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NDA 20560

FOSAMAX

1 OF 7

NDA 20560

FORNRY

NDA 20-560

SEP 29 1995

Merck Research Laboratories
Attention: Edwin L. Hemwall, Ph.D.
Director, Regulatory Affairs
BLA-30
West Point, PA 19486

Dear Dr. Hemwall:

Please refer to your March 31, 1995, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosamax (alendronate sodium tablets) 10 and 40 mg Tablets.

We acknowledge receipt of your presubmission dated December 29, 1994, amended March 2, 1995, and your correspondence dated April 7 and 19, May 1, 5, 8, 11, 15, 23, 25(2), and 31, June 1, 2(2), 6, 7, 8, 16, 20, 21, 23, 27, 28, and 29, July 6(2), 27(2), and 31, August 1(2), 3, 7(2), 15(2), 21(3), 22, 23, 30, and 31, and September 29(2), 1995.

This new drug application provides for the treatment of two disorders of bone metabolism: osteoporosis in postmenopausal women, and Paget's Disease of bone.

We have completed the review of this application, as amended, 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 dated September 29, 1995, and subsequent fax dated September 29, 1995. Accordingly, the application is approved effective on the date of this letter.

Please submit 15 copies of the final printed labeling (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 NDA 20-560. Approval of this labeling by FDA is not required before it 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 send one copy to the Division of Metabolism and Endocrine Drug Products 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-240
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Also, we remind you that the lot number and expiration date should be included on the carton label for blister packages.

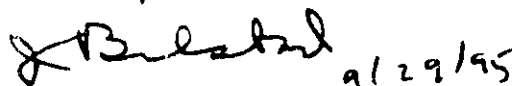
Please submit one market package of the drug product when it is available

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
(301) 443-3520

Sincerely yours,



James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

FOSAMAX®

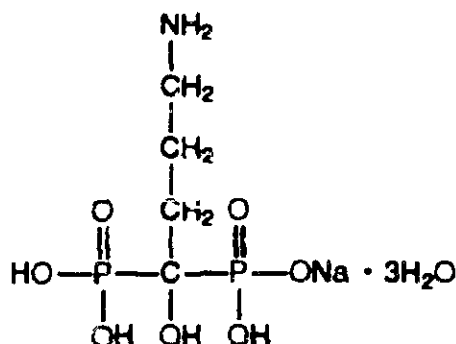
(ALENDRONATE SODIUM TABLETS)

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 either 13.05 mg or 52.21 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 10.0 mg and 40.0 mg, respectively, of free acid, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, and magnesium stearate.

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 [^3H]alendronate in bone showed about 10-fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bones examined 6 and 49 days after [^3H]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. 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%.

In a trial in elderly patients given 5 mg of alendronate (n = 86) 30 minutes before breakfast, similar bone mineral density changes were noted when compared to the pivotal trials, in which one of the treatment arms was 5 mg alendronate administered 60 minutes before breakfast.

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 [¹⁴C]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 H₂ antagonists is unknown; no other specific drug interaction studies were performed.

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

Summary of Pharmacokinetic Parameters in the Normal Population

	Mean	90% Confidence Interval
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 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.

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) 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. 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 addition, the markers of bone formation, serum osteocalcin and alkaline phosphatase, were also reduced by approximately 50% and 25 to 30%, respectively, to a plateau after 6 to 12 months. 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. 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

Paget's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disorderly bone remodelling. 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.

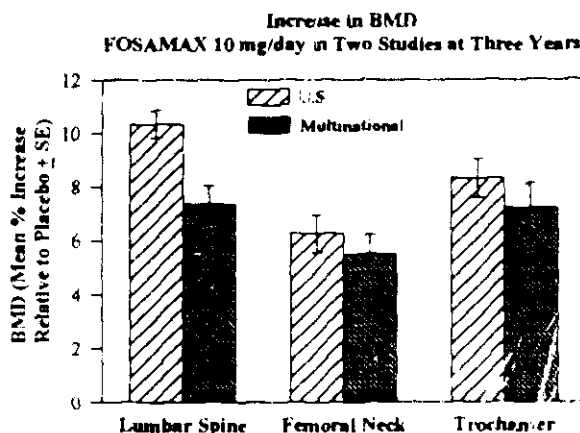
Clinical manifestations of Paget's disease range from no symptoms to severe morbidity due to bone pain, bone deformity, pathological fractures, and neurological and other complications. Serum alkaline phosphatase, the most frequently used biochemical index of disease activity, provides an objective measure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

Osteoporosis in postmenopausal women

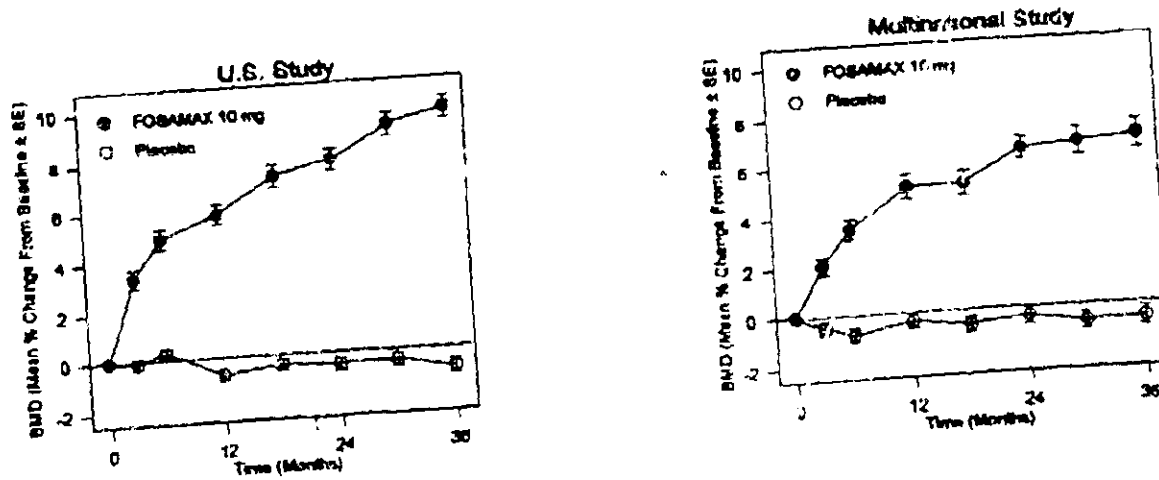
The efficacy of FOSAMAX 10 mg once daily in postmenopausal women, 44 to 84 years of age, with osteoporosis (lumbar spine bone mineral density [BMD] of at least 2 standard deviations below the premenopausal mean) was demonstrated in four double-blind, placebo-controlled clinical studies of two or three 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).

FOSAMAX®
(Alendronate Sodium Tablets)

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



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.

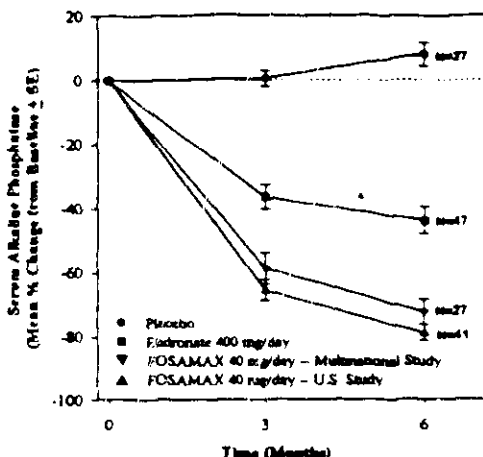
The effects of treatment withdrawal were assessed in a study that included patients treated with FOSAMAX for one or two years. Following discontinuation, neither further increases in bone mass nor accelerated rate of bone loss was noted. These data indicate that continuous daily treatment with FOSAMAX is required to maintain the effect of the drug.

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.

Paget's disease

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

Effect on Serum Alkaline Phosphatase of FOSAMAX 40 mg/day versus Placebo or Etidronate 400 mg/day



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 $\geq 60\%$) 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, Osteoporosis in postmenopausal women*), 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 of:

- Osteoporosis in postmenopausal women
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*.)
- 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

- Hypersensitivity to any component of this product
- Hypocalcemia (see PRECAUTIONS, *General*)

PRECAUTIONS

General

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

As with other bisphosphonates, caution should be used when FOSAMAX is given to patients with active upper gastrointestinal problems, such as dysphagia, symptomatic esophageal diseases, gastritis, duodenitis, or ulcers.

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 taken with plain water the first thing in the morning at least 30 minutes before the first food, beverage, or medication of the day. Patients should also be instructed that waiting longer than 30 minutes will improve the absorption of FOSAMAX. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of FOSAMAX (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption). Patients should be instructed to take FOSAMAX with a full glass of water (6-8 oz.) and not to lie down for at least 30 minutes following administration to facilitate delivery to the stomach and reduce the potential for esophageal irritation.

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

A small number of postmenopausal women in the osteoporosis trials received estrogen (intravaginal, transdermal, or oral) while taking FOSAMAX. No adverse experiences attributable to their concomitant use were identified.

Concomitant use of hormone replacement therapy and FOSAMAX in the treatment of osteoporosis in postmenopausal women is not recommended because of lack of clinical experience.

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.

NSAIDs/Aspirin

The risk of upper gastrointestinal adverse events associated with NSAIDs does not appear to be greater with concomitant treatment with FOSAMAX 10 mg/day. However, in patients receiving concomitant therapy with doses of FOSAMAX greater than 10 mg/day and aspirin-containing compounds, the incidence of upper gastrointestinal adverse events was increased.

Other

Although specific interaction studies were not performed, FOSAMAX 10 mg/day was used in postmenopausal osteoporosis studies with a wide range of commonly prescribed drugs without evidence of clinical adverse interactions. These included antacids, anticholinergics, aspirin-containing compounds, benzodiazepines, beta-blockers, calcium channel blockers, diuretics, gastric acid secretion inhibitors, glucocorticoids, nonsteroidal antiinflammatory drugs (NSAIDs), sedative hypnotics, thiazides, thyroid hormones, vasoconstrictors, and vasodilators.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Harderian gland (a retroorbital 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/m².

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 sternal 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/m². 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/m²).

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

Alendronate was secreted in the milk of rats after an IV dose. It is not known whether alendronate is excreted in human milk. FOSAMAX has not been studied in nursing women and should not be given to them.

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 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

Adverse experiences associated with FOSAMAX usually have been mild, and generally have not required discontinuation of therapy.

Osteoporosis in postmenopausal women

FOSAMAX has been evaluated for safety in clinical studies in more than 1800 postmenopausal patients. 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)
<i>Gastrointestinal</i>		
abdominal pain	6.6	4.8
nausea	3.6	4.0
dyspepsia	3.6	3.5
constipation	3.1	1.3
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
<i>Musculoskeletal</i>		
musculoskeletal pain	4.1	2.5
muscle cramp	0.0	1.0
<i>Nervous System/Psychiatric</i>		
headache	2.6	1.5
dizziness	0.0	1.0
<i>Special Senses</i>		
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.

Paget's disease

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 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.

OVERDOSAGE

Significant lethality after single oral doses was seen in female rats and mice at 552 mg/kg (3256 mg/m²) and 966 mg/kg (2898 mg/m²), 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/m²).

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. Administration of milk or antacids, to bind alendronate, should be considered.

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 longer than 30 minutes before eating will improve the absorption of FOSAMAX. 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, FOSAMAX should be taken with a full glass of water (6-8 oz.) and patients should avoid lying down for at least 30 minutes thereafter (see PRECAUTIONS, *Information for Patients*).

Patients with osteoporosis or Paget's disease 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.

Osteoporosis in postmenopausal women

The recommended dosage is 10 mg once a day.

Safety of treatment 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. 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

FOSAMAX®
(Alendronate Sodium Tablets)

7957000

NDC 0006-0936-58 unit-of-use bottles of 100

NDC 0006-0936-28 unit dose packages of 100.

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.

Storage

Store in a well-closed container at controlled room temperature 20-25°C (68-77°F).

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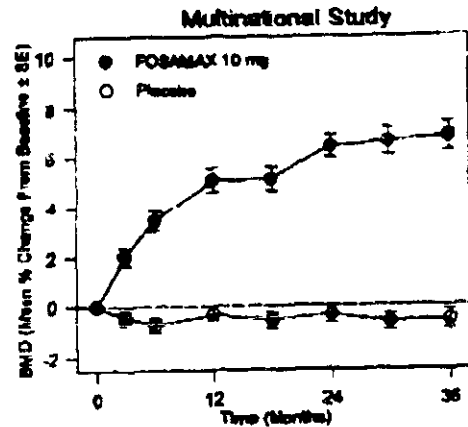
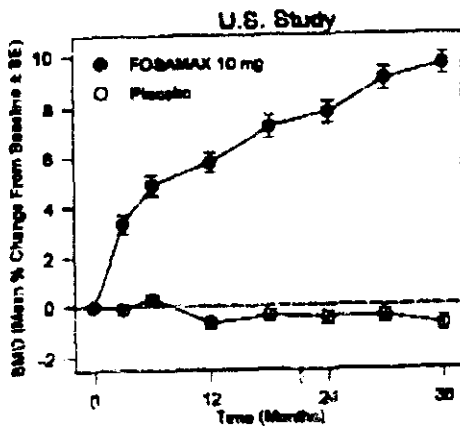
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FOSAMAX®
(Alendronate Sodium Tablets)

**Time Course of Effect of FOSAMAX Therapy Versus Placebo:
Lumbar Spine BMD Percent Change From Baseline**



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 effects of treatment withdrawal were assessed in a study that included patients treated with FOSAMAX for one or two years. Following discontinuation, neither further increases in bone mass nor accelerated rate of bone loss was noted. These data indicate that continuous daily treatment with FOSAMAX is required to maintain the effect of the drug.

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.

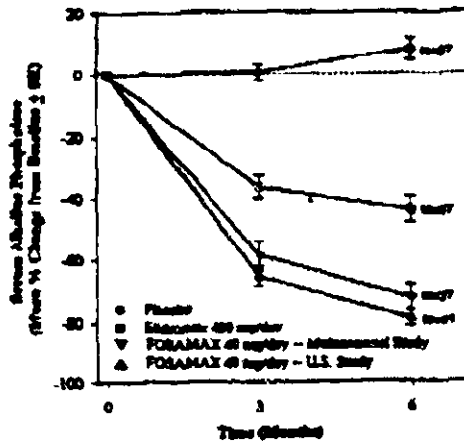
Paget's disease

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.

FOSAMAX®
(Alendronate Sodium Tablets)

7957000

Effect on Serum Alkaline Phosphatase of FOSAMAX 40 mg/day versus Placebo or Etidronate 400 mg/day



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 $\geq 60\%$) 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, Osteoporosis in postmenopausal women*), 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 of:

- Osteoporosis in postmenopausal women
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.)
- 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

- Hypersensitivity to any component of this product
- Hypocalcemia (see PRECAUTIONS, General)

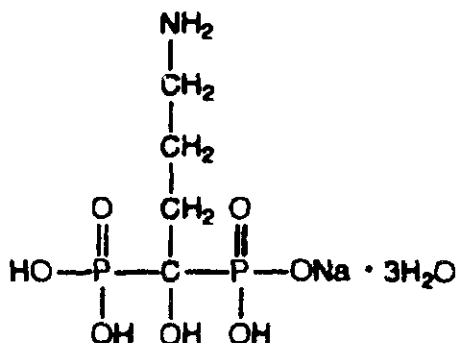
FOSAMAX®
(ALENDRONATE SODIUM TABLETS)

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 either 13.05 mg or 52.21 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 10.0 mg and 40.0 mg, respectively, of free acid, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, and magnesium stearate.

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 [³H]alendronate in bone showed about 10-fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bones examined 6 and 49 days after [³H]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. 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%.

In a trial in elderly patients given 5 mg of alendronate (n = 86) 30 minutes before breakfast, similar bone mineral density changes were noted when compared to the pivotal trials, in which one of the treatment arms was 5 mg alendronate administered 60 minutes before breakfast.

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. Concentration 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 [¹⁴C]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 H₂ antagonists is unknown; no other specific drug interaction studies were performed.

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

Summary of Pharmacokinetic Parameters in the Normal Population

	Mean	90% Confidence Interval
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 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.

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) 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. 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 addition, the markers of bone formation, serum osteocalcin and alkaline phosphatase, were also reduced by approximately 50% and 25 to 30%, respectively, to a plateau after 6 to 12 months. 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. 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

Paget's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disorderly bone remodelling. 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.

