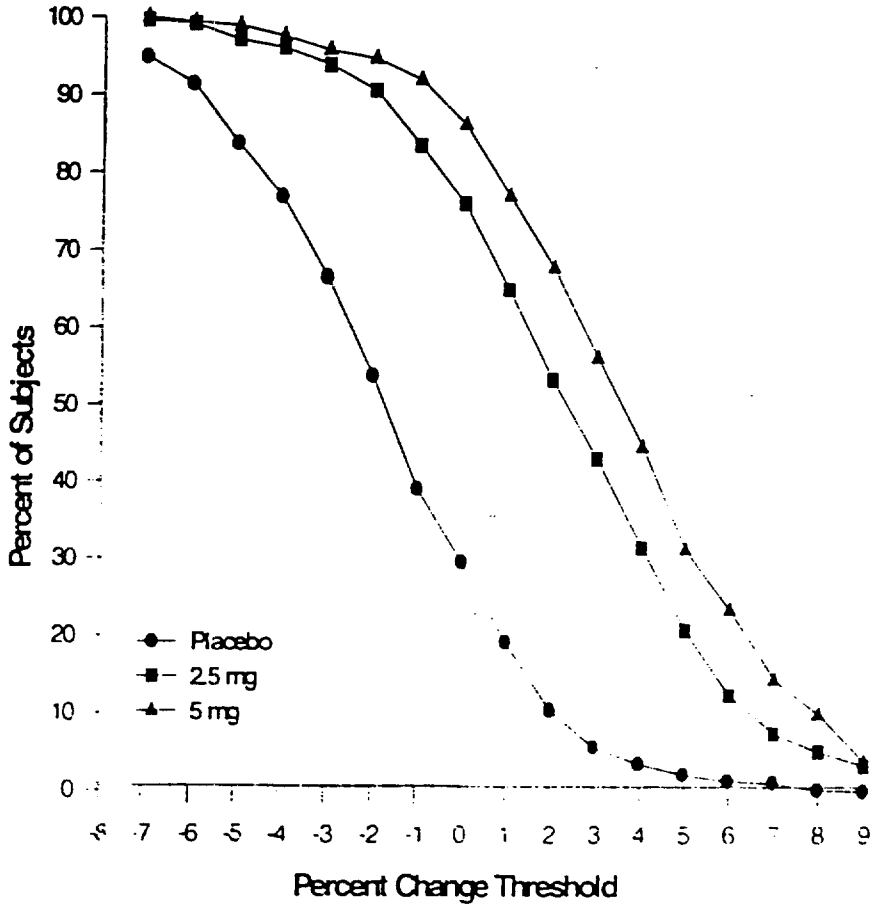


TABLE 6

STUDY 055

LUMBAR SPINE BMD (g/cm^2)

INTENT-TO-TREAT 24 MONTH ANALYSIS

STRATUM 1: EUROPEAN COHORT

Treatment	*N*	*Baseline*	*Month 24*	*Mean Percent Change*
Placebo	50	.94	.92	-2.06
Alendronate 2.5 mg	50	.93	.95	1.98*
Alendronate 5 mg	46	.91	.94	3.34*a
Estrogen/Progestin[b]	49	.93	.98	5.14*+#
				p<.001

* p<.001 in favor of active treatment over placebo

\+ p<.001 in favor of estrogen/progestin over alendronate 2.5 mg

\# p<.01 in favor of estrogen/progestin over alendronate 5 mg

a p<.05 in favor of alendronate 5 mg over alendronate 2.5 mg

b Trisequens

TABLE 7

STUDY 055

LUMBAR SPINE BMD (g/cm^2)

INTENT-TO-TREAT 24 MONTH ANALYSIS

STRATUM 2: U.S. COHORT

Treatment	*N*	*Baseline*	*Month 24*	*Mean Percent Change*
Placebo	51	.96	.94	-1.68
Alendronate 2.5 mg	44	.97	.98	1.85*
Alendronate 5 mg	47	.94	.97	2.85*
Estrogen/Progestin[b]	53	.93	.96	4.04*+#
				p<.001

* p<.001 in favor of active treatment over placebo

\+ p<.001 in favor of estrogen/progestin over alendronate 2.5 mg

\# p=.055 in favor of estrogen/progestin over alendronate 5 mg

b Premarin and Provera

TABLE 8

STUDY 038

LUMBAR SPINE BMD (g/cm^2)