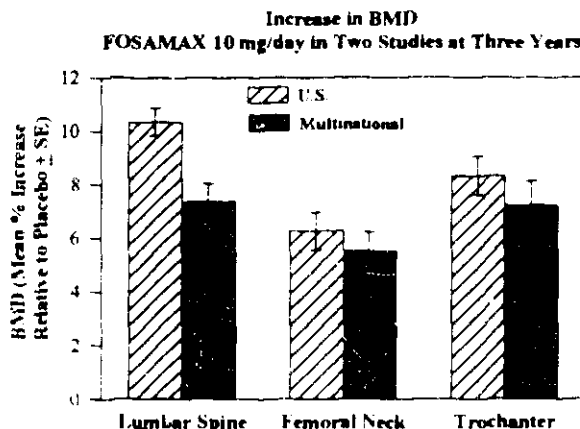
Clinical manifestations of Paget's disease range from no symptoms to severe morbidity due to bone pain, bone deformity, pathological fractures, and neurological and other complications. Serum alkaline phosphatase, the most frequently used biochemical index of disease activity, provides an objective measure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

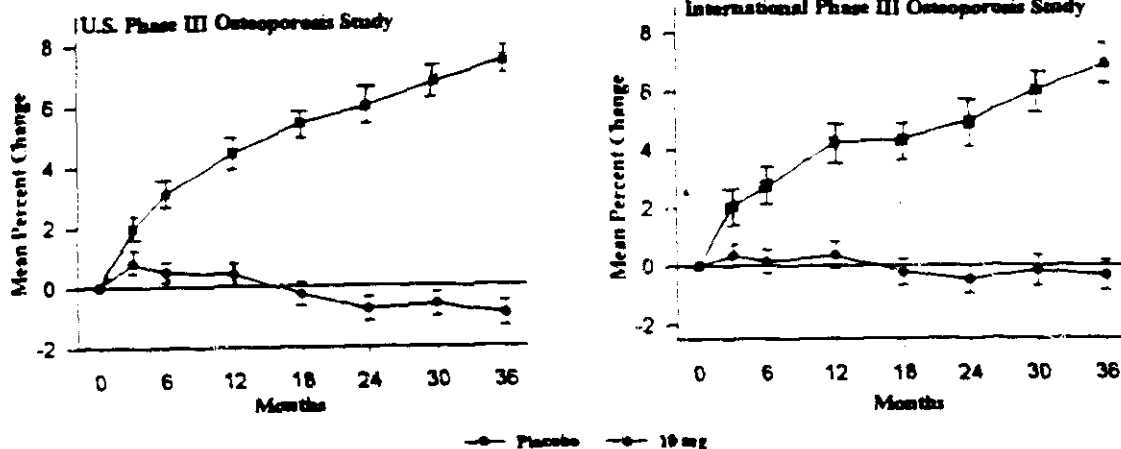
Osteoporosis in postmenopausal women

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 10mg/day Versus Placebo:
Lumbar Spine BMD Percent Change From Baseline



Handwritten note:
These are the
data for the
osteoporosis
studies

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.

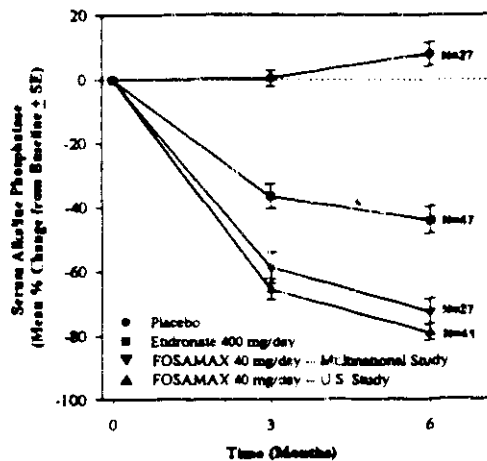
The effects of treatment withdrawal were assessed in a study that included patients treated with FOSAMAX for one or two years. Following discontinuation, neither further increases in bone mass nor accelerated rate of bone loss was noted. These data indicate that continuous daily treatment with FOSAMAX is required to maintain the effect of the drug.

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.

Paget's disease

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.

Effect on Serum Alkaline Phosphatase of FOSAMAX 40 mg/day versus Placebo or Etidronate 400 mg/day



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 $\geq 60\%$) 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, Osteoporosis in postmenopausal women*), 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 supports 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 the therapeutic doses is highly unlikely to induce osteomalacia.

INDICATIONS AND USAGE

FOSAMAX is indicated for the treatment of:

- Osteoporosis in postmenopausal women
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*.)
- 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

- Hypersensitivity to any component of this product
- Hypocalcemia (see PRECAUTIONS, *General*)

PRECAUTIONS

General

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

As with other bisphosphonates, caution should be used when FOSAMAX is given to patients with active upper gastrointestinal problems, such as dysphagia, symptomatic esophageal diseases, gastritis, duodenitis, or ulcers.

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 taken with plain water the first thing in the morning at least 30 minutes before the first food, beverage, or medication of the day. Patients should also be instructed that waiting longer than 30 minutes will improve the absorption of FOSAMAX. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of FOSAMAX (see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Absorption*). Patients should be instructed to take FOSAMAX with a full glass of water (6.5 oz.) and not to lie down for at least 30 minutes following administration to facilitate delivery to the stomach and reduce the potential for esophageal irritation.

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

A small number of postmenopausal women in the osteoporosis trials received estrogen (intravaginal, transdermal, or oral) while taking FOSAMAX. No adverse experiences attributable to their concomitant use were identified.

Concomitant use of hormone replacement therapy and FOSAMAX in the treatment of osteoporosis in postmenopausal women is not recommended because of lack of clinical experience.

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.

NSAIDs/Aspirin

The risk of upper gastrointestinal adverse events associated with NSAIDs does not appear to be greater with concomitant treatment with FOSAMAX 10 mg/day. However, in patients receiving concomitant therapy with doses of FOSAMAX greater than 10 mg/day and aspirin-containing compounds, the incidence of upper gastrointestinal adverse events was increased.

Other

Although specific interaction studies were not performed, FOSAMAX 10 mg/day was used in postmenopausal osteoporosis studies with a wide range of commonly prescribed drugs without evidence of clinical adverse interactions. These included antacids, anticholinergics, aspirin-containing compounds, benzodiazepines, beta-blockers, calcium channel blockers, diuretics, gastric acid secretion inhibitors, glucocorticoids, nonsteroidal antiinflammatory drugs (NSAIDs), sedative hypnotics, thiazides, thyroid hormones, vasoconstrictors, and vasodilators.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Harderian gland (a retroorbital 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/m².

Parathyroid 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 the *in vitro* mammalian cell mutagenesis assay, in an *in vitro* alkaline elution assay in rat hepatoma cells, 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/m². 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/m²).

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

Alendronate was secreted in the milk of rats after an IV dose. It is not known whether alendronate is excreted in human milk. FOSAMAX has not been studied in nursing women and should not be given to them.

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 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

Adverse experiences associated with FOSAMAX usually have been mild, and generally have not required discontinuation of therapy.

Osteoporosis in postmenopausal women

FOSAMAX has been evaluated for safety in clinical studies in more than 1800 postmenopausal patients. 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

ences reported by the investigators as possibly, probably, or definitely drug related in $\geq 1\%$ of ents 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)
<i>Gastrointestinal</i>		
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
<i>Musculoskeletal</i>		
musculoskeletal pain	4.1	2.5
muscle cramp	0.0	1.0
<i>Nervous System/Psychiatric</i>		
headache	2.0	1.5
dizziness	0.0	1.0
<i>Special Senses</i>		
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

Paget's disease

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 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.

OVERDOSAGE

Significant lethality after single oral doses was seen in female rats and mice at 552 mg/kg (3256 mg/m²) and 966 mg/kg (2898 mg/m²), 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/m²).

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. Administration of milk or antacids, to bind alendronate, should be considered.

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 longer than 30 minutes before eating will improve the absorption of FOSAMAX. 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, FOSAMAX should be taken with a full glass of water (6-8 oz.) and patients should avoid lying down for at least 30 minutes thereafter (see PRECAUTIONS, *Information for Patients*).

Patients with osteoporosis or Paget's disease 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.

Osteoporosis in postmenopausal women

The recommended dosage is 10 mg once a day

Safety of treatment 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. 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

FOSAMAX®
(Alendronate Sodium Tablets)

7957000

NDC 0006-0936-58 unit-of-use bottles of 100

NDC 0006-0936-28 unit dose packages of 100.

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.

Storage

Store in a well-closed container at controlled room temperature 20-25°C (68-77°F)

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

Issued September 1995

Printed in USA

Edwin L. Hemwall, Ph.D.
Director
Regulatory Affairs

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215 652 5000

September 8, 1995

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine
Drug Products, HFD-510, Room 14B04
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



**NDA 20-560: FOSAMAX™
(Alendronate Sodium)**

REVISED DRAFT PATIENT PACKAGE INSERT

Dear Dr. Sobel:

Reference is made to the NDA cited above, our letter of August 31, 1995, and telephone conversations between Edwin L. Hemwall, Ph.D., MRL, and Mr. Randy Hedin, FDA, on September 8, 1995. As per those conversations, we have agreed to further revise the Patient Package Insert (PPI) as follows:

- Under the heading "*Who should not take FOSAMAX?*", the sentence "FOSAMAX has not been studied in pregnant women or nursing mothers." has been deleted
- The entire section "*How does FOSAMAX work?*" has been relocated to appear earlier in the PPI, immediately after the section entitled "*What is FOSAMAX?*"

A copy of the PPI which has been revised as described above is attached. As previously noted, this PPI is undergoing readability and comprehension testing which may result in further editorial refinement, pending Agency agreement.

Please direct questions or need for additional information to Edwin L. Hemwall, Ph.D. (610/397-2306) or, in my absence, Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely yours,

A handwritten signature in cursive script that reads "Edwin L. Hemwall".

Edwin L. Hemwall, Ph.D.
Director
Regulatory Affairs

q Antell Ltrs fda 0223doc

Attachment

Federal Express #1

Desk Copy w/Attachment Mr. Randy Hedin, HFD-510, Room 14B04 - Via Facsimile
Confirmation Copy - Federal Express #2

FOSAMAX® (Alendronate) Tablets
Patient Information about
FOSAMAX® (FOSS-ah-max) for Osteoporosis
Generic name: alendronate sodium (2-LEN-dro-nate)

Please read this information before you start taking FOSAMAX. Also, read the leaflet each time you renew your prescription, just in case anything has changed. Remember, this leaflet does not take the place of careful discussions with your doctor. You and your doctor should discuss FOSAMAX when you start taking your medication and at regular checkups.

What is FOSAMAX used for?

FOSAMAX is for the treatment of osteoporosis (thinning of bone) in women after menopause. You will find more information about osteoporosis at the end of this leaflet.

How should you take FOSAMAX?

There are six important things you must remember if you want to make sure that you will benefit from FOSAMAX.

- Take FOSAMAX once a day, every day.
- Take FOSAMAX first thing in the morning with plain water only.
Not mineral water
Not coffee or tea
Not juice

FOSAMAX is effective only if taken when your stomach is empty.

- Take FOSAMAX at least 30 minutes before your first meal, beverage, or any other medication including antacids, calcium supplements and vitamins.

Waiting for less than 30 minutes or taking FOSAMAX with food, beverages other than plain water, or other medications will lessen the effect of FOSAMAX by interfering with its absorption into the body. Waiting longer than 30 minutes will improve the absorption of FOSAMAX.

- Take 1 tablet with a full glass (6-8 ozs.) of plain water. Do not lie down for at least 30 minutes after taking FOSAMAX.

This will help the FOSAMAX tablet reach your stomach quickly and help avoid irritation of your esophagus (the tube that connects your mouth with your stomach).

- It is important that you continue taking FOSAMAX for as long as your doctor prescribes it. FOSAMAX can treat your osteoporosis only if you continue to take it.
- If you miss a dose do not take it later in the day. Begin your usual schedule of 1 tablet once a day the next morning.

Who should not take FOSAMAX?

Patients with:

- Low blood calcium
- Severe kidney disease
- Allergy to FOSAMAX

Patients who are:

- Pregnant or Nursing
FOSAMAX is for use by women after menopause. FOSAMAX has not been studied in pregnant women or nursing mothers. If you are pregnant or nursing, you should not be taking FOSAMAX. Talk to your doctor.

What should you discuss with your doctor?

- Any swallowing, stomach or digestive problems.
- Any other medical problems you have or have had in the past

What about side effects?

Like all prescription drugs, FOSAMAX may cause side effects. Side effects usually have been mild. They generally have not caused patients to stop taking FOSAMAX. Some patients treated with FOSAMAX in clinical studies experienced abdominal (stomach) pain, which was the most commonly reported side effect. Less frequently reported were other digestive disturbances such as:

Nausea, heartburn, irritation or pain of the esophagus (the tube that connects your mouth with your stomach), vomiting, difficulty swallowing, a full or bloated feeling in the stomach, constipation, diarrhea and gas.

Some patients also had muscle/bone pain, headache, or an altered sense of taste. Rarely, a rash has occurred.

Anytime you have a medical problem you think may be related to FOSAMAX, talk to your doctor.

What should you know about osteoporosis?

Normally your bones are being rebuilt all the time. First, old bone is removed (resorbed). Then new bone is formed. This balanced process of resorbing and forming bone keeps your skeleton healthy and strong.

Osteoporosis is a thinning and weakening of the bones. It is common in women after menopause. Menopause happens when the ovaries stop producing the female hormone, estrogen, or are removed (which may occur, for example, at the time of a hysterectomy). After menopause, bone is removed faster than it is formed, so bone loss occurs and bones become weaker.

At the start osteoporosis usually has no symptoms, but it can result in fractures (broken bones). Fractures usually cause pain. Fractures of the bones of the spine may not be painful, but over time they cause height loss. Eventually the spine becomes curved and the body becomes bent over. Fractures may happen during normal, everyday activity, such as lifting, or from minor injury that would normally not cause bone to break. Fractures most often occur at the hip, spine, or wrist. This can lead to pain, severe disability, or loss of mobility.

How can osteoporosis in postmenopausal women be treated?

- **Medication.**

Your doctor may prescribe FOSAMAX. See "How does FOSAMAX work?" below.

- **Lifestyle changes.**

In addition to FOSAMAX, your doctor may recommend one or more of the following lifestyle changes:

Stop smoking. Smoking appears to increase the risk of osteoporosis.

Reduce the use of alcohol. Too much alcohol appears to increase the risk of osteoporosis and injuries that may cause fractures.

Exercise regularly. Like muscles, bones need exercise to stay strong and healthy. Exercise must be safe to prevent injuries including fractures. You should consult your doctor before you begin any exercise program.

Eat a balanced diet. Adequate dietary calcium is important to patients with osteoporosis. Your doctor can advise you whether you need to change your diet or take any dietary supplements such as calcium or vitamin D.

How does FOSAMAX work?

FOSAMAX reduces the activity of the cells that cause bone loss. FOSAMAX decreases the faster rate of bone loss that occurs after menopause. FOSAMAX also increases the amount of bone in most patients. These effects are seen as soon as three months after therapy with FOSAMAX has begun. These effects continue in women treated over the long term. The density of bone increases and the bone is less likely to fracture. Thus, FOSAMAX reverses the progression of osteoporosis (see "What should you know about osteoporosis" above).

Do not share FOSAMAX with anyone else. FOSAMAX was prescribed only for you.

Keep FOSAMAX and all medicines out of the reach of children.

FOR MORE INFORMATION ABOUT 'FOSAMAX' AND OSTEOPOROSIS,
TALK WITH YOUR DOCTOR.

IN ADDITION, TALK TO YOUR PHARMACIST OR OTHER HEALTH CARE PROVIDER.

Issued XXXX 1995

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

FOSAMAX® (Alendronate) Tablets
Patient Information about
FOSAMAX® (FOSS-ah-max) for Osteoporosis
 Generic name: alendronate sodium (a-LEN-dro-nate)

Please read this information before you start taking FOSAMAX. Also, read the leaflet each time you renew your prescription, just in case anything has changed. Remember, this leaflet does not take the place of careful discussions with your doctor. You and your doctor should discuss FOSAMAX when you start taking your medication and at regular checkups.

What is FOSAMAX?