INTENT-TO-TREAT 24 MONTH ANALYSIS+

Treatment	*N*	*Baseline*	*Month 24*	*Mean Percent Change*
Placebo	44	.94	.93	-1.47
Alendronate 2.5 mg	47	.97	.99	2.00*
Alendronate 5 mg	52	.97	1.01	4.40*#
				p<.001

* p<.001 in favor of alendronate over placebo. Treatment-by-center interaction p=.17

\# p=.01 in favor of alendronate 10 mg over alendronate 5 mg

\+ Analysis only includes treatment groups which received the same treatment for 24 months

3. Efficacy (Cont.)

Figure 5

Lumbar Spine BMD
Mean Percent Change From Baseline ± SE of the Mean
(Intention-to-Treat Approach)

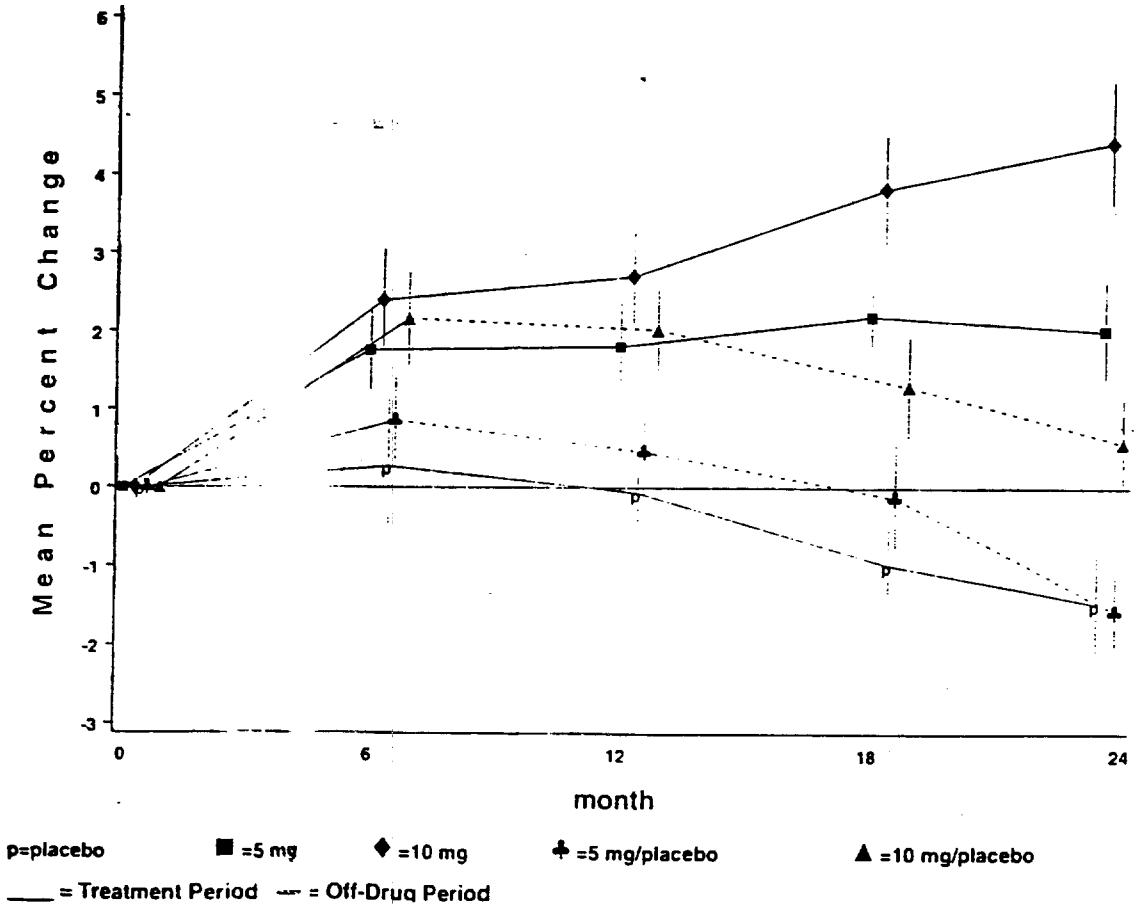


TABLE 9

STUDY 038

LUMBAR SPINE BMD (g/cm^2)

INTENT-TO-TREAT 6-24 MONTH ANALYSIS+

Treatment	*N*	*Baseline*	*Month 24*	*Mean Percent Change*
Placebo	38	.95	.94	-1.58
Alendronate 5 mg	48	.99	.99	.39*
Alendronate 10 mg	49	1.00	1.01	1.91**
Alendronate 5/0 mg	43	.96	.94	-2.22#
Alendronate 10/0 mg	48	.99	.97	-1.88##

* p=.014 in favor of alendronate 5 mg over placebo

** p<.001 in favor of alendronate 10 mg over placebo

\# p=.001 in favor of alendronate 5 mg over alendronate 5/0 mg

p<.001 in favor of alendronate 10 mg over alendronate 10/0 mg

\+ Primary comparisons were alendronate 5 mg versus alendronate 5/0 mg and alendronate 0 mg versus alendronate 10/0 mg in order to evaluate the effect of cessation of alendronate treatment after 6 months

TABLE 10

LUMBAR SPINE BMD (g/cm^2)

INTENT-TO TREAT 24 MONTH ANALYSIS

STUDIES 029, 038, 055

	Study 029		*Study 038*		*Study 055*	
	N	*Mean Percent Change*[+]	*N*	*Mean Percent Change*[+]	*N*	*Mean Percent Change*[+]
Placebo	82	-3.28 (-3.51)[++]	44	-1.47	461	-1.78
Alendronate 1 mg	88	- .76 (-1.16)[++]				
Alendronate 2.5 mg					452	2.28
Alendronate 5 mg	84	2.65 (2.89)[++]	47	2.00	445	3.46
Alendronate 10 mg	84	3.91 (3.95)[++]	52	4.40		
Alendronate 20 mg	78	5.46 (4.37)[++]				

\+ Mean percent change from baseline

++ 36 month percent change in parenthesis. Alendronate 20 mg patients received placebo in third year.

Notes:

1. Placebo patients experience a significant decrease ($p<.001$ in Studies 029 and 055, $p<.01$ in Study 038) in BMD from baseline.

2. Alendronate patients experienced a significant increase (decrease for alendronate 1 mg in Study 029) from baseline in BMD. P-values were <.001 in each case except for alendronate 5 mg in Study 038 where $p<.01$.

3. $p<.001$ in favor of each alendronate treatment group over placebo in each study.

4. Alendronate 10 mg patients experienced significantly (Study 029: $p=.05$, Study 038: $p=.01$) greater increases in BMD than did alendronate 5 mg patients.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-560/S03/S06

ADMINISTRATIVE DOCUMENTS

NDA 20-560 FOSAMAX®
Alendronate sodium
Patent Information Item 13

Pursuant to the provisions of Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act [21 USC 335 (b)(1)] attached hereto please find the patent information for the above-identified application.

The undersigned declares that U.S. Patent Nos. 4,621,077 and 5,358,941 cover the formulation, composition and/or method of use of FOSAMAX® (alendronate sodium tablet), the subject of this application for which approval is being sought.

U.S. Patent No. 4,621,077, having an expiration date of November 4, 2003, claims the use of FOSAMAX® for inhibiting bone resorption. Patent Term Restoration of U.S. Patent 4,621,077 has been applied for pursuant to 35 U.S.C. § 156. When granted, the expiration date will be August 4, 2007. This patent is owned by Istituto Gentili S.p.A., Pisa, Italy.

The undersigned declares that U.S. Patent No. 4,621,077 covers the method of using of FOSAMAX®. The subject of this application for which approval is being sought is covered by this patent.

U.S. Patent No. 5,358,941, having an expiration date of December 2, 2012, claims a formulation of FOSAMAX®. It is owned by Merck & Co., Inc., Rahway, NJ.

The undersigned declares that U.S. Patent 5,358,941 claims a formulation of FOSAMAX®. This product is the subject of this application for which approval is being sought.

A claim of patent infringement could be asserted if a person not licensed by the owner of either of U.S. Patent Nos. 4,621,077 or 5,358,941 engaged in the manufacture, use or sale of FOSAMAX® for the prevention of osteoporosis.

Joanne M. Giesser
Senior Patent Attorney

Attachment

NDA 20-560 FOSAMAX®
Alendronate sodium
Patent Information Item 13

PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

1. Active Ingredient	Alendronate sodium
2. Dosage	5 mg
3. Trade Name	FOSAMAX®
4. Dosage Form Route of Administration	Tablet Oral
5. Applicant Firm Name	Merck Research Laboratories
6. NDA Number	20-560
7. Approval Date	
8. Exclusivity- Date First ANDA Could Be Submitted	Three (3) Years from this NDA approval date or Five (5) Years from September 29, 1995 (September 29, 2000)
9. Applicable Patent Numbers	US Patent 4,621,077 Expires November 4, 2003* US Patent 5,358,941 Expires December 2, 2012

*Patent Term Restoration of U.S. Patent 4,621,077 has been applied for pursuant to 35 U.S.C. § 156. When granted, the expiration date will be August 4, 2007.