FOSAMAX is for the treatment of osteoporosis (thinning of bone) in women after menopause. You will find more information about osteoporosis at the end of this leaflet.

How does FOSAMAX work?

FOSAMAX reduces the activity of the cells that cause bone loss. FOSAMAX decreases the faster rate of bone loss that occurs after menopause. FOSAMAX also increases the amount of bone in most patients. These effects are seen as soon as three months after therapy with FOSAMAX has begun. These effects continue in women treated over the long term. The density of bone increases and the bone is less likely to fracture. Thus, FOSAMAX reverses the progression of osteoporosis.

How should I take FOSAMAX?

There are six important things you must remember if you want to make sure that you will benefit from FOSAMAX:

- Take FOSAMAX once a day, every day.
- Take FOSAMAX first thing in the morning with plain water only.
 Not mineral water
 Not coffee or tea
 Not juice

FOSAMAX is effective only if taken when your stomach is empty.

- Take FOSAMAX at least 30 minutes before your first meal, beverage, or any other medication including antacids, calcium supplements and vitamins.

Waiting for less than 30 minutes or taking FOSAMAX with food, beverages other than plain water, or other medications will lessen the effect of FOSAMAX by interfering with its absorption into the body. Waiting longer than 30 minutes will improve the absorption of FOSAMAX.

- Take 1 tablet with a full glass (6-8 ozs.) of plain water. Do not lie down for at least 30 minutes after taking FOSAMAX.

This will help the FOSAMAX tablet reach your stomach quickly and help avoid irritation of your esophagus (the tube that connects your mouth with your stomach).

- It is important that you continue taking FOSAMAX for as long as your doctor prescribes it. FOSAMAX can treat your osteoporosis only if you continue to take it.

- If you miss a dose do not take it later in the day. Begin your usual schedule of 1 tablet once a day the next morning.

Who should not take FOSAMAX?

Patients with:

- Low blood calcium
- Severe kidney disease
- Allergy to FOSAMAX

Patients who are:

- Pregnant or Nursing
FOSAMAX is for use by women after menopause. If you are pregnant or nursing, you should not be taking FOSAMAX. Talk to your doctor.

Also talk to your doctor about:

- Any swallowing, stomach or digestive problems
- Any other medical problems you have or have had in the past.

What are the possible side effects of FOSAMAX?

Like all prescription drugs, FOSAMAX may cause side effects. Side effects usually have been mild. They generally have not caused patients to stop taking FOSAMAX. Some patients treated with FOSAMAX in clinical studies experienced abdominal (stomach) pain, which was the most commonly reported side effect. Less frequently reported were other digestive disturbances such as:

Nausea, heartburn, irritation or pain of the esophagus (the tube that connects your mouth with your stomach), vomiting, difficulty swallowing, a full or bloated feeling in the stomach, constipation, diarrhea and gas.

Some patients also had muscle/bone pain, headache, or an altered sense of taste. Rarely, a rash has occurred.

Anytime you have a medical problem you think may be related to FOSAMAX, talk to your doctor.

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Normally your bones are being rebuilt all the time. First, old bone is removed (resorbed). Then new bone is formed. This balanced process of resorbing and forming bone keeps your skeleton healthy and strong.

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Reduce the use of alcohol. Too much alcohol appears to increase the risk of osteoporosis and injuries that may cause fractures.

Exercise regularly. Like muscles, bones need exercise to stay strong and healthy. Exercise must be safe to prevent injuries including fractures. You should consult your doctor before you begin any exercise program.

Eat a balanced diet. Adequate dietary calcium is important to patients with osteoporosis. Your doctor can advise you whether you need to change your diet or take any dietary supplements such as calcium or vitamin D.

This medication was prescribed for your particular condition. Do not use it for another condition or give the drug to others. Keep FOSAMAX and all medicines out of the reach of children. If you suspect that more than the prescribed dose of this medicine has been taken, contact your local poison control center or emergency room immediately.

This leaflet provides a summary of information about FOSAMAX. If you have any questions or concerns about either FOSAMAX or osteoporosis, contact your doctor or pharmacist.

Issued XXXX 1995

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

Unit Dose Package of 100
10 mg

FOSAMAX® 10 mg (Alendronate Sodium Tablets)	
Each tablet contains 13.05 mg Alendronate Sodium (10 mg free acid equivalent)	
Dist. by	
 MERCK & CO., INC. West Point, PA 19486, USA	
Store in a well-closed container at controlled room temperature 15-30°C (59-86°F)	
100 Tablets	BAR CODE 0006-0936-28
FOSAMAX® 10 mg (Alendronate Sodium Tablets)	
NDC 0006-0936-28	
USUAL ADULT DOSE: See accompanying circular	
CAUTION: Federal (USA) law prohibits dispensing without prescription	
This is a bulk package and not intended for dispensing	
100 Tablets	BAR CODE 0006-0936-28
1001 No. 3600	

FOSAMAX® 10 mg (Alendronate Sodium Tablets)	
Each tablet contains 13.05 mg Alendronate Sodium (10 mg free acid equivalent)	
Dist. by	
 MERCK & CO., INC. West Point, PA 19486, USA	
Store in a well-closed container at controlled room temperature 15-30°C (59-86°F)	
100 Tablets	BAR CODE 0006-0936-28
1001 No. 3600	

EXCLUSIVITY SUMMARY FOR NDA # 20-560 SUPPL # _____

Trade Name Fosamax Generic Name Alendronate sodium

Applicant Name Mevco HFD # 510 tablets, 10 & 40 mg

Approval Date If Known _____

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 question 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.) _____

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?

Five

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# _____
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.

(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?

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:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

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 /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

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"):

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: _____

Ray T. White
Signature _____
Title: CSO

9/2/95
Date _____

John J. Schell
Signature of Office/ _____
Division Director

9/7/95
Date _____

cc: Original NDA

Division File

HFD-85 Mary Ann Ward

Edwin J. Herwall, Ph.D.
Director
Regulatory Affairs

Merck & Co., Inc.
BLA-30
West Point, PA 19486
Fax: 610 397 2335
Tel: 610 397 2306
215 652 5000

March 31, 1995



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

Original New Drug Application: NDA 20-560

**FOSAMAX
(Alendronate Sodium Tablets)**

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 New Drug Application for FOSAMAX (alendronate sodium tablets).

FOSAMAX, also referred to as alendronate sodium or MK-217, is a potent, orally active, aminobisphosphonate. It is a structural analogue of inorganic pyrophosphate that binds to bone and inhibits osteoclastic activity and, therefore, bone resorption.

This New Drug Application provides for the use of FOSAMAX in the treatment of two disorders of bone metabolism; osteoporosis in postmenopausal women and Paget's disease of bone. The recommended oral dose for osteoporosis treatment is 10 mg once daily and for Paget's disease of bone is 40 mg once daily for six months.

The bulk of the clinical efficacy program for osteoporosis treatment includes over 1800 patients from five Phase IIb and III placebo-controlled studies of up to three years duration. The main clinical efficacy program for Paget's disease of bone consists of four Phase II and III placebo- or active-controlled studies enrolling over 200 patients.

The safety profile of FOSAMAX is derived from a total database of over 13,600 patients, with the major focus being on data from eight core osteoporosis studies (total n = 2661, alendronate n = 1802), four Paget's disease studies (total n = 235, alendronate n = 153) and 17 clinical pharmacology studies (total n = 368).

The results of the osteoporosis preclinical and clinical program reported in this application are consistent with the requirements identified in the FDA's Draft "Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention and Treatment of Postmenopausal Osteoporosis". Briefly, this includes 1) demonstration of no detrimental effect on bone quality (including histology, density, and strength) in appropriate animal models, 2) data from two 3-year clinical trials demonstrating that bone mineral density is enhanced to a degree that is statistically and clinically significant, 3) normal bone histomorphometry from a subset of 3-year clinical trial patients subjected to bone biopsy, and 4) fracture data after three years of treatment showing a trend toward decreased fracture incidence and no deterioration in the third year. For the fracture results, the requirements of the FDA Guidelines have actually been exceeded, whereby FOSAMAX has been demonstrated to significantly reduce the risk of vertebral and nonvertebral fractures.

There are no FDA Guidelines for the evaluation of drugs for use in the treatment of Paget's disease of bone. In the clinical program reported here, the efficacy of FOSAMAX 40 mg orally once daily for six months in men and women with Paget's disease was demonstrated in two randomized, double-blind studies, one with a placebo control, the other with an etidronate control. The primary efficacy endpoint was the decrease in serum alkaline phosphatase, a clinical and biochemical index of disease activity.

Merck Research Laboratories (MRL) has met on several occasions with FDA personnel to discuss the clinical development program for FOSAMAX. These meetings have been summarized in the Regulatory Background Information section in this application. The understandings and agreements reached at these meetings have been incorporated into this application.

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 293 volumes and 5 "review" copies as described in the Statement of Organization which is attached to this letter. Please note that there are two separate Item 8 Clinical Documentation Sections, one for osteoporosis and one for Paget's disease.

Solomon Sobel, M.D., Director
Original New Drug Application
NDA 20-560 FOSAMAX
Page 3

Electronic versions of appropriate sections of this application for computer assisted (CANDA) review will be, or have already been, the subject of separate communications leading to training and installation of relevant hardware and software, based on individual reviewer preference.

In accordance with the Prescription Drug User Fee Act of 1992, a check (Check No C3193482), in the amount of _____ was sent to the Food and Drug Administration, P.O. Box 7777-W7745, Philadelphia, PA on March 24, 1995.

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 Philadelphia District Office (Attention: Ms. Karyn Bowen). 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.

As provided for in 21 CFR 312.102, 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 New Drug Application to be a confidential matter and request that the Food and Drug Administration not make its existence public without first obtaining written permission from Merck & Co., Inc.

Solomon Sobel, M.D., Director
Original New Drug Application
NDA 20-560 FOSAMAX
Page 4

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)

Sincerely yours,



Edwin L. Hemwall, Ph.D.
Director
Regulatory Affairs

q:\Antel\...tr\fa0150.doc

Attachment

Hand Delivered

Desk Copies (Letter Only) - Hand Delivered

Dr. Elizabeth Barbehenn, HFD-510, Room 14B19
Dr. James Bilstad, HFD-500, Room 13B28
Dr. Yuan Yuan Chiu, HFD-510, Room 14B26
Dr. Michael Fossler, HFD-426, Room 14B31
Mr. Randy Hedin, HFD-510, Room 14B04
Dr. Daniel Marticello, HFD-713, Room 18B45
Dr. Ruth Merkatz, HF-8, Room 1561
Dr. Solomon Sobel, HFD-510, Room 14B04
Dr. Gloria Troendle, HFD-510, Room 14B04

Desk Copy (Letter and Patent Information Only) - Hand Delivered

Mr. George Scott, HFD-84, Room 8B37

September 11, 1995

Memorandum

To the File: NDA 20-560 -alendronate sodium (Fosamax)

From: Solomon Sobel M.D. Director DMEDP

Subject : NDA approval

The Division recommends approval of this NDA for the indications: Treatment of osteoporosis in post menopausal women and Paget's disease of bone.

We have qualified the definition of osteoporosis by the finding of a low bone mass at least 2 standard deviations below the premenopausal mean or by the presence or history of osteoporotic fracture. The sponsor called me several days ago and wanted to remove the specific qualifications, stating that we had not imposed these qualifications on the recently approved nasal calcitonin. I stated that we would keep the qualifications. However, I said that I would review the situation in respect to the calcitonin labeling and see if the type of qualification in respect to bone mass that we placed on the Fosamax osteoporosis indication was applicable to calcitonin or even feasible (based on the calcitonin data base).

Another issue which we have resolved previously in respect to the duration of treatment is fully accepted by the sponsor. In the dosage and administration section the statement:

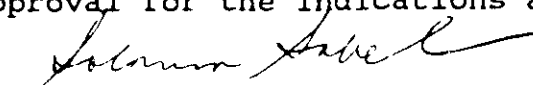
"Safety of treatment with Fosamax for longer than four years has not been studied; extension studies are ongoing."

I believe that this statement will satisfy the conservative stance taken by some of our Advisory Committee members.

I believe, also, that the dosing instructions in regard to the effects of food on absorption are now satisfactory.

Conclusion:

The Division recommends approval for the indications as stated above.


Solomon Sobel

CC: Arch NDA 20-560

HFD-510

HFD-510/SSobel/GTraendle/RHedin

Page 1

AUG 30 1995

NDA 20-560
Alendronate (Fosamax)

Merck Research Laboratories
Comments written August 30, 1995

Group Leader's Comments on Approvable NDA

The efficacy of allendronate has been demonstrated for reducing alkaline phosphatase, an indicator of bone activity. Other indicators of bone resorption similarly decreased significantly in the allendronate group, and the reduction was considerably greater than that seen with etidronate. However, clinical efficacy has not been shown. A pain score analysis in 111 patients reported having pain at baseline failed to demonstrate improvement greater than placebo (baseline 2.48 A vs 2.0 P, and change -1.50 vs -1.71) or than etidronate (baseline, 3.4 A vs 3.1 E and change -0.69 vs + 0.19). Similarly, a functional impairment score (2.06 A vs 1.7 P, and change -2.10 vs -2.29) in the placebo study (3.3 A vs 2.4 E, and change -0.32 vs +0.20) in the etidronate study; no significant difference between groups. However, by xray, there was some improvement in lytic lesions of bone in 32.4% of alendronate patients and 26.5% of etidronate patients vs only 4.3% of placebo patients. Worsening was seen in 8.8% of alendronate and 14.7% of etidronate patients vs none of the placebo patients.

In spite of good changes in alkaline phosphatase, actual improvement of patients has been hard to demonstrate. There is more improvement in lytic lesions than in etidronate-treated patients. Approval seems to be warranted by the biochemical and xray changes.

Gloria Troendle
Gloria Troendle 8-30-95

Medical Officer's Review of Safety Update

This safety update was submitted 7-31-95. It contains information on 1942 patients with osteoporosis and 177 with **Paget's Disease**. 660 osteo and 23 Paget's patients were in the core studies and had continued exposure to alendronate beyond that reported in the NDA. There were no newly enrolled patients, but the update includes patients who received placebo during the core studies and then began alendronate for the first time. Cutoff dates for the March 31, 1995 NDA differed with the individual studies as reported in the NDA. The cut-off for data to be included in this update was January 31, 1995. Spontaneous adverse event reports (foreign marketed) and serious adverse experience reports between the NDA cutoff of October 31, 1994 and March 31, 1995 are also reported. Most of the safety data are, therefore, **in osteoporosis patients**. Because Dr. Dutta will review this data, I will be concerned primarily with review of the ADRs in Paget's patients. Also, since Dr. Lutwak will review the safety data presented in the NDA, I will concentrate on additional adverse experiences during the update period. While core osteoporosis studies included 611 patients treated for 3.5 years, only 86 Paget's patients were treated for 6 mo double blind and continued on open-label drug for at least 6 mo. It would be useful to have the ADEs/patient month, because of the wide range of exposure duration.

In one Paget's study (059), it was planned that one group receive 40 mg alendronate and the other group receive placebo for 6 months, then the placebo patients were to receive open-label 40 mg alendronate, and the treated patients were to be followed off drug. However, the treatments were **erroniously given to the wrong groups**, so 22 patients received alendronate 40 mg for more than 9 months and up to 369 days.

Only the 40 mg dose was used during the update period. The 177 Paget's patients (160 continued from NDA) were **43 to 85 years old**, and **97 were male, 80 female; 5 were black, 2 other**. Concomitant therapies most commonly used were CNS agents (58%), vitamins and minerals (44%), anti-infective agents (41%), cardiovascular drugs (35%), GI agents (21%), anti-inflammatories (18%), water balance agents (18%), endocrine drugs (15%), and autonomic drugs(15%).

In the update period, there was 1 **death** (esophageal cancer), 5.6% reported serious adverse events, and 7.3% withdrawals due to an adverse event. The death on day 439 of the study followed discontinuation of alendronate therapy at day 389 and diagnosis of esophageal cancer at day 407. He had not received drug from day 183 to day 379. This single death is not informative.

70% reported at least one clinical adverse event (same as NDA).

The most commonly reported events (cumulative, NDA and update) were musculoskeletal pain (32%), abdominal pain (8%), dyspepsia (7%), diarrhea (6%), headache 5.5%, flatulence (5.5%), nausea (5%). None of these were markedly increased in the update period, but musculoskeletal pain increased from 27 to 37%. Abdominal pain, headache, flatulence, and nausea were zero in the update, diarrhea decreased, and dyspepsia increased slightly. It seemed that tolerance might have developed for GI complaints (all digestive system complaints without the abdominal pain were 15 vs 28%). Hypertension increase was reported 1 time in the NDA and 3 post NDA, 0.9 vs 7.5%. Musculoskeletal pain did not increase during the update period (37.5 vs 36.4% of patients). So the only things that even suggest an increased problem with prolonged use are musculoskeletal pain and blood pressure. The osteoporosis population did not show an increase in blood pressure, but used 1/4 the dose used by Paget's. It seems unlikely that this very small number of reports is indicative of any problem.

4/110 (4%) patients had non-fatal serious events in the NDA and 4/40 (10%) in the update. The serious events in the update were 2 episodes of anaphylaxis in one patient, leg pain (lasting 91 days and still present), fracture of femur (fell from ladder), and hypesthesia (still present). The leg pain is probably included in the musculoskeletal pain (See above).

Four patients withdrew from therapy due to adverse experiences, including the cancer death and the serious leg pain. Another had a gastric ulcer, and the fourth had acid regurgitation and dyspepsia.

Laboratory adverse experiences were reported at least once for 34 of the 177 patients; 10 of these reports were in the update period (26% vs 18% in the NDA). No patient in the update period had a serious adverse laboratory experience, or withdrew from therapy because of an adverse laboratory experience. Decreased lymphocytes occurred at slightly higher frequency in the update (5.1 vs 2.8% = 2/39 vs 3/108). Blood urea increased in 4/34 (12%) vs 1/27 (3.7%). All 4 had elevated urea at baseline.

Nonfatal, serious clinical adverse experiences are also reported in 7 patients following the update cutoff: heart failure, malignancy of the pancreas, arthritis, contusion, cataract, skin neoplasm, and prostate neoplasm.

There are no results from this review that indicate any additional safety concerns.

S. T. Tinsdale
8-30-75

Group Leader's Comments on Approvable NDA

Part I, Osteoporosis

Alendronate is a bisphosphonate; the Indications for which this application is submitted are osteoporosis and Paget's disease of bone. The pre-clinical osteoporosis studies suggested in our Guidelines were completed and indicated no safety problem, but showed increased BMD, increased bone strength, and normal bone structure by histopathology.

Principal clinical efficacy data are from 3 clinical trials in postmenopausal women. All were double-blind, randomized, and placebo-controlled. All patients had 500 mg/d Calcium supplement. Alendronate was taken orally once daily. Protocols 35 and 37 included women with bone mineral density 2.5 SD below the mean for premenopausal caucasian women; Pr26 was conducted in women with BMD about 2SD below the mean of premenopausal women and with body weight 85 to 130% of ideal. In Pr26, drug was discontinued after 24 months, and patients were followed for another 12 months, during which time BMD decreased 1.5 and 0.2% in 5 and 10 mg groups respectively. Only the patients randomized to 24 (Pr26) or 36 (Pr 35 and 37) months at 5 or 10 mg are reviewed below, because there was no increased effect at 20 mg.

Mean (adjusted) changes in BMD (per cent from baseline) are given for the lumbar spine, the femoral neck and the trochanter. All patients evaluated for efficacy are reported below - a modified ITT analysis of patients with BMD determinations pre and post treatment. Mean BMD changes were adjusted for baseline inequalities in the placebo and treatment groups.

BMD results, in % change from baseline (95% confidence limits):

Pr	dose mg/d	N	duratn mo	lumbar spine	femoral neck	trochanter
026	0	24	24	-1.3(-2.3,-0.3)	-1.2(-2.3,-.02)	-0.9(-2.0,-.2)
	5	24		7.3(6.3,8.3)	2.8(1.6,3.9)	5.2(4.1,6.2)
	10	25		7.2(6.2,8.2)	4.8(3.7,5.9)	7.3(6.3,8.4)
035	0	186	36	-0.7(-1.2,-0.3)	-1.5(-2.1,-1.0)	-0.8(-1.4,-0.2)
	5	89		5.6(5.0,6.2)	2.8(2.0,3.6)	5.1(4.3,5.9)
	10	88		9.5(8.9,10.1)	4.7(3.9,5.5)	7.4(6.6,8.2)
037	0	188	36	-0.1(-.6,-.51)	-0.6(1.1,.03)	
	5	89		5.2(4.4,6.0)	2.9(2.0,3.7)	
	10	92		7.2(6.4,8.0)	4.7(3.9,5.6)	

Total body BMD was also determined by DEXA, and was increased.

Studies 35 and 37 were very similar, so they were pooled (prospectively planned analysis) across studies and across doses (including a group that had 20 mg alendronate for 24 months and then 5 mg for the third year) for fracture data. The pooled data included 881 patients, 355, 175 and 178 in the 0, 5 and 10 mg

groups, of which, 22 (6.2%), 5 (2.9%), and 5 (2.8%) had vertebral fractures for relative risks of .47 and .45. When pooled across doses, there were 526 treated women, of whom 17 (3.2%) had fractures, RR 0.52 (0.28,0.95). RR for women with fracture at entry is 0.70 (N's: 68 P and 97 A with 13 fractures each), and without fracture at entry is 0.52 (253 and 384 with 5 and 4 fractures). RR for age <65 is .79 and for 65+ is .33.

Thus, efficacy is reasonably well established for alendronate in treatment of post-menopausal osteoporosis. There are some issues, which are discussed below. The 36-month studies (35 and 37) had 597 patients on alendronate and 397 on placebo that were assessed for safety. Altogether, there were 2071 patients on drug who were assessed for safety. Of this number, 273 and 256 were treated with 5 and 10 mg respectively for over 24 months, and another 261 and 98 were treated for over 12 months. About 90% of patients had at least one adverse experience: 358/397 of the placebo patients, 181/202 of the 5 mg patients, and 173/196 of the 10 mg patients in studies 35 and 37. 24, 11 and 8 patients were withdrawn because of these ADRs, and 69, 26 and 27 were deemed to be serious. 3, 1 and 2 patients died. Abdominal pain and dysphagia were statistically more frequent in alendronate patients. Nothing of great concern was seen in analysis of these safety experiences.

Oral bioavailability of alendronate, measured by urinary excretion, is known to be less than 1% of the administered dose. Absorption when drug is administered 1/2 or 1 hr before breakfast is further reduced about 40% below that when drug is taken 2 hr before breakfast, and patients in clinical studies were instructed to take alendronate 2 hours before breakfast. The proposed labeling, however, recommends that drug be taken one half hour before the meal. The Advisory Committee was not worried about this difference between the studied and the recommended dosage regimen. It did seem that, in some sites and studies, 5 mg was almost as good as 10, and perhaps 10 taken 1/2 hr before eating will result in availability similar to that of 5 taken 1/2 hr before. I believe that compliance with the 1/2 hr will be much better, and it is possible that calling for 2 hr will just result in many instances of taking the dose after eating, which produced about twice as much decrease in availability as taking it 1/2 hr before a meal.

The data are convincing that alendronate inhibits bone resorption, decreases bone turnover, and increases BMD over three years in postmenopausal women with low bone mass. Data are suggestive that this increased bone density is accompanied by decreased risk of fractures. It is easy to see how a drug that inhibits resorption leads to increased bone density, because it is known that osteoblasts fill in the resorption pits, and, if no more (or fewer/less extensive) pits are being made, density should be increased. Since each cycle results in a little under-filling, decreasing resorption and thereby producing fewer cycles per unit time should slow bone loss. However, it is conceivable

that bone quality will decline because the remodeling is impaired. I don't think anyone knows how long the life of these microscopic bone units can be extended without weakening bone. Our guidelines require three years treatment, with evidence trending over three years (and without deterioration in the third year) toward decreased fracture risk. Three years is chosen because of evidence that some bisphosphonates weaken bone in the third year by inhibiting osteoblasts and decreasing mineralization. This is a different mechanism from the aging described above, and three years may not be the interval over which changes in remodeling become detrimental; that may be 5 years, 10 years, or more.

Additionally, alendronate gets down into the resorption pits and gets covered with new bone. Consequently it remains in the bones at least until that particular piece of bone comes up for remodeling again, and no one knows how long that interval is. Based on this mechanism, alendronate has a very long residence time in bone. There must come a time when alendronate is being uncovered at a rate that significantly affects the levels of alendronate present in the circulation. If alendronate is still being given at that time, will it result in levels toxic to bone or other tissues? BMD does decrease when alendronate is withdrawn after two years of treatment. How long should alendronate be given to a patient?

It is not reasonable to require adequate data to address these questions, because there is adequate information available to indicate at least three-year safety and efficacy. Alendronate should be approved with labeling to indicate the extent and limits of our knowledge of its long-term effects.

Specific Labeling Recommendations:

The Indication should be to increase bone density, unless we believe that a secondary endpoint in a single study is adequate to give an indication for reducing the risk of fractures.

Alendronate must be taken at least 1/2 hour, and preferably at least 2 hours, before breakfast.

Alendronate remains in bone for more than 10 years.

One of the actions of alendronate is to reduce the amount of bone that is rebuilt and renewed over time. Studies of alendronate treatment for 3 years have not shown any weakening of bone due to this reduced bone remodeling. Longer studies of alendronate treatment are underway.

Gloria Troendle/7/24/95

Gloria Troendle
7-25-95

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-560

Trade (generic) names Foximox

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&W 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.

b. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

This drug is for post-menopausal women only, but if it is studied, pediatric studies should be requested.

Alana Tremble

Signature of Preparer

9-19-95

Date

cc: Orig NDA
HFD- /Div File
NDA Action Package

MEDICAL OFFICER'S REVIEW

NDA No. 20-560

DATE OF SUBMISSION: 31 MARCH 1995

DATE RECEIVED, CDER: 19 APRIL 1995

DATE RECEIVED, M.O.: 19 APRIL 1995

DATE REVIEW COMPLETED, M.O.: 24 Aug 1995

DRUG:**GENERIC NAME: ALENDRONATE SODIUM TABLETS****PROPOSED TRADE NAME: FOSAMAX****CHEMICAL NAME: (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate****SYNONYMS: MK-217, MK-0217, L-670,452; amino-butane bisphosphonate; alendronate**

SPONSOR: Merck Research Laboratories
Merck & Co., Inc
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PHARMACOLOGIC CATEGORY: Inhibitor of osteoclast mediated bone resorption.

PROPOSED INDICATION(S): (1) Treatment of Osteoporosis in Postmenopausal women.
(2) Treatment of Paget's Disease of Bone.
Osteoporosis Indication reviewed by S. Dutta, M.D.
This review limited to Paget's Disease Indication

DOSE FORM(S) AND ROUTE(S) OF ADMINISTRATION: Tablets, 10 mg and Tablets, 40 mg, for oral administration.

NDA DRUG CLASSIFICATION:**RELATED DRUGS:** Etdronate; pamidronate

RELATED REVIEWS: Review by S. Dutta, M.D. (HFD-510) of indication for Treatment of Postmenopausal Osteoporosis; E. Barbehenn, Ph.D. (Pharmacology/Toxicology), D. Marticello (Biomathematics), M. Fossler, Ph.D. (Biopharmacology), (Chemistry).

MATERIAL REVIEWED: Volumes 2.1 and 2.3 of submission (2 vols. of 293), CANADA

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SUMMARY:

FOSAMAX® (alendronate sodium) is a geminal bisphosphonate capable of inhibiting osteoclastic bone resorption and, unlike the bisphosphonate previously approved for treatment of Paget's disease of the bone (etidronate), does not directly impair bone mineralization except at doses greatly in excess of those which maximally inhibit bone resorption.

Paget's disease of the bone is a localized, usually progressive, skeletal disorder characterized by a marked increase in the rate of bone remodeling, associated with bone pain, bone deformity, pathological fractures, secondary arthritis, neurological complications, and high output cardiac failure. Although the primary phenomenon is increased osteoclastic activity, this is coupled with increased osteoblastic function resulting in woven bone leading to disorganized osseous structure. Diagnosis and monitoring is usually accomplished by measurement of serum levels of bone-derived alkaline phosphatase.

Preclinical studies with alendronate showed no abnormalities of new bone at doses several times those used clinically. When administered to ovariectomized rats or baboons, alendronate increased trabecular bone volume and strength.

Dose finding studies in patients with Paget's disease demonstrated a linear relationship of suppression of serum alkaline phosphatase over the range of 5 to 80 mg daily administered for 3 months. In a treatment duration study of 6 months, a linear increase in incidence of adverse events of the gastrointestinal tract was also seen and because the effect on bone diminished with higher doses, a dosage of 40 mg daily was selected. Preliminary studies showed increasing response of serum alkaline phosphatase at 6 months compared to 3 months treatment and therefore the 6 month period was selected for the pivotal studies, resulting in the same clinical therapeutic effect as 80 mg daily for 3 months with decreased adverse events.

Protocol 056 was a pivotal, randomized, double-blind study comparing 40 mg daily of alendronate in 42 patients with 400 mg daily of etidronate in 47 patients for six months. At that time point, the per cent change (expressed as geometric means) in serum alkaline phosphatase was -43.9 (84% confidence interval -52.2, -37.2) for the etidronate group and -79.0 (C.I. -82.1, -76.1) for the alendronate patients, with a $p < 0.001$.

Protocol 059 was a pivotal, randomized, double-blind study comparing 27 patients on placebo to 27 patients on alendronate 40 mg daily for six months. At that time point, the per cent change (as geometric means) in serum alkaline phosphatase was +8.0 (84% C.I. -1.8, 39.0) for the placebo group and -72.5 (C.I. -75.2, -65.6) for the alendronate patients, with a $p < 0.001$.

When the data were examined in different ways - 3 month response, prevalence of responders (decrease of at least 60% from baseline or normalization of serum alkaline phosphatase) - the data were similarly significant.

Secondary endpoints examined included decrease in urinary excretion of deoxypyridonoline/creatinine and of N-telopeptide/creatinine, at 3 and 6 months, all of which showed similar differences between alendronate versus etidronate and alendronate versus placebo.

In 11 patients treated successfully with alendronate 40 mg for 6 months, followed off medication for an additional 6 months, serum alkaline phosphatase remained in the responder range in all.

Similar findings were noted in 14/14 treated with 80 mg daily of alendronate for 3 months and 14/14 treated for 6 months.

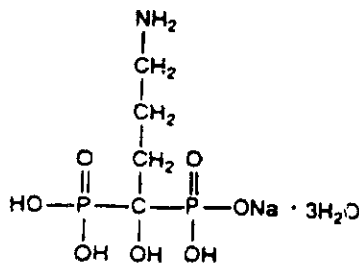
Safety observations were based on the pivotal studies discussed above, other Paget's disease studies, clinical pharmacology studies, osteoporosis studies, miscellaneous indication studies, and studies performed by companies other than Merck, for a total of 13,644 patients observed. Of these 603 patients were in the Paget's Disease and Clinical Pharmacology Studies. Although the per cent incidences of serious adverse experiences and withdrawals due to adverse experiences were lower in the alendronate groups as compared to the etidronate patients, the actual numbers of subjects involved were very small. Based on investigators' assessments, drug related adverse experiences of significance were those related to the digestive system and musculoskeletal pain.

I. CHEMISTRY/MANUFACTURING CONTROLS

See Chemistry Reviewers comments.

II. BACKGROUND

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



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

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

III. Rationale for Use of Alendronate in the Treatment of Paget's Disease of Bone

A. Introduction

Paget's disease of bone is a localized, progressive, skeletal disorder characterized by a marked increase in the rate of bone remodeling. This leads to the replacement of the normal bone architecture by a disorganized and weakened structure.

B. Prevalence of Paget's Disease of Bone

Since Paget's disease of bone is commonly asymptomatic and may affect few skeletal sites, its true prevalence is difficult to estimate. Radiographic surveys in the United Kingdom indicate a prevalence of 5% in the population older than 55 years of age. Paget's disease also appears to be common in countries such as Australia, New Zealand, and South Africa, where significant British immigration has occurred, as well as in other Western European countries, such as France and Ireland. It is estimated that up to 3% of people older than 55 years of age in the United States have Paget's disease, making it the

second most prevalent bone disorder (following osteoporosis). In contrast, the condition seems to be uncommon in Scandinavia and Southern Europe and extremely rare in the Middle East, China, and Japan.