EXCLUSIVITY SUMMARY for NDA # 20-560 SUPPL # 003

Trade Name Fosamax Generic Name Alendronate

Applicant Name Merck HFD- 510

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA?

YES /__/ NO /✓/

b) Is it an effectiveness supplement?

YES /✓/ NO /__/

If yes, what type? (SE1, SE2, etc.) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO /__/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

~~If yes, NDA #~~ _____ ~~Drug Name~~ _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /✓/ NO /___/

If "yes," identify ~~the approved~~ drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-560 _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_✓_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

   YES /_✓_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /✓/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 029

Investigation #2, Study # 038

Investigation #3, Study # 054

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /✓/
Investigation #3	YES /___/	NO /✓/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /✓/
Investigation #3	YES /___/	NO /✓/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES /✓/ NO /___/ Explain: _____

Investigation #2

IND # YES /✓/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____

_____

_____

NO /___/ Explain _____

_____

_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

_____

_____

Signature
Title: CSO

4/6/97
Date

Signature of Division Director

4/25/97
Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-560/S-003 Trade (generic) names Fosamax (alendronate sodium)

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Signature of Preparer

4/9/97
Date

cc: Orig NDA
HFD-___/Div File
NDA Action Package

Meeting Date: March 27, 1997 Time: 11:00 - 12:20 am Location: 14-56

NDA 20-560/S-003 & S-006 Fosamax (alendronate sodium) Tablets

Type of Meeting: General

External participant: None

Meeting Chair: Dr. Troendle

External participant lead: None

Meeting Recorder: Mr. Randy Hedin

DRAFT

FDA Attendees and titles:

Dr. Solomon Sobel, Division Director, DMEDP
Dr. Gloria Troendle, Deputy Division Director, DMEDP
Dr. Sam Dutta, Medical Reviewer, DMEDP
Dr. Leo Lutwak, Medical Reviewer, DMEDP
Dr. James Bilstad, Office Director, ODEII
Mr. Dan Marticello, Team Leader, Division of Biostatistics
Mr. Randy Hedin, CSO, DMEDP

External participant Attendees and titles:

None

Meeting Objectives:

This meeting was held to discuss the labeling for Supplements 003 and 006.

Discussion Points:

- See attached draft labeling.

Decisions (agreements) reached:

- See attached draft labeling.

Unresolved or issues requiring further discussion:

- None

Action Items:

- Schedule a labeling meeting with the sponsor.

Signature, minutes preparer:_____

Concurrence Chair:_____

cc: NDA Arch
HFD-510
Attendees
HFD-510/EGalliers
HFD-511/RHedin/3.19.97/N20560.M15

Concurrences:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-560/S03/S06

CORRESPONDENCE

Edwin L. Hemwall, Ph.D.
Senior Director
Regulatory Affairs

NDA No. 20560 003
NDA SUP ..... SE1- .....

ORIGINAL

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486-0004
Fax 610 397 2516
Tel 610 397 2306
215 652 5000

April 29, 1996

MERCK
Research Laboratories

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products
HFD-510, Room 14B-04
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

CENTER FOR DRUG
REC'D
APR 30 1996
HFD-510
EVALUATION AND RESEARCH

FOSAMAX™ (Alendronate Sodium Tablets)

NDA 20-560: Supplemental New Drug Application

Dear Dr. Sobel:

Pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act and in accordance with Title 21 of the Code of Federal Regulations, we are submitting a Supplemental New Drug Application for FOSAMAX™ (alendronate sodium tablets).

This submission supplements the previously approved application for use of FOSAMAX™ for treatment of postmenopausal osteoporosis and Paget's disease of bone, and provides clinical efficacy and safety documentation supporting the use of FOSAMAX™ for the prevention of osteoporosis in postmenopausal women. Additionally, chemistry, manufacturing and controls data are provided for a 5 mg tablet. The contents of this submission were previously discussed with the agency at a meeting on March 9, 1995. The Data Analysis Plans for the three primary clinical studies were submitted to the agency on October 13, 1995.

This application is formatted as required in Title 21, paragraph 314.50 of the Code of Federal Regulations. It consists of a complete "archival" copy (Blue Binders), comprising 37 volumes and 5 "review" copies as described in the Statement of Organization which is attached to this letter.

In accordance with the Prescription Drug User Fee Act of 1992, a check (Check

Pursuant to 21 CFR 314.50(h)(3), a complete field copy of the Chemistry, Manufacturing and Controls technical section (Item 3) has been submitted to the FDA Pittsburgh District Office. This field copy is a true copy of Item 3 as contained in the archival copy and review copies of this application.

Merck affirms that all sites listed in this application to support the manufacturing, packaging and labeling of FOSAMAX™ for the market are available for pre-approval inspection at the time of this submission.

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc. did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

MRL would like to meet with the FDA approximately 90 days following receipt of this application. The purpose of this meeting will be to discuss the general progress and status of the review of this application and to determine if there are any important deficiencies identified at that time. MRL will contact the FDA to arrange for this meeting.

We consider the filing of this Supplemental New Drug Application to be a confidential matter and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining written permission from Merck & Co., Inc.

Questions concerning this application should be directed to Edwin L. Hemwall, Ph.D. (610/397-2306) or, in my absence, Bonnie J. Goldmann, M.D. (610/397-2383).

REVIEWS COMPLETED

CSO ACTION

☐ LETTER ☐ MEMO

CSO INITIALS DATE

Sincerely yours,

Edwin L. Hemwall

Edwin L. Hemwall, Ph.D.
Senior Director
Regulatory Affairs

Attachment
Federal Express #1
Desk Copy (Letter and Patent Information only):
Mr. George Scott, HFD-84, Room 8B-37

Federal Express #2

Desk Copy (Letter only):
Philadelphia District Office, Food and Drug Administration Room 900
U.S. Custom House, 2nd & Chestnut Streets, Philadelphia, PA

Federal Express #3

q/bafallen/bf/mk217/fda0148.doc

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 20-560/S-003 & S-006

Food and Drug Administration
Rockville MD 20857

Merck Research Laboratories
Attention: Michelle W. Kloss, Ph.D.
Director, Regulatory Affairs
P.O. Box 4
West Point, PA 19486-0004

MAR 18 1997

Dear Dr. Kloss:

Please refer to your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosamax (aldendronate sodium) 10 and 40 mg Tablets.

Reference is also made to your letters of October 29 and November 13, 1996, requesting a waiver of the requirements for the submission of paper case report forms and/or case report tabulations in conjunction with supplements 003 and 006 for Fosamax Tablets.

You have represented in your letters that the electronic case report forms and case report tabulations have been prepared in a manner that is substantially consistent with the FDA's proposed rules regarding electronic signatures and electronic records, proposed 21 CFR Part 11 [59 FR 45160 (August 31, 1994)].

Therefore, we have concluded that, under 21 CFR 314.90(b)(2), your alternative electronic submissions justify a waiver of the "hard copy" requirements of 21 CFR 314.50(f). Consequently, your waiver requests are granted.

Should future retrieval be deemed necessary, and as a condition of granting this waiver, you are required to maintain paper copies of the case report forms and tabulations as required under 21 CFR 312.57(b).

If you have any questions, please contact Randy Hedin, R.Ph., Consumer Safety Officer, at (301) 443-3520.

Sincerely yours,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

DESK COPY

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486-0004
Fax 610 397 2516
Tel 610 397 2905
215 652 5000

April 14, 1997

MERCK
Research Laboratories

Solomon Sobel, M.D., Director
Division of Metabolism & Endocrine Drug Products
HFD-510, Room 14B-04
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 20-560/S-003 and S-006: FOSAMAX™
(Alendronate Sodium Tablets)

AMENDMENT TO PENDING APPLICATIONS

Dear Dr. Sobel:

Reference is made to the pending supplemental new drug applications for FOSAMAX cited above and to correspondence from FDA to Merck Research Laboratories (MRL) dated March 31, 1997 which contained the Agency's revisions to the draft labeling for these supplements. Additional reference is made to a teleconference on April 9, 1997 between MRL and FDA during which this draft labeling was discussed.

With this submission, we are providing a revised draft package circular that incorporates the revisions discussed and agreed upon at the aforementioned MRL/FDA teleconference and a draft patient package insert (PPI) that has been revised to be consistent with the changes in the package circular.