Paget's disease of bone rarely presents before the age of 40 and is found with increasing frequency with advancing age. Most surveys indicate that the disease is slightly more common among men than women (1.4-1.9:1). Paget's disease may have a significant genetic component; a positive family history has been reported in several series.

C. Clinical Characteristics of Paget's Disease of Bone

Paget's disease is a focal disorder of the skeleton that may affect only a single bone or nearly the whole skeleton. The clinical presentation ranges from a benign, asymptomatic, incidental finding to a debilitating condition associated with bone pain, bone deformity, pathological fractures, secondary arthritis, neurological complications, and high output cardiac failure, as well as with an increased incidence of osteogenic sarcoma. The most common sites of involvement are the pelvis, femur, spine, skull, and tibia. Involvement is often asymmetrical. In most instances, bones involved at the time of diagnosis are the only ones that will ever be affected, since the sudden appearance of new sites of pagetic involvement is uncommon.

Bone pain is the most common presenting complaint. It is classically described as a deep-seated constant pain, unaffected by exercise or rest, and usually worse at night. Pagetic pain is often multifactorial in origin, and may be difficult to distinguish from that due to other causes, such as osteoarthritis. True pagetic pain may be due to increased vascularity of bone, leading to increased intramedullary pressure or periosteal stretching, or to microfractures or complete fractures. Another cause of pain is joint disease, due either to coincidental osteoarthritis or to secondary arthritis resulting from altered load-bearing stress on bones and joints. Neurological compression syndromes, vascular steal syndromes, and malignant transformation may also cause pain.

Bones affected by Paget's disease often enlarge; bone deformity, most frequently bowing of long bones or enlargement of cranial or facial bones, is a presenting complaint in approximately one-fifth of the patients. Bone enlargement and deformity are clinically important because they contribute significantly to neurological complications and joint disease.

Pagetic bone is weakened and may deform or break under normal weight bearing. Fissure and complete fractures of the long bones and compression fractures of vertebrae are relatively common complications. Fissure fractures, most often of the femur, tibia, and humerus, characteristically occur on the convex aspects of the bones, particularly in long bones with active areas of advancing lytic disease. Complete fractures occur most frequently in the femur, followed by the tibia and forearm. The increased vascularity of actively remodeling pagetic bones may lead to substantial blood loss if fracture occurs.

Neurological complications of Paget's disease are among the most serious clinical sequelae. They arise mainly from involvement of the skull or spine. Platibasia (invagination of the base of the skull by the cervical vertebrae) may result in brain stem compression, manifested by ataxia, muscle weakness, and disturbances of the control of respiration. Cranial nerve palsies due to narrowing or distortion of cranial nerve foramina

and vascular steal from the internal carotid system due to increased blood flow through the external carotid arteries have also been described. The most common complication of Paget's disease of the skull is hearing loss, which may be multifactorial in origin. Possible causes include involvement of the internal auditory canal (temporal bone) or auditory ossicles or, less commonly, direct compression of the eighth cranial nerve.

The vertebral column is one of the most commonly affected sites, and pain and neurological complications have been widely described. Spinal cord dysfunction, due to either compression by pagetic bone or a vascular steal syndrome, is a rare but serious complication. Cardiac output may be increased in extensive Paget's disease, owing to increased blood flow through pagetic bone, causing high output cardiac failure. Sarcoma arising in pagetic bone occurs in less than 1% of pagetic patients, but is highly malignant and rapidly progressive.

The proportion of affected individuals who would benefit from treatment is not known since many patients never come to medical attention and the diagnosis often does not require specific therapy. In some cases, for example, asymptomatic Paget's disease confined to non-weight-bearing bones in an elderly patient, the decision not to treat may be justified. A patient with mono-ostotic disease not involving a weight-bearing joint usually does not require treatment.

D. Pathophysiology of Paget's Disease of Bone

Skeletal turnover continues throughout life. At sites where preexisting bone is removed by osteoclasts, new bone is then formed by osteoblasts. Normally, turnover is coordinated, maintaining microstructural and macrostructural organization associated with optimal mechanical properties.

Paget's disease is characterized by a marked increase in the metabolic activity of bone. Increased osteoclastic bone resorption in advancing pagetic lesions is followed by a wave of new osteoblastic bone formation. The primary abnormality in Paget's disease is osteoclastic. Pagetic osteoclasts are increased in number, size, and activity. They show intracellular viral-like inclusions, which appear to be paramyxovirus nucleocapsids. Other viruses, including measles, respiratory syncytial virus, and canine distemper virus, have been proposed as possible causative agents. However, no virus has been isolated from osteoclasts at involved sites.

Although the osteoblasts themselves are not abnormal, their increased activity produces disorderly new bone matrix, giving the histologic appearance of non-lamellar (woven) bone. Woven bone is not normally present in the adult, except during fracture repair, but is found in other disorders characterized by rapid rates of bone formation, such as hyperparathyroidism, renal bone disease, and fluorosis. The abnormal bone turnover results in the replacement of the normal bone macroarchitecture with a disorganized osseous structure, loss of definition between cortical and trabecular bone, areas of trabecular thickening and other areas where trabeculae are completely resorbed. The initial surge in osteoclastic activity leads to predominant bone resorption (lytic phase). This is followed by both new bone formation and continued bone resorption with lytic and sclerotic lesions in the same area (mixed phase). Finally, osteoblastic bone formation predominates, leading to the production of enlarged, osteosclerotic, coarsely trabeculated bone (sclerotic phase).

The abnormalities in bone remodeling are reflected in several biochemical changes. Although the primary pathophysiologic event is abnormal osteoclasts, no reliable index of this phenomenon is available. Serum alkaline phosphatase is the most frequently used biochemical marker for Paget's disease. It is used as an index of functional osteoblastic and, hence, as a surrogate for disease activity. Based upon clinical experience, there is a good correlation between the alkaline phosphatase response and clinical response to treatment. Reduction in serum alkaline phosphatase is associated with significant clinical improvement. Alkaline phosphatase was used as a surrogate means for assessment of the response to alendronate treatment in pagetic patients.

E. Pharmacologic Action of Alendronate

1. General

The geminal bisphosphonates are synthetic analogs of inorganic pyrophosphate, a regulator of calcium metabolism that inhibits both calcium phosphate dissolution and crystallization *in vitro*. All bisphosphonates (including alendronate) act on bone by virtue of the high affinity of their P-C-P moiety for hydroxyapatite and are capable of inhibiting osteoclastic bone resorption, although their potency varies widely. In contrast to pyrophosphate, which is rapidly metabolized by a variety of phosphatases, the P-C-P backbone of bisphosphonates is resistant to enzymatic breakdown *in vivo* and does not appear to be metabolized by any animal species so far examined.

2. Alendronate Mode of Action

The mode of action of any bisphosphonate at the molecular level has not been elucidated. At the cellular level, alendronate is localized preferentially to sites of bone resorption under osteoclasts (studied in rodents). Osteoclasts attach normally to the bone surface. The lack of a ruffled border (a convoluted membrane at the bone-osteoclast interface, indicative of active resorption) does not seem to interfere with osteoclast recruitment or attachment, but prevents osteoclast activity. When osteoclasts are seeded on bone slices *in vitro*, they acquire the ability to extrude acid (H^+). This ability is lost when the bones are pre-incubated with alendronate. Studies on the localization of radioactive ^3H -ALN in bone showed about 10-fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bones examined six days and 49 days after administration of a single dose of ^3H -ALN *in vivo* showed that normal bone was formed on top of the ALN label, which was buried inside the matrix. Based on the mode of action described above, the buried drug is not pharmacologically active; this provides the rationale for continuous, rather than intermittent, administration of the drug.

Histomorphometry showed that at the tissue level the mechanism of action involved reduction of activation frequency (the number of sites at which resorption is initiated) and increases in wall thickness (the amount of bone formed in a remodeling cycle). Histomorphometric analysis showed that, at the same dose, etidronate labeled more osteoblast surface than did alendronate.

Alendronate normalizes the elevated rate of bone turnover caused by ovariectomy in animals. Treatment of ovariectomized rats, intact rats, and ovariectomized baboons with alendronate increases trabecular bone volume and strength proportionately. In dogs and minipigs, bone formed during alendronate treatment also shows the normal, positive

relationship between bone mass and strength. The preclinical data indicate that the bone formed during alendronate therapy has normal biomechanical characteristics and is of normal quality. Even at high doses for periods up to three years, alendronate therapy has not been associated with osteomalacia, woven bone, marrow fibrosis, fractures, or other qualitative abnormalities in several animal models. Alendronate reduces bone resorption by directly inhibiting the activity of osteoclasts, with no direct effect on osteoblastic new bone formation.

F. Anticipated Clinical Benefits of Alendronate Treatment

The aim of treatment is not only to obtain biochemical control of Paget's disease, but also to treat the clinical manifestations and prevent the complications of the disease. Despite the difficulties of assessing the effects of medical treatment on the clinical manifestations of Paget's disease, several observations suggest that suppression of the biochemical manifestations of the disease significantly alters the natural history of the disorder. In addition to the histologic and radiographic improvements observed, the most convincing evidence is the sustained remission from neurologic syndromes. There appears to be a good correlation between the degree of biochemical control and the attainment of clinical remission, and this, in turn, helps to validate the use of biochemical monitoring of disease activity as a surrogate endpoint.

IV. ANIMAL PHARMACOLOGY & TOXICOLOGY

A. Nonclinical Pharmacodynamics

1. Summary

<u>Study Title</u>	<u>Species</u>
Localization in Bone (Autoradiography)	Rat, mouse
Mechanism of Action	
Treatment of Osteopenia Caused by Estrogen Deficiency, Bone Biomechanics	Rat
Prevention of Estrogen-Deficiency Bone Deficiency Bone Loss, Histomorphometry and Biomechanics	Baboons
Secondary Hyperparathyroidism and Hypercalcemia of Malignancy	Rat
Prevention of Bone Loss in Immobilization	Rat
Effects of ALN on Hyperthyroidism	Rat
Effects on Bone Formation Following	Rat

Marrow Ablation

Effects on Mineralization, Comparison to Etidronate (EHDP)	Rat
Effects on Bone, Comparison to Sodium Fluoride	Minipig
Ancillary Pharmacology	Dog, rat, mouse

2. Alendronate Effects in Estrogen-Deficient Rats

Estrogen deficiency causes increased bone turnover and cancellous bone loss in rats. Rats, 250 to 280 g, were ovariectomized and ALN was administered for 12 weeks at different doses between 0.224 mg/kg/mo s.c. (equivalent to about 1 mg/kg/day per os) to 28 mg/kg/mo s.c. The treatment completely prevented bone loss, the lowest dose increasing bone volume above that of non-ovariectomized controls. Histomorphometric analysis of bone from ALN-treated animals showed a 30% reduction in eroded surfaces (resorption) and in osteoid surface (formation), thus in bone turnover. The number of osteoclasts was not reduced, indicating inhibition of osteoclast activity, rather than recruitment. The mineral apposition rate (distance between two sequential tetracycline markers which measures mineralization) was the same in all groups.

Figure 1 Strength (Compression Load) of L6 Vertebra in Ovariectomized Rats Follow-

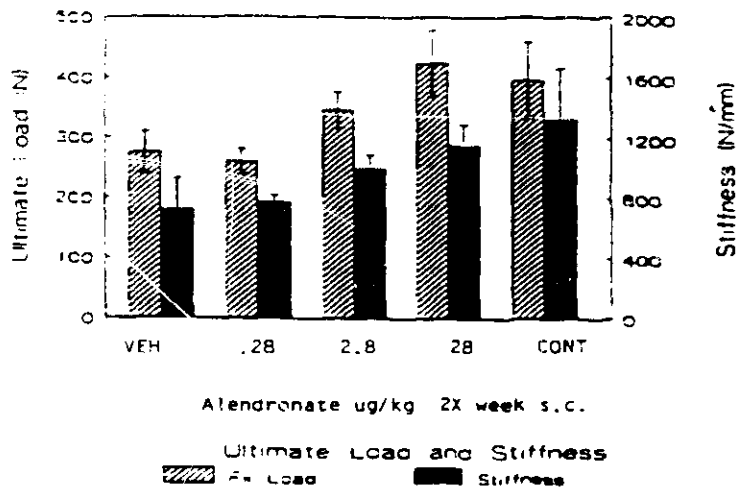


Figure 1 Strength (Compression Load) of L6 Vertebra in Ovariectomized Rats Following Six Months Treatment With Alendronate.

VEH = Non-ovariectomized group

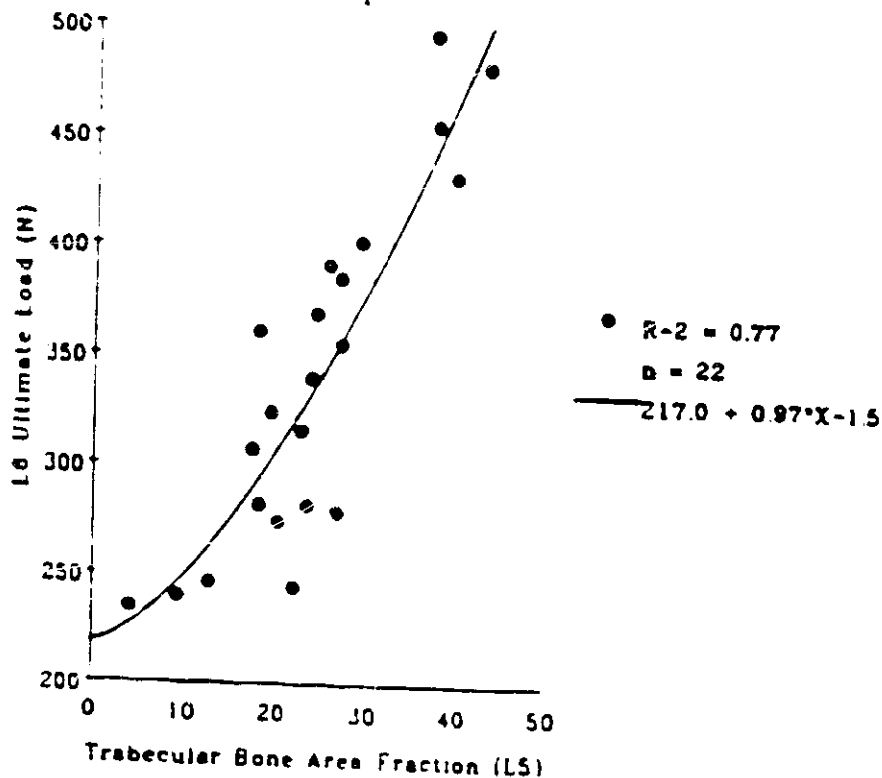
CONT = Ovariectomized saline group

Fx load in vehicle-treated animals was significantly different from the high-dose and control groups ($p < 0.05$, Tukey analysis)

Stiffness in the alendronate 0.28 g/kg group was significantly different from the high- and medium-dose groups ($p < 0.05$, Tukey analysis)

To examine ALN effects on animals which had already lost bone, treatment was started 4 months after ovariectomy. Bone strength was tested *ex vivo* in vertebrae in a compression test and in femora in a three-point bending test. ALN was given at 0, 2.8, and 28 g/kg s.c. twice weekly for 6 months. The bone strength (ultimate load) of the L6 vertebra was 30% lower in ovariectomized animals than in non-ovariectomized controls. ALN dose-dependently increased the mechanical strength of the vertebrae (Figure 1), statistically significant differences being observed at a dose equivalent to a human dose of about 6 mg/50 kg/day per os (absorption, 0.7%). There was a strong positive correlation between bone strength (ultimate load) and bone volume (area fraction) of individual vertebrae (Figure 2).