Attached are the following for the draft package circular and the draft patient package insert:

1. Summary of revisions
2. Hard copy mock-up illustrating revisions (3 column format)
3. Clean-running text
4. Hard copy of Word Perfect 6.1 version of running text illustrating revisions
5. Diskette containing the Word Perfect 6.1 version of running text illustrating revisions of both the package circular and the PPI

The draft package circular is formatted with three columns: the left column contains the revisions accepted by FDA and MRL at the April 9, 1997 teleconference; the middle column contains MRL proposed wording to address items conceptually agreed to by FDA and MRL at the teleconference; the right column provides MRL rationale/comments concerning the middle

column proposed wording. The attached PPI is also formatted with three columns: the left column contains the text previously submitted on March 20, 1997; the middle column contains MRL proposed revisions based on the package circular revisions agreed to by FDA and MRL at the April 9, 1997 teleconference; the right column provides MRL rationale/comments concerning the changes in the middle column.

In these documents, there are two items containing new text that we would like to summarize briefly as follows:

The first item involves the Agency's revision to the package circular regarding the use of caution in patients receiving concomitant FOSAMAX and NSAID therapy. As discussed and tentatively agreed to at the 4/9/97 teleconference, MRL has placed this cautionary statement under PRECAUTIONS, *Drug Interactions, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)*, rather than under WARNINGS, and has included reference to data obtained in a controlled clinical trial in patients on FOSAMAX who also received NSAIDs during the course of the study.

The second item involves changes made to the PPI in response to the Agency's request that distinction be made between FOSAMAX and estrogen regarding prevention and treatment of postmenopausal osteoporosis. MRL has proposed a revision to the PPI under the heading **"How can osteoporosis in postmenopausal women be treated or prevented?"** in response to this concern. This proposed revision includes text explaining that 1) the action of FOSAMAX is specific to bone, 2) either FOSAMAX or estrogen can be used in the treatment and prevention of postmenopausal osteoporosis, 3) FOSAMAX, unlike estrogen, does not have other non-bone effects. This proposed revision also provides text suggesting that the patient discuss these options with her physician.

We are looking forward to reaching a mutual consensus on any outstanding items relating to this labeling as soon as possible. Please direct any questions or need for additional information to Michelle W. Kloss, Ph.D. at (610) 397-2905 or, in my absence, Edwin L. Hemwall, Ph.D. at (610) 397-2306.

Sincerely,

Edwin L. Hemwall

for Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

Hand-Delivered

(15) Desk Copies: Mr. Randy Hedin, HFD-510, Room 14B-19 (Hand-Delivered)
(1) Desk copy: Dr. Samarendra Dutta, HFD-510, Room 14B-19 (Hand-Delivered)

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Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

Merck & Co., Inc.
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DESK COPY

April 10, 1997

MERCK
Research Laboratories

Solomon Sobel, M.D., Director
Division of Metabolism & Endocrine Drug Products
HFD-510, Room 14B-04
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 20-560/S-003: FOSAMAX
(Alendronate Sodium)

Response to Request for Information

Dear Dr. Sobel:

Reference is made to the supplemental application cited above and to a telephone conversation on April 9, 1997 between Mr. Randy Hedin (FDA) and Dr. Michelle Kloss (MRL) in which Mr. Hedin requested an additional copy of Volume 8 (Clinical Documentation) from the above supplemental application.

With this submission, we are providing the requested information.

Please direct questions or need for additional information to Michelle W. Kloss, Ph.D. (610/397-2905) or, in my absence, Edwin L. Hemwall, Ph.D. (610/397-2306).

Sincerely,

Michelle W. Kloss

Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

Q:sar\ltr\covltr
Federal Express #1

(1) Desk copy w/att.: Mr. Randy Hedin, CSO, HFD 510, Room 14B-19, Federal Express #2

NDA SUPPL AMENDMENT

These copies are
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not desk copies.

ORIGINAL

Michelle W. Kloss, Ph.D
Director
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March 20, 1997

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Rockville, Maryland 20857

MERCK
Research Laboratories

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HFD-510
EVALUATION AND RESEARCH

NDA 20-560 / S-003 and S-006: FOSAMAX™
(Alendronate Sodium Tablets)

Amendment to a Pending Supplemental Application

Dear Dr. Sobel:

Reference is made to the pending supplemental applications cited above and to a telephone conversation between Mr. Randy Hedin (FDA) and Dr. Edwin Hemwall (Merck) on March 19, 1997 in which Mr. Hedin requested a revised version of the proposed labeling for these applications.

Attached are the running text with revision marks for the draft Package Circular and Patient Package Insert for supplements S-003/S-006. These versions include the text of the Changes Being Effected supplements of October 24, 1996 (S-008; to enhance the safe use of FOSAMAX) and November 12, 1996 (S-009; update regarding potential for gastric and duodenal adverse events). Also provided is a diskette with the draft labeling in WordPerfect for Windows 6.1.

Please direct questions or need for additional information to Michelle W. Kloss, Ph.D. (610/397-2905) or, in my absence, Edwin L. Hemwall, Ph.D. (610/397-2306).

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS DATE

Sincerely,

for Michelle W. Kloss, Ph.D.
Director, Regulatory Affairs

Q:CAT\AS\20560\319

Attachment

Federal Express - Document Control Room

cc: Mr. Randy Hedin (12 copies/1 copy w/diskette), HFD-510, Room 14B-04 - Hand Deliver
Federal Express to Merck Rockville Office - Hand Deliver to Mr. Hedin

Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

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DESK COPY

February 28, 1997

MERCK
Research Laboratories

Solomon Sobel, M D., Director
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5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-560/S-003: FOSAMAX™
(Alendronate Sodium Tablets)

Amendment to a Pending Supplemental Application

Dear Dr. Sobel:

Reference is made to the pending supplemental application cited above which was submitted on April 29, 1996 and to a January 22, 1997 meeting between Merck Research Laboratories and FDA representatives. In this meeting, the Agency suggested that the INDICATIONS AND USAGE section of the FOSAMAX™ draft package circular (originally submitted with S-003 and amended on November 12, 1996) be revised to include bone mass in the list of risk factors to be considered when evaluating patients who are candidates for prevention therapy. Reference is also made to a letter submitted on February 11, 1997 which provided advance notification of a proposed revision to the INDICATIONS AND USAGE section to include the term "moderately low bone mass" into the list of risk factors, along with a commitment to provide a full amendment for the proposed revision. With this submission we are providing this full amendment.

This submission supersedes all previous labeling amendments to S-003. The version contained in this amendment should be used as the basis for all future labeling discussions for S-003.

Please note that the "Changes Being Effected" supplements submitted to NDA 20-560 on October 24, 1996 (S-008) and November 12, 1996 (S-009) containing revisions to enhance the safe use of FOSAMAX™ are not included in this amendment, but will be incorporated into the final printed package circular.

Attached for submission are the following:

- A summary of revisions for package circular 7957002.
- A mock-up package circular 7957002 showing revisions.
- A running text copy of package circular 7957002.
- A copy of the Patient Package Insert
- A diskette containing the above circular revisions and Patient Package Insert (not provided previously) to facilitate review.

An amendment incorporating identical labeling revisions to NDA 20-560/S-006 is also being submitted to facilitate the ongoing simultaneous review of both supplemental applications.

Please direct any questions or need for additional information to Michelle W. Kloss, Ph.D. (610/397-2905) or, in my absence, to Edwin L. Hemwall, Ph.D. (610/397-2306).

Sincerely,

Michelle W. Kloss

Michelle W. Kloss, Ph.D.
Director, Regulatory Affairs

Q:BLANKEM\LETTERS\FSMXLTR3

Attachment

Federal Express

Desk Copies w/att:
Mr. Randy Hedin, HFD-510, Rm 14B04
Dr. Samarendra Dutta, HFD-510, Rm 14B19

Michelle W. Kloss, Ph.D.
Director
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12/27/97

MERCK
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Rockville, Maryland 20857

NDA 20-560 / S-003: FOSAMAX
(Alendronate Sodium Tablets)

Amendment to a Pending Supplemental Application

Dear Dr. Sobel:

Reference is made to the pending supplemental NDA cited above and to an amendment to this supplemental NDA submitted on November 12, 1996. We recently discovered that this amendment contained an inadvertent error and, and as such, we are herewith providing a corrected version of the entire amendment. Please replace the November 12, 1996 amendment with the amendment provided herein.

With this submission, we are providing an amendment to the above supplemental NDA that incorporates revisions to the INDICATIONS AND USAGE section to define the patient population for the prevention of osteoporosis. In addition, all of the proposed changes supported by the S-006 (FIT) supplement have been incorporated into the S-003 draft. An amendment incorporating labeling revisions to NDA 20-560/S-006 was submitted on November 12, 1996 such that the resulting draft package circulars for both S-003 and S-006 are now identical. This will facilitate the ongoing simultaneous review of both applications.

Attached for submission are the following:

1. A summary of revisions.
2. A running text of the draft amended package circular.
3. A side-by-side comparison of original S-006 versus this newly amended draft package circulars.
4. A diskette containing the newly amended draft labeling in WORDPERFECT version 6.1.