Figure 2 Relationship Between the Ultimate Load of L6 Vertebral Body and the L5 Trabecular Bone Volume in Ovariectomized Rats Following Six Months Alendronate Treatment



In another rat study, ovariectomy was carried out at 6.5 to 7 months of age, treatment was initiated six months later and was continued for one year to mimic the osteoporosis treatment population in the elderly. Animals were given 1.8 g/kg or 18 g/kg twice weekly s.c., corresponding to human doses of 3.7 and 37 mg/50 kg/d per os (0.7% absorption). At the initiation of treatment, animals had lost 39% of cancellous bone in the proximal tibia and had reached 50 to 60% of life span. Histomorphometric analysis at the end of the study showed a twofold increase in bone turnover in ovariectomized (OVX) vehicle-treated animals and reduction of turnover to control (non-ovariectomy) levels by the lower ALN dose and below controls by the higher dose. The mineral apposition rate, measured between two tetracycline markers, was not affected by treatment, showing normal mineralization. Both the total and cortical bone volume in the vertebrae were significantly increased at both treatment doses. This increase was also detected by bone mineral density measurements using Dual Energy X-ray Absorptiometry (DXA) and was associated with a significant increase in bone strength, which

showed a strong correlation with ash weight

The combined effects of estrogen replacement and ALN were examined in rats, ovariectomized at the age of 12 weeks, six months later treatment was started with either 17β -estradiol (0.83 μ g/day by pellet) or ALN (1 mg/kg/day P.O.), or both treatments together, and was continued for six months. Estrogen deficiency increased bone turnover and reduced cancellous bone volume and bone strength in the vertebrae (28% in L6). Either treatment increased bone volume and bone strength but only combined treatment increased it to control (non-ovarectomy) levels. The suppression of bone turnover produced by combined treatment was not significantly greater than that produced by ALN alone.

3 Pharmacodynamic Studies

a Lack of Metabolism in Rats and Dogs

No metabolites of alendronate were found in blood or urine.

b Absorption

Alendronate was poorly absorbed in mice, rats, dogs, and monkeys, drug concentrations in plasma were too low to be measured after an oral dose. Since alendronate was not significantly metabolized and largely deposited in bone tissues (60 to 70% of the dose) after IV administration where it had a long terminal half-life (>200 days), the absorption could be estimated from the drug concentration in bone. Based on the ratios in bone of the radiolabels from the ^{14}C -labeled oral dose and the ^3H -labeled IV reference, the absorption in fasted animals was estimated to be about 0.7% for the rat, 1.8% for the dog and 1.7% for the monkey (Table I).

Table I Absorption of Alendronate in Fasted Animals Receiving an IV Dose of ^3H -alendronate and An Oral Dose of ^{14}C -alendronate as Determined by the Isotope Ratios in the Bones Identified in the First Column

Bone Tissues	% of the Dose		
	Rats (N=6)	Dogs (N=2)	Monkeys (N=2)
Tibia	0.73 $\pm$ 0.26	1.76	1.72
Femur	0.68 $\pm$ 0.26	--	--
Fibulae	--	1.82	1.61
Mandible	--	1.85	1.70

In a similar study in non-fasted mice the extent of absorption was estimated to be about 0.12 to 0.24%. Similar values were found for non-fasted rats.

Whereas food markedly decreased the absorption of alendronate in rats, chelating agents such as EDTA enhanced absorption in a dose-dependent manner suggesting that sequestration of calcium prevents the formation of a poorly absorbed calcium-alendronate complex in the GI tract.

The concentrations of alendronate in the tibia were much higher by direct injection of the drug into the GI tract rather than by conventional gavage and in the order of jejunum > duodenum > ileum > gavage, suggesting that the absorption of alendronate occurred most readily in the upper region of small intestine

Because alendronate is a zwitterion with five different pKa values, the effect of pH on absorption was investigated. Drug was administered by gavage at pH 2 and pH 11, and directly into the duodenum at pH ranging from 2 to 11. There was no significant difference in the absorption at different pH values, indicating that ionic state had little effect on the absorption of alendronate

The poor absorption of alendronate can be attributed to its very poor lipophilicity (octanol/buffer partition coefficient = 0.0017) which prohibits transcellular transport across the epithelial barriers, and to its relatively large molecular weight (250 dalton) which hinders paracellular transport. Alterations of the integrity of the intestinal membrane may affect the absorption of alendronate. Experimental peptic ulcers induced by very high doses of mepirizole, acetylsalicylic acid or indomethacin caused a 4- to 7-fold increase in alendronate absorption in rats. The increased absorption was due to the breakdown of the gastrointestinal mucosa, as shown by proportionate increases in the urinary excretion of phenolphthalein, which is not normally absorbed from the gastrointestinal tract

c Excretion

Following IV administration (1 or 0.8 mg/kg), alendronate disappeared rapidly from the plasma of rats, dogs and monkeys in a multiphasic fashion. Approximately 30 to 40% of the dose was excreted in the urine in twenty-four hours with most of the drug being excreted in the first three to four hours. Biliary excretion of alendronate was minimal in the rat, about 0.13% of the dose in six hours after 1 mg/kg IV. These results indicate that renal excretion is the principal route of alendronate elimination

d Tissue Distribution

1) Noncalcified Tissues

Following IV administration (1 mg/kg), alendronate was widely distributed in calcified and noncalcified tissues of rats. The drug in all noncalcified tissues declined rapidly with time from about 63% of the dose at 5 min to about 5% at one hour. When the dose was raised to 30 mg/kg IV (equivalent to 210 grams orally in a 50 kg individual assuming 0.7% absorption), approximately 23% of the dose remained in noncalcified tissues 48 hours after dosing. The highest concentration of alendronate was found in the kidneys with levels persisting for at least 48 hours. Liver, lung, spleen, and stomach also had substantially higher concentrations than plasma. Similar accumulation of other bisphosphonates has also been reported by other laboratories when high intravenous doses were given. It is postulated that phagocytosis of complexes of bisphosphonates with metal ions might account for soft tissue accumulation

2) Uptake by Bone Tissues

Since alendronate is not significantly metabolized and renal excretion is the only mode of elimination, with little or no accumulation in soft tissues at low dose, it is assumed that the remainder (60 to 70% of the dose) accumulated in bone tissues. Alendronate was taken up rapidly by rat bone tissues. Peak concentrations of the drug in tibia and femur occurred about 1 hour after 1 mg/kg IV. Unlike noncalcified tissues, the concentration of drug in bones remained virtually unchanged over a 72-hour period.

In an 80-day experiment, the concentrations of alendronate in bone of rats appeared to decline in a multiphasic manner after an IV dose (1 mg/kg) with a half-life of about 30 days for the earlier phase (the 11- to 40-day period) and of the order of 200 days for the 40- to 80-day period. Urinary excretion rate in rats also exhibited multiple phases. Within the same time period, the half-lives of the urinary excretion rate were similar to those in bone, indicating that the elimination of drug from bone tissues is rate-limiting. A multiphasic profile of urinary excretion rate of alendronate with a long terminal half-life greater than 1000 days was also observed in dogs. The distribution of the drug in bone was not homogeneous. The joints of the tibia and femur had significantly higher concentrations of alendronate than the middle portions after an IV dose (0.2 mg/kg) in rats. The fore cranium had a greater concentration than the side cranium, and the lumbar vertebra had a higher concentration than the sacral vertebra (Table II).

Table II Distribution of Radioactivity in Bone Tissues of Rats Receiving an IV Dose of ^{14}C -alendronate (0.2 mg/kg)

Ra:	Concentration (g eq/g)							
	Tibia		Femur		Cranium		Vertebra	
	Joint	Middle	Joint	Middle	Fore	Side	Lumbar	Sacral
1	2.41	0.76	1.69	1.18	1.72	1.09	2.15	0.70
2	4.13	1.10	1.99	1.02	2.64	0.94	1.76	0.52
3	2.96	0.95	2.36	0.91	2.26	1.84	0.88	1.01
Mean	3.16	0.937	2.01	1.04	2.20	1.29	1.59	0.74
SD	0.88	0.170	0.33	0.14	0.46	0.48	0.65	0.24

A less than proportional increase in the concentration of alendronate in bone was observed when the drug was given intravenously at 0.1 to 50 mg/kg, suggesting saturation of uptake of the drug by bone tissues. A 500-fold increase in dose resulted in a 350-fold increase in the concentration in bone, increasing from about 1 $\mu\text{g/g}$ to 320 $\mu\text{g/g}$. However, chronic dosing using low repetitive doses with cumulative dose up to 35 mg/kg IV over a 24-day period showed no evidence of saturation.

The uptake of alendronate by bone was substantially higher, about two- to three-times at 1 mg/kg IV, in young rats (2 months old) than in old rats (12 and 20 months old). There was no significant difference in bone uptake between the 12- and 20-month-old rats. The effect of age was less when the dose was increased.

to 10 mg/kg. In general, the concentration of alendronate in the bones of male rats was higher than that in female rats by about 30 to 40%, but significant sex differences were only observed after a low dose (1 mg/kg) in young rats, not after a high dose (10 mg/kg) or in older rats.

Since alendronate is not significantly metabolized in the body and is excreted only by the kidneys, the disposition of alendronate can be described by a three-compartment model, a central compartment from which the drug is excreted renally and peripheral compartments of bone and noncalcified tissues. The uptake clearance (CL_{up}) is the ability of bone tissue to bind alendronate and is described in clearance terms (mL/min/g of bone) determined by $X_{Bn}/[AUC]$ where X_{Bn} is the amount of the drug in bone tissue and [AUC] is the area under the plasma concentration-time curve from time zero to time t.

The effects of three experimental disease states, hypo- and hypercalcemia and renal failure, on the uptake of alendronate by the bone were also studied. These disease states are known to affect calcium metabolism in bone. Experimental hypercalcemia induced by parathyroid hormone infusion caused a substantial decrease in the uptake clearance (CL_{up}) of alendronate by the tibia by a factor of 3, whereas hypocalcemia induced by thyroparathyroidectomy resulted in a significant increase in the (CL_{up}) by 60%.

Experimentally induced uremia caused no change in the (CL_{up}) at 1 mg/kg IV. The decreased bone uptake of alendronate in hypercalcemia may be due to a substantial decrease in the effective surface of hydroxyapatite in bone as a result of increased osteoclast-mediated bone resorption. Since the binding of alendronate to plasma protein is decreased as calcium is suppressed, the increased bone uptake of alendronate in hypocalcemia can be explained by an increase in the unbound fraction in plasma.

c Renal Excretion

Renal clearance of alendronate in rats decreased from 7.37 mL/min/kg at 1 mg/kg IV to 3.25 mL/min/kg at 20 mg/kg IV, at which doses alendronate had no effect on GFR, indicating that renal excretion of the drug was dose-dependent. A six-hour infusion study was conducted to establish the relationship between renal secretion and plasma concentration at steady state. Both renal clearance and net secretion decreased as steady-state plasma concentrations increased, indicating that it is secreted by an active transport mechanism.

However, high doses of cimetidine, quinine, probenecid or p-aminohippuric acid had no effect on the renal excretion of alendronate, suggesting that alendronate is not secreted by conventional anionic or cationic transport systems. In contrast, the renal clearance of alendronate was inhibited by etidronate, another bisphosphonate-pyridate, in a dose-dependent manner (Table III), indicating that these two bisphosphonates compete for an as yet uncharacterized renal transport system.

Table III Effect of Etidronate on Renal Clearance of Alendronate in Rats Receiving an IV Dose of 1 mg/kg (Mean $\pm$ SD)

Dose of Etidronate mg/kg	CL _r mL/min/kg	GFR mL/min/kg
Control (N = 6)	7.37 $\pm$ 1.62	11.9 $\pm$ 2.8
7 (N = 5)	6.00 $\pm$ 0.97	8.87 $\pm$ 0.92
14 (N = 7)	4.19 $\pm$ 1.35	8.99 $\pm$ 1.39
35 (N = 5)	1.35 $\pm$ 0.80	10.5 $\pm$ 3.0
70 (N = 5)	0.75 $\pm$ 0.15	8.23 $\pm$ 1.25

Pretreatment of rats with uranyl nitrate (5 mg/kg, IV) resulted in a significant decrease in renal function. GFR fell from the normal value of 12 mL/min/kg to 1 mL/min/kg and renal clearance of alendronate decreased from 7.4 mL/min/kg in control rats to 0.71 mL/min/kg in uremic rats. As a consequence of renal impairment, alendronate accumulated in plasma following an IV dose (1 mg/kg) and there was an increase in the concentration of the drug in bone, increasing from 9.6 g/g in the tibia of control rats to 14.9 g/g in the tibia of uremic rats. The increase in alendronate concentration in the tibia was only ~55%, despite a 10-fold decrease in both GFR and renal clearance.

Calcium plays a significant role in plasma protein binding and renal secretion of alendronate. Compared to control rats, the plasma protein binding of alendronate was substantially lower in hypocalcemic rats but unchanged in hypercalcemic rats. In both hypo- and hypercalcemic rats, the net secretion of alendronate was significantly lower by a factor of 2 to 3. The GFR was normal in hypocalcemia but significantly below normal in hypercalcemia, suggesting that hypercalcemia causes renal dysfunction. It has been reported that calcium excess is toxic to cells in general, and the kidney is particularly susceptible to hypercalcemia.

The renal handling of the model cationic and anionic compounds, tetraethylammonium bromide (TEAB) and p-aminohippuric acid (PAH), respectively, was not altered in hypocalcemic rats, but was significantly reduced in hypercalcemia associated with a reduction in GFR. Since the decreased renal secretion in hypocalcemia was only observed with alendronate, but not with TEAB and PAH, these data suggest that calcium plays an important role in the secretion of alendronate. On the other hand, the decrease in secretion of alendronate, TEAB and PAH in hypercalcemia may be due to nephrotoxicity induced by calcium excess.

f. Plasma Protein Binding

Binding of alendronate to plasma protein is species-dependent. The drug was highly bound to rat plasma protein, but not to dog, monkey and human plasma protein (Table IV).

Table IV Protein Binding of ^{14}C -alendronate to Rat, Dog, Monkey and Human Plasma Protein at Physiological pH (Mean $\pm$ SD, N=4)

Concentration		Unbound (Fraction %)			
(g/mL)	(M)	Rat Plasma	Human Plasma	Monkey Plasma	Dog Plasma
0.2	0.8	3.01	22.3	--	--
		$\pm$ 0.48	$\pm$ 4.4		
0.5	2	3.10	24.2	27.3	74.5
		$\pm$ 0.53	$\pm$ 2.4	$\pm$ 5.6	$\pm$ 5.4
1	4	3.92	21.7	38.1	80.1
		$\pm$ 0.24	$\pm$ 3.0	$\pm$ 3.7	$\pm$ 2.1
5	20	7.33	33.1	27.9	71.7
		$\pm$ 0.06	$\pm$ 3.7	$\pm$ 2.0	$\pm$ 1.6
10	40	8.85	37.0	--	--
		$\pm$ 0.19	$\pm$ 4.9		

In the case of rat plasma, the binding of alendronate was concentration-, pH- and calcium-dependent. The fraction of unbound alendronate in rat plasma (pH 7.4) increased from about 3% to 9% over the drug concentration range of 0.2 to 10 g/mL. The binding of alendronate in plasma increased with pH from about 50% at pH 6.6 to 98% at pH 8.6. Similar results were observed with rat serum albumin in isotonic phosphate buffer containing calcium at 2.5 mM.

Supplementation with calcium resulted in a substantial increase in the binding of alendronate to rat serum albumin in a calcium concentration-dependent manner. The binding of the drug to albumin was negligible in the absence of calcium, and more than 90% of the drug was bound to the protein when the calcium concentration was 1.5 mM. The addition of EDTA to plasma caused a significant decrease in the binding of alendronate to plasma protein in an EDTA concentration dependent manner. Complete inhibition of binding was observed when the EDTA concentration was greater than 2 mM. These results demonstrate that calcium plays an important role in the binding of alendronate in rats.

As in rat plasma, the binding of alendronate to human plasma protein was also concentration-, pH- and calcium-dependent. An unexpected finding in the binding of alendronate to human plasma is that the binding of alendronate to purified human serum albumin was more extensive than to plasma; the unbound fraction was about 22% in human plasma and only 4.5% in purified albumin. The difference suggests the presence of displacers in plasma. To study further the displacer hypothesis, binding of alendronate to human serum albumin was determined in isotonic buffer and protein-free plasma water obtained from human plasma. The unbound fraction in an albumin/plasma water preparation was much greater (ca 7-fold) than the unbound fraction in an albumin/isotonic buffer preparation, indicating that displacers are present in human plasma.