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We regret any inconvenience that this inadvertent error may have caused the Agency. Questions concerning this submission should be addressed to Michelle W. Kloss, Ph.D. (610/397-2905) or, in my absence, Edwin L. Hemwall, Ph.D. (610/397-2306).

Sincerely,

Edwin L Hemwall

for Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

Attachment

Federal Express

Desk copy w/diskettes: Mr. Randy Hedin, CSO, HFD-510, Room 14B-19

Desk copy w/o diskettes: Dr. Samarendra Dutta, HFD-510, Room 14B-19

Dr. Gloria Troendle, HFD-510, Room 14B-04

q/bafallen/mk217/corr1112

Michelle [illegible], M.D.
Director
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November 12, 1996

DESK COPY

Solomon Sobel, M D., Director
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Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

MERCK
Research Laboratories

NDA 20-560/S-003: FOSAMAX™
(Alendronate Sodium Tablets)

Amendment to a Pending Supplemental Application

Dear Dr. Sobel:

Reference is made to the pending supplemental NDA cited above which was submitted on April 29, 1996 and our pending September 23, 1996 supplement S-006 which supports an expansion of the indication to include the prevention of fractures in the treatment of postmenopausal osteoporosis. Further reference is made to a September 4, 1996 meeting between Merck Research Laboratories and FDA in which the Agency requested that the INDICATIONS AND USAGE section of the FOSAMAX™ draft package circular originally submitted with the S-003 be revised to better define the patient population for the prevention of osteoporosis.

With this submission, we are providing an amendment to the supplemental NDA that incorporates revisions to the INDICATIONS AND USAGE section to define the patient population for the prevention of osteoporosis. In addition, all of the proposed changes supported by the S-006 (FIT) supplement have been incorporated into the S-003 draft. An amendment incorporating labeling revisions to NDA 20-560/S-006 is being submitted simultaneously such that the resulting draft package circulars for both S-003 and S-006 are now identical. This will facilitate the ongoing simultaneous review of both applications.

Attached for submission are the following:

1. A summary of revisions
2. A running text of the draft amended package circular
3. A side-by-side comparison of original S-003 version versus this newly amended draft package circulars
4. A diskette containing the newly amended draft labeling in WORDPERFECT version 6.1.

Questions concerning this submission should be addressed to Michelle W. Kloss, Ph.D. (610/397-2905) or, in my absence, Edwin L. Hemwall, Ph.D. (610/397-2306).

Sincerely,

Michelle W. Kloss

Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

Attachment

Federal Express#1

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Federal Express #2

Desk copy w/o diskette : Dr. Samarendra Dutta, HFD-510, Room 14B-19
Federal Express #3

Dr. Gloria Troendle, HFD-510, Room 14B-04
Federal Express #4

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Michelle W. Kloss, Ph.D.
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April 21, 1997

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NDA 20-560/S-003 and S-006: FOSAMAX™
(Alendronate Sodium Tablets)

AMENDMENT TO PENDING APPLICATIONS

Dear Dr. Sobel:

Reference is made to the pending supplemental new drug applications for FOSAMAX cited above and to correspondence from FDA to Merck Research Laboratories (MRL) dated March 31, 1997 which contained the Agency's revisions to the draft labeling for these supplements. Additional reference is made to a teleconference on April 9, 1997 between MRL and FDA during which this draft labeling was discussed and to an amendment submitted on April 14, 1997 which contained labeling revisions as discussed at this teleconference. Further reference is made to FDA's facsimile communication dated April 18, 1997 which provided additional revisions to this draft labeling.

We have accepted all of the Agency revisions in the draft package circular and Patient Package Insert (PPI) noted in the April 18, 1997 communication cited above. We believe that the draft package circular and PPI included in this submission represent final agreement on labeling between FDA and MRL.

Attached are the following for both the draft package circular and the draft patient package insert:

1. Hard copy of Word Perfect 6.1 version of clean running text
2. Diskette containing the Word Perfect 6.1 version of clean running text of both the package circular and the PPI

Please direct any questions or need for additional information to Michelle W. Kloss, Ph.D. at (610) 397-2905 or, in my absence, Edwin L. Hemwall, Ph.D. at (610) 397-2306.

Sincerely,

Michelle W. Kloss

Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

Hand-Delivered

(3) Desk Copies: Mr. Randy Hedin, HFD-510, Room 14B-19 (Hand-Delivered)
(1) Desk copy: Dr. Samarendra Dutta, HFD-510, Room 14B-19 (Hand-Delivered)

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