4 Overall Conclusions

a Alendronate is poorly absorbed after oral administration. The extent of dose absorbed is about 0.2% for the mouse, 0.7% for the rat, 1.7% for the monkey, and 1.8% for the dog. Absorption of alendronate occurs most readily in the upper region of small intestine.

b Whereas food markedly decreases the absorption of alendronate in rats, chelating agents such as EDTA enhance absorption in a dose-dependent manner, suggesting that EDTA, by sequestration of calcium, prevents the formation of a poorly absorbed calcium-alendronate complex in the GI tract. A greater than proportional increase in the absorption in the dose range of 2 to 40 mg/kg is in agreement with this conjecture.

c There is no significant difference in the absorption at different pH values ranging from 2 to 11, indicating that ionic states have little effect on the absorption of alendronate.

d Based on the observations of absorption studies, it is concluded that the poor absorption of alendronate is attributed to both its poor lipophilicity (octanol/buffer partition coefficient = 0.0017) which prevents transcellular transport across the epithelial barriers, and its relatively large molecular weight (250 dalton) which hinders paracellular transport.

e HPLC radiohistograms of radiolabeled materials in bone and urine from rats and dogs receiving ³H- or ¹⁴C-alendronate indicate that alendronate is not significantly metabolized in the body.

f Approximately 30 to 40% of the dose is excreted in the urine in 24 hours after IV administration (1 mg/kg) in rats, while biliary excretion of alendronate is minimal (<1%), indicating that renal excretion is the only significant route of alendronate elimination.

g Alendronate is distributed widely in calcified and noncalcified tissues. Drug concentration in the noncalcified tissues declines very rapidly with time from about 63% of the dose at 5 min to about 5% in one hour after IV administration (1 mg/kg) in rats.

h Unlike noncalcified tissues, the concentration of alendronate in bones peaks at about one hour after dosing and declines very slowly with a terminal half-life greater than 200 days in rats and 1000 days in dogs.

i A less than proportional increase in the concentration of alendronate in bone is observed in rats when the drug is given intravenously at 0.1 to 50 mg/kg, suggesting saturation of uptake of drug by bone tissues. However, chronic dosing with cumulative dose up to 35 mg/kg IV over a 24-day period shows no evidence of saturation.

j Uptake of alendronate by the bone is lower in old rats (12 and 20 months) than in young rats (2 months) by a factor of 2 to 3. Bone uptake is lower in female rats than in male rats by about 30 to 40%, but this sex difference is only observed at low doses in young rats.

k The excretion of alendronate by the kidney is concentration- and dose-dependent, and saturable, indicating that it is secreted by an active transport mechanism

l High doses of cimetidine, quinine, probenecid, or p-aminohippuric acid do not affect the renal excretion of alendronate, suggesting alendronate is not secreted by anionic or cationic transport systems

m In contrast, renal clearance of alendronate is inhibited by etidronate, another bisphosphonate, in a dose-dependent manner, suggesting that these two bisphosphonates compete for an as yet uncharacterized renal transport system

n Binding of alendronate to plasma protein is species-dependent. The drug is highly bound to rat plasma protein, but not dog, monkey and human plasma protein

o In the case of rat plasma, the binding of alendronate is concentration-, pH- and calcium-dependent. The fraction of unbound alendronate in rat plasma (pH 7.4) increases from about 3% to 9% over the drug concentration range of 0.2 to 10 µg/mL. The binding of alendronate to plasma increases with pH from about 50% at pH 6.6 to 98% at pH 8.6

p The binding of alendronate in rat serum albumin is negligible in the absence of calcium, but more than 90% of the drug binds to the protein when the calcium concentration is 1.5 mM. The addition of EDTA to rat plasma causes a significant decrease in the binding of alendronate to plasma protein in an EDTA concentration-dependent manner. Complete inhibition of binding is observed when the EDTA concentration is greater than 2 mM.

q Like rat plasma, the binding of alendronate to human plasma protein is also concentration-, pH- and calcium-dependent. An unexpected finding in the binding of alendronate to human plasma is that the binding of alendronate to purified human serum albumin is more extensive than to plasma; the unbound fraction is about 22% in human plasma and only 4.5% in purified albumin.

V. Clinical Studies of Paget's Disease

A. Overview of Paget's Studies:

1. Overview of Clinical Efficacy and Safety

The data supporting the efficacy and safety of alendronate in the treatment of Paget's disease of bone are derived primarily from four studies, two each in Phases II and III. These studies are referred to as the Dose-Ranging and Treatment Duration Studies, and the Etidronate Comparison and Placebo-Controlled Studies, respectively.

a. Endpoints

Serum alkaline phosphatase was the primary efficacy endpoint. The secondary efficacy endpoints were urinary resorption markers, pain score, functional impairment score, and radiologic changes in osteolytic lesions. Safety endpoints included standard clinical and laboratory assessments as well as bone

histomorphometry.

b. Efficacy

Treatment with daily oral alendronate 40 mg for six months markedly and significantly reduced serum alkaline phosphatase relative to baseline, placebo, and etidronate. Alendronate was similarly effective in all patient subgroups studied, including subgroups stratified according to baseline alkaline phosphatase and prior use of other bisphosphonates. Alendronate also induced radiologic improvement of pagetic osteolytic lesions and markedly reduced urinary resorption markers (deoxypryridinoline and the cross-linked N-telopeptides of type I collagen, both corrected for creatinine).

c. Safety

The safety profile of oral alendronate 40 mg daily is in most regards similar to that of placebo. Musculoskeletal pain, the most common clinical adverse experience increased relative to placebo, was generally mild to moderate and only occasionally led to patient discontinuation. Upper gastrointestinal adverse experiences consistent with local irritation of the gastrointestinal mucosa also occurred with alendronate and rarely led to discontinuation. The most common of these, abdominal pain, was increased compared with placebo.

Laboratory adverse experiences, such as asymptomatic, transient decreases in serum calcium and phosphorus, reflect alendronate's mechanism of action. Histomorphometry revealed that alendronate did not impair mineralization and that, overall, alendronate-treated bone was of normal quality.

d. Conclusions

Oral alendronate 40 mg/day for six months treated Paget's disease of bone effectively, as reflected by marked reductions in serum alkaline phosphatase in most patients, normalization of alkaline phosphatase in the majority of patients, and improvement in osteolytic lesions. It had a favorable safety and tolerability profile.

B. Efficacy

1. Rationale for the Clinical Efficacy Program in the Treatment of Paget's Disease of Bone

a. Selection of Serum Alkaline Phosphatase as the Primary Endpoint

Paget's disease of bone is a skeletal disorder characterized by focal increases in the rate of bone remodeling. Excessive osteoclastic bone resorption, followed by a secondary increase in osteoblastic activity, leads to the replacement of normal bone architecture by disorganized, enlarged, and weakened osseous structure. The increase in the rate of bone remodeling is reflected in several biochemical abnormalities that may be used to monitor the activity of the disease. Serum alkaline phosphatase, which reflects the secondary increase in osteoblastic bone formation seen in active Paget's disease, is the most frequently used biochemical marker for assessment of disease activity and has the advantage of being almost universally available as a routine test to practicing physicians.

Bone alkaline phosphatase is derived from osteoblasts. In healthy individuals, about half of the total serum alkaline phosphatase originates from bone, with the rest mainly from the liver. Minor sources include the intestine and the placenta in pregnancy. In Paget's disease, most of the increase in total serum alkaline phosphatase is accounted for by the bone-derived isozyme. In metabolic bone disorders, serum activity of alkaline phosphatase is an index of the number of functional osteoblasts.

Serum alkaline phosphatase is relatively constant in untreated patients with Paget's disease, with a less than 10% coefficient of variation of repeated measurements over a period of many months. The activity of this enzyme and radiographic abnormalities may increase over several years; there is good correlation between serum alkaline phosphatase and the extent of skeletal involvement in Paget's disease. Thus, alkaline phosphatase measurements are useful in monitoring the effects of treatment. Currently approved therapies for the treatment of Paget's disease generally reduce this parameter by about 40 to 50% from baseline. Due to the variable clinical presentation of Paget's disease, it has been difficult to clearly correlate changes in biochemical markers induced by treatment with improvement in any specific clinical endpoint. However, based upon clinical experience, it is apparent that the vast majority of patients with symptomatic Paget's disease who respond to therapy with a marked fall in alkaline phosphatase will also demonstrate positive clinical responses, such as relief of pagetic pain, halting in the progression of osteolytic lesions, and resolution of neurological syndromes. Conversely, poor biochemical responses are associated with suboptimal or absent clinical responses. Thus, serum alkaline phosphatase provides an objective, reliable, and widely available index of disease severity as well as an indication of the efficacy of a particular therapeutic regimen.

Urinary markers of bone resorption (deoxypyridinoline, hydroxyproline, and N-telopeptide of type I collagen) can be used as a means to assess response to anti-pagetic treatment but, with the exception of hydroxyproline, are not as widely available as alkaline phosphatase and their measurements have lower precision. For this reason markers of bone resorption were secondary efficacy endpoints.

b Patient Selection

The patients selected for the Phase II Paget's disease clinical efficacy studies were men and women between the ages of 18 and 85 years with clinically active Paget's disease of bone as documented by standard clinical and radiologic criteria and a serum alkaline phosphatase above the upper limit of normal (ULN). All the patients were otherwise in good health. Patients who had received anti-pagetic therapy with calcitonin within three months of study start were excluded. Additionally, patients who had received bisphosphonate or plicamycin treatment within the last six months were excluded unless their alkaline phosphatase had increased from its posttreatment nadir by at least 66% of the absolute decrease produced by the prior treatment.

The selection criteria for patients in the Phase III Studies were similar to those of the Phase II Studies except that all the patients had to have baseline serum alkaline phosphatase at least two times the ULN as measured in the central

laboratory. If the patient had been previously treated with a bisphosphonate or plicamycin, the baseline serum alkaline phosphatase had to be at least four times the ULN and must have increased by at least twice the ULN since the most recent posttreatment nadir. These stratifications were applied because both the activity of Paget's disease and previous bisphosphonate treatment influence the response of serum alkaline phosphatase to treatment. Due to these differences in selection criteria, the patients in the Phase III Studies tended to have more active or extensive disease. Patients with vitamin D deficiency or with any evidence of osteomalacia were also excluded from both phases. Overall, the population studied was representative of the disease population requiring treatment. Patients with very mild elevations of, or normal, alkaline phosphatase were excluded in the Phase III Studies because they generally do not require therapy. More than 90% of all patients recruited were white, reflecting the relative rarity of the disease among non-white races.

c. Study Duration

The three considerations in selecting the appropriate study duration were the length of time required (1) to demonstrate a clinically meaningful benefit, (2) to reach a new steady state of effect on bone turnover from which the likely longer-term effects of treatment could be assessed, and (3) to address adequately any safety concerns.

This NDA contains data of the safety and efficacy of alendronate treatment for six months in Paget's disease. The rationale for selecting a six-month duration is:

(1) Based on studies of other antipaget treatments, six months is adequate to detect a treatment effect to decrease serum alkaline phosphatase in patients with Paget's disease; usually maximal responses are observed by six months. The longer follow-up of up to six months off treatment in the Phase II Studies provides an assessment of the duration of the response to alendronate treatment.

(2) Irritation of the upper gastrointestinal mucosa at higher doses of alendronate was generally manifested within the first weeks to months of treatment and was the only likely safety concern raised by the early clinical studies. Therefore, a six-month study duration should be more than adequate to examine the effects of continuous, high-dose alendronate on the upper gastrointestinal tract in patients with Paget's disease.

d. Dosing Schedule

Oral bisphosphonates, including alendronate, are relatively poorly absorbed, particularly if food or liquids other than water are present in the upper gastrointestinal tract at the time of dosing.

In the Phase II Studies, based on recommendations for other bisphosphonates, alendronate was administered either two hours prior to or two hours after breakfast. Two subsequent bioavailability studies demonstrated that, in comparison to a two-hour postdosing interval, administration of alendronate one hour before a standardized breakfast reduced its oral absorption by approximately 30 to 40%. Still another study suggested that dosing 30 minutes before breakfast,

although decreasing absorption, still permitted adequate absorption of drug. In the same studies, dosing alendronate either with, or two hours after, a standardized breakfast reduced its oral absorption by 90% or more. Considering these results, and assuming that requiring a two-hour wait from the time of dosing to breakfast might result in poor patient compliance, dosing instructions for the Phase III Placebo-Controlled Study incorporated the one-half hour pre-breakfast timing. However, in the Etidronate Comparison Study, patients were instructed to consume study medication at least two hours before breakfast for consistency with the dosing recommendations for etidronate and to maintain the double-blind. Despite the different dosing recommendations, alendronate was equally effective in decreasing serum alkaline phosphatase in the two Phase III Studies.

2 Design of Clinical Studies

a Comparison of Protocol Designs

The designs of the four Paget's Disease Studies are summarized in Table V. The Phase II Dose-Ranging Study, Protocol 015, was divided into three periods. The first was a two-week period, during which the patients were screened for inclusion and exclusion criteria and informed consent was obtained. The second treatment period was a 20-week oral dosing period with alendronate doses of 20, 40, and 80 mg, administered for 12 weeks followed by placebo for 8 weeks, with monthly safety and efficacy (biochemical, radiologic, and symptomatic) evaluations. The third period was 24 weeks of continued monitoring for safety and for the persistence of biochemical efficacy. The original design of the other Phase II study, the Treatment Duration Study, Protocol 024, required that all 60 patients entered into the study be given 80 mg/day alendronate as two 40 mg tablets for either three or six months. However, safety concerns arising from the 40 mg dose in the Phase IIb Osteoporosis Study indicated that the 80 mg dose might be associated with significant upper gastrointestinal adverse effects. Thus, the protocol was changed so that the last 30 patients entered were given alendronate 40 mg/day as one 40 mg tablet for either three or six months. Patients were then followed off drug for an additional six months to assess the duration of the biochemical response.

Table V Design of Paget's Disease Studies

Protocol Phase	Study Title	Dose-Ranging	Treatment Duration	End-point Comparison	Placebo-Controlled
		015 II	024 II	056 III	059 III
Treatment duration		3 months	3 to 6 months	6 months	6 months
Study duration		44 weeks	12 months	6 months	12 months ^a
Alendronate (Al 5) doses (mg)		20, 40, 80	40, 80	40	40
Patients enrolled (Al N)		51*	60**	42	27
Patients enrolled (PBO or comparative agent)				47***	28
Total patients enrolled		31	60	89	55
Age range (years)		48 to 83	44 to 84	43 to 85	49 to 87
Males		15	29	58	31
Females		16	31	31	24
Primary efficacy endpoint		AlP	AlP	AlP	AlP
Secondary biochemical efficacy endpoint		DPYR	HYPRO	DPYR	NIX
AlP normal range (U/L)		30 to 90	35 to 105	39 to 117	50 to 136

An open-label Phase II Study, Protocol 005, is considered in Section on Safety, but not in this section for several reasons. First, this was not a Merck-designed study and Merck acquired the data after the fact. Only 9 of the 54 patients received oral therapy in addition to IV therapy, and the free acid formulation administered orally was not comparable to the formulation used in the four other studies that constitute the basis of the efficacy conclusions. Furthermore, the duration of oral therapy was only 27 to 42 days (70 days in one patient). Finally, no conclusions were drawn regarding the efficacy of the oral dose.

^a A 14-planned six-month interim analysis is presented here only.

- * Counts include 21 patients who received alendronate for 12 weeks followed by placebo for 8 weeks, 7 who received placebo for 8 weeks followed by alendronate for 12 weeks, and 3 who received open-label alendronate (80 mg)
- ** Counts include 30 patients who received open-label alendronate for 3 months followed by placebo for 3 months
- *** Endronate disodium 400 mg/day

AlP = Alkaline phosphatase
 DPYR = Deoxypyridinoline
 HYPRO = Hydroxyproline
 NIX = N = Cross-linked telopeptide of type I collagen
 PBO = Placebo

The Phase III program included the U.S. Etidronate Comparison Study, Protocol 056, and the multinational Placebo-Controlled Study, Protocol 059. The Etidronate Comparison Study was a randomized, double-blind, stratified, parallel-group study to evaluate the safety, tolerability, and clinical and biochemical efficacy of daily oral alendronate 40 mg in 89 patients with Paget's disease of bone in comparison with daily oral etidronate 400 mg/day. Treatment with either agent was continuous for six months. The study was conducted in 11 centers. The Placebo-Controlled Study was a randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and clinical and biochemical efficacy of daily oral alendronate 40 mg in 55 patients with Paget's disease. The study was conducted at three centers.

Patients in the Phase III Studies received calcium and vitamin D supplements containing 450 to 500 mg calcium as the carbonate and 400 to 600 IU of vitamin D, respectively, which were taken daily with the evening meal. These supplements were not to be taken within four hours of the study medication.

b Rationale for Dose Selection

The treatment regimen of alendronate 40 mg/day for six months for the Phase III Studies was selected for several reasons based on results of the Phase II Studies. In the Dose-Ranging Study, alendronate 20 mg/day for three months clearly had suboptimal effects on serum alkaline phosphatase, whereas 80 mg/day was highly effective. The effects of alendronate 40 mg/day for three months were intermediate between those of 20 and 80 mg. However, in the Phase IIb Osteoporosis Study, a higher incidence of upper gastrointestinal adverse experiences was noted in patients receiving alendronate 40 mg relative to patients on lower doses or placebo. Based upon this relationship between dose and tolerability, it was considered likely that the 80 mg dose would have greater potential for upper gastrointestinal side effects. This was one of the reasons it was decided to limit the dose for treatment of Paget's disease in the Phase III Studies to a maximum of 40 mg, but to extend therapy to six months to achieve a total dose equivalent to 80 mg daily for three months.

In the Treatment Duration Study, patients received alendronate 40 or 80 mg for three or six months. Patients treated with alendronate 40 mg/day for six months showed a 63% decrease in serum alkaline phosphatase at the end of the treatment period, versus a 55% decrease observed in the group receiving 40 mg alendronate for only three months. In addition, all patients in the six-month 40 mg group responded to treatment, as defined by a decline in serum alkaline phosphatase of at least 60% from baseline or to within the normal range, whereas two patients in the three-month treatment group failed to respond. This evidence that longer treatment produced greater efficacy was another reason for selecting 40 mg/day for six months as the most appropriate dosing regimen.

c Serum Alkaline Phosphatase

As noted above, serum alkaline phosphatase was selected as the primary efficacy endpoint in all the Paget's disease clinical studies. Serum alkaline phosphatase was measured at baseline and at all subsequent visits for each of the studies.

d Secondary Endpoints

1) Urinary Resorption Markers

Several urinary markers are available for assessment of bone resorption in Paget's disease. The urinary bone resorption markers assayed in the Paget's disease studies were hydroxyproline and deoxypyridinoline, measured by HPLC, and cross-linked N-telopeptide of type I collagen (NTX), measured by immunoassay.

Hydroxyproline is derived mostly from degradation of collagen by collagenases. Since half of human collagen is found in bone, and in Paget's disease bone resorption accounts for most of collagen breakdown, excretion of hydroxyproline can be used as a marker of activity of Paget's disease. However, dietary sources of collagen also increase urinary hydroxyproline excretion. Furthermore, urinary hydroxyproline is poorly correlated with bone resorption when assessed by calcium kinetics or bone histomorphometry and is a less sensitive index than alkaline phosphatase. Therefore, urinary hydroxyproline was used only as a secondary marker in the Phase II Studies.

More specific and more sensitive markers of bone collagen degradation are the pyridinium cross links. Although their assays are not yet well standardized or generally available they are useful markers of bone resorption. Deoxypyridinoline is a useful and highly specific marker of bone resorption, which is not derived in significant quantities from nonosseous tissues. Pyridinoline is more abundant and more easily measured but is slightly less specific to bone than deoxypyridinoline and, therefore, deoxypyridinoline was used as a secondary endpoint in the Dose-Ranging Study and in the Etidronate Comparison Study.

In the Placebo-Controlled Study, urinary N-telopeptide (NTX) excretion was measured by immunoassay. The N-telopeptide intermolecular cross-linking domain of bone type I collagen (NTX) is a pyridinoline-containing fragment excreted in the urine and provides a quantitative index of the total bone-derived pyridinium cross links. The N-telopeptide is estimated to contain about 60% of the total deoxypyridinoline in human bone type I collagen. As such, NTX can be used as a quantitative measure of the total skeletal rate of bone resorption. Results of the NTX immunoassay can be expressed as equivalent moles of bone collagen (BCE), normalized for creatinine. These units have the merit of being more readily interpretable in terms of the mass of bone resorbed.

2) Pain Score

Pagetic pain was evaluated in the Phase II Dose-Ranging Study by pagetic pain index (Courts Index) of Delmas and Meunier. In the two Phase III Studies, pain was assessed with a Brief Pain Inventory questionnaire, completed by the patients at each study visit. The Brief Pain Inventory was used in place of the pagetic pain index because the Inventory had been employed in other alendronate clinical studies and has more extensive use and validation than the pagetic pain index.

3) Functional Impairment Score

In the Phase III Studies, the patients' functional impairment was assessed by the seven Pain Interference questions of the Brief Pain Inventory.

4) Radiologic Changes in Osteolytic Lesions

The earliest phase of Paget's disease is characterized by osteolytic lesions, followed by a phase of predominant bone formation. The typical radiographic presentation is mixed areas of focal bone resorption and formation in a disorderly pattern. For each patient in the Phase III Studies, radiologic changes in osteolytic lesions were evaluated by a single central expert radiologist, who, blinded to film sequence, scored each pair of radiographs (representing baseline and six months of treatment) on a scale of 1 to 5, where 1 indicated definite improvement and 5 definite worsening (Table VI). The scores were inverted (e.g., 5 became 1) if the film labeled "A" was the six-month film and "B" was the baseline film. Up to five pagetic bones were evaluated for each patient, and, when more than one long bone was analyzed, the final score represented the average of all bones assessed.

Table VI Radiologic Changes in Osteolytic Lesions

Score	Assessment
1	Osteolysis definitely better at Month 6
2	Osteolysis probably/marginally better at Month 6
3	No apparent difference in osteolysis
4	Osteolysis probably/marginally worse at Month 6
5	Osteolysis definitely worse at Month 6

e Effects on Mineral Metabolism

In the Phase III Studies, changes in mineral metabolism homeostasis were evaluated by examining the change from baseline in calcium, unadjusted and corrected for serum albumin, and phosphate.

f Duration of Response Following Treatment Discontinuation

In the Treatment Duration Study, patients were followed for six to nine months and in the Dose-Ranging Study for approximately eight months, after the cessation of active treatment. Continued efficacy was assessed by periodic measurements of serum alkaline phosphatase.

3. Statistical Methodology

This is evaluated in detail in the report by D. Marticello, Biomathematician.

a Approach to Efficacy Analyses

The results presented in the Clinical Study Reports for the Treatment Duration Study and the two Phase III Studies focused on Month 6, the primary efficacy timepoint. In the Dose-Ranging Study, the primary endpoint was Week 12.

Two approaches to the analysis of efficacy data were used, intention-to-treat and per-protocol. These approaches differed in the handling of protocol deviations and dropouts. The principal analysis was intention-to-treat. This means that all patients with a baseline measurement and at least one on-treatment measurement were included in the analysis. In addition, in cases where at least one on-treatment data point existed, if subsequent data

were missing, data from the last available measurement were carried forward within each group

Per-protocol analyses excluded patients based on a set of prespecified criteria (e.g., dropouts, noncompliers) and did not carry data forward

At the primary timepoints in the studies, 84% confidence intervals were computed for the mean percent change in each treatment group. If the intervals for each of the treatment groups did not overlap, then the difference between the means was significantly different from zero at the 5% level.

b. Treatment Comparisons

Treatment effects were assessed with an analysis of variance (ANOVA) model. The response variable was percent change in alkaline phosphatase from baseline and the explanatory variables were treatment group and study center in the Treatment Duration Study and in the Placebo-Controlled Study and strata in the Etidronate Comparison Study, defined by prior bisphosphonate use and levels of serum alkaline phosphatase at baseline. In the Dose-Ranging Study, the 20, 40, and 80 mg dose groups were compared with placebo using the Tukey trend test adjusted for multiplicity.

Parametric model assumptions were tested by visual examination of the residual plots, the Kolmogorov-D statistic for verification of the normality, and the Levene's test for the homogeneity of variance. Nonparametric ANOVA based on normalized ranks were used to corroborate the parametric analysis. All computations were done using SAS.

c. Within-Group Tests

All within-group tests were performed using a paired t-test. Within-group p-values ≤ 0.05 are considered significant.

d. Analysis of Biochemical Efficacy Parameters

The primary efficacy endpoint in all Paget's Studies was the percent change from baseline in serum alkaline phosphatase. Baseline was defined as the average of data collected within 100 days prior to treatment initiation. Secondary efficacy endpoint for serum alkaline phosphatase was the prevalence of response, defined as either normalization or at least a 60% reduction from baseline. Percent changes from baseline were evaluated for several urinary resorption markers: deoxypyridinoline, hydroxyproline, and N-telopeptide, each expressed as a ratio to urinary creatinine.

Strata in the Etidronate Comparison Study were defined by bisphosphonate use and levels of serum alkaline phosphatase at baseline:

- (1) Patients never treated with any bisphosphonate or plicamycin and having a serum alkaline phosphatase at least four times the ULN.
- (2) Patients never treated with any bisphosphonate or plicamycin and having a serum alkaline phosphatase between two and four times the ULN.
- (3) Patients previously treated with any bisphosphonate or plicamycin and having a serum alkaline phosphatase at least four times the ULN.

In the Phase III Studies, the preferred statistic for drawing inferences about the differ-

ences in the proportion of responders or normalizers was the odds ratio. The odds ratio is a commonly used measure of the relative probabilities of a condition. For each treatment group, the odds of being a responder at a specific timepoint were computed as the proportion of responders divided by the proportion of nonresponders. The odds ratio is the odds of responding among the alendronate-treated patients divided by the odds of responding by etidronate- or placebo-treated patients. An odds ratio significantly greater than 1 would be evidence that the proportion of responders in the alendronate group is greater than that in the etidronate or placebo group.

The Mantel-Haenszel estimate of the odds ratios, controlling for center and stratum effect, was used to evaluate the difference between the two treatment groups at the last timepoint. The Breslow-Day Test was used to test for homogeneity of the odds ratios across stratum or center.

Since there were no responders or normalizers in the placebo group in the Placebo-Controlled Study, the odds ratio was not computed in that study.

e. Analysis of Pain Score and of Functional Impairment

In the Phase III Studies, the Brief Pain Inventory was administered to each patient. At each visit, a mean pain measurement score, using Questions 2 through 5, was computed for each patient who answered at least three of the four questions. The functional impairment score for each patient was computed as the mean score of Sections a) through g) of Question 7, if at least five of the seven questions were answered.

The effects of alendronate, etidronate, and placebo on pain and functional impairment as assessed by the Brief Pain Inventory were compared. Changes from baseline in the bone pain assessment and the interference scores were evaluated at Month 1 (in the Etidronate Comparison Study only) and at Months 3 and 6 in both Phase III Studies.

The endpoints, change from baseline in mean pain score and change from baseline in mean functional impairment score at Month 6, were both considered as secondary endpoints. Assessment of these data was performed for patients reporting some pain or functional impairment at baseline.

Analgesic consumption at Month 6 in the two treatment groups was compared. Analysis of covariance was performed to analyze between-group changes in mean scores of bone pain. In addition to the terms for treatment group and stratum/center, analgesic consumption at Month 6 was included in the models as covariates.

f. Analysis of Radiologic Changes in Osteolytic Lesions

The effects of alendronate versus etidronate and versus placebo on osteolysis at Month 6 were assessed in a subgroup of patients who had at least one osteolytic lesion at baseline in the Etidronate Comparison and Placebo-Controlled Studies, respectively.

A two-way ANOVA with radiograph scores as the response variable or the treatment groups as a factor was used to estimate the least-squares means for the treatment groups. These means were adjusted for the stratum effect (in the Etidronate Comparison Study) and for study center effect (in the Placebo-Controlled Study).

g Pooled Analyses

Data were pooled post hoc to obtain better point and interval estimates in the analysis of change from baseline for pain score and functional impairment for alendronate-treated patients in the two Phase III Studies. Consistency of change from baseline in alendronate-treated patients was assessed by examining the protocol effect in an ANOVA model. Analgesic consumption was also included in the model. No formal comparison between alendronate and etidronate or alendronate and placebo was made using the pooled data. A similar pooling was done for the data on radiologic changes in osteolytic lesions and selected laboratory safety parameters.

To explore the relationship between selected baseline variables or use of concomitant medications at any time during the study and percent change from baseline in serum alkaline phosphatase at Month 6, data from patients treated with alendronate in the Phase III Studies were pooled. Mean percent change and 95% confidence intervals are reported.

4 Efficacy of Treatment

The activity of Paget's disease is commonly monitored by the level of serum alkaline phosphatase. Data are provided for the four studies in which three-month and six-month data analyses were performed. Of the four studies, the Phase III Studies are considered the most important due to their size and the inclusion of a parallel control group.

a Primary Endpoint: Serum Alkaline Phosphatase--Percent Change From Baseline

(1) Baseline

Table VII lists separately the baseline values for the four protocols by treatment group. The average age of all the patients in the studies was approximately 70 years and is representative of the population of people with Paget's disease, who tend to be elderly. The entry criteria for serum alkaline phosphatase varied among the protocols and hence there is some variation in the mean or median serum alkaline phosphatase across protocols. However, within each study, the median values for serum alkaline phosphatase were similar for the treatment groups that were compared. Comparisons were performed within but not across the 80 and 40 mg cohorts, which were recruited separately.

Although all patients in the two Phase III Studies were required to have a baseline serum alkaline phosphatase at least twice the ULN, some patients with symptomatic disease (12 of 69 on alendronate, 7 of 47 on etidronate, and 5 of 28 on placebo) were admitted with slightly lower values. These patients were technically protocol violators (and therefore excluded from the per-protocol analysis), but enhanced the representativeness of the population studied.

Table VII Summary of Baseline Serum Alkaline Phosphatase (U/L) Values
Intention-to-Treat Approach

Daily Treatment	N	Age (Years)		Serum Alkaline Phosphatase (U/L)			
		Mean	SD	Mean	SD	Median	Range
Dose-Ranging Study (015)							
ALN 20 mg	7	69.9	8.0	353.4	285.2	228.5	(167.0 to 985.5)
ALN 40 mg	8	65.0	10.0	373.9	201.8	303.5	(180.0 to 683.0)
ALN 80 mg	6	68.7	12.1	354.8	200.4	297.3	(154.0 to 713.0)
Placebo	7	70.0	6.7	301.4	92.3	313.0	(185.5 to 400.0)
Treatment Duration Study (024)							
ALN 40 mg 3 month	15	72.3	7.9	252.6	141.7	219.0	(105.0 to 599.5)
ALN 40 mg 6 month	15	68.8	9.8	418.3	795.1	207.5	(119.5 to 3285.0)
ALN 80 mg 3 month	15	69.1	7.2	635.1	787.2	319.0	(103.0 to 2987.5)
ALN 80 mg 6 month	15	71.5	6.8	522.4	412.6	313.5	(114.0 to 1432.5)
Etidronate Comparison Study (056)							
ETD 400 mg	47	69.4	8.0	623.1	383.5	486.7	(151.0 to 1770.0)
ALN 40 mg	41	68.2	8.6	757.4	702.1	533.0	(153.0 to 4135.0)
Placebo-Controlled Study (059)							
Placebo	27	68.8	9.7	602.2	385.4	501.0	(204.0 to 1729.5)
ALN 40 mg	27	70.9	7.0	680.0	396.1	574.0	(193.5 to 1582.5)
ALN = Alendronate ETD = Etidronate							

(2) Month 6 Studies

Table VIII reports the % change from baseline at Month 6, the primary timepoint in the Treatment Duration Study, Placebo-Controlled Study, and Etidronate Comparison Study. All four groups in the Treatment Duration Study reported a highly significant mean % change from baseline. Within each of the cohorts, the difference between the treatment groups was not significant, although in both cohorts the reduction in serum alkaline phosphatase was numerically greater in those receiving six months versus three months of therapy with alendronate. This difference approached significance in the 80 mg cohort ($p = 0.09$).

In the Etidronate Comparison Study, the difference in the mean % change from baseline between the alendronate- and etidronate-treated groups was significant, ($p < 0.001$). The % change from baseline in the alendronate-treated group was consistent across strata. In contrast, the decrease observed in the etidronate group was smaller in patients with a baseline alkaline phosphatase greater than four times the ULN.

In the Placebo-Controlled Study, there was also a highly significant difference in the % change from baseline between the alendronate and placebo groups ($p < 0.001$). The reduction in the alendronate group of 72.5% is consistent with that seen in the Etidronate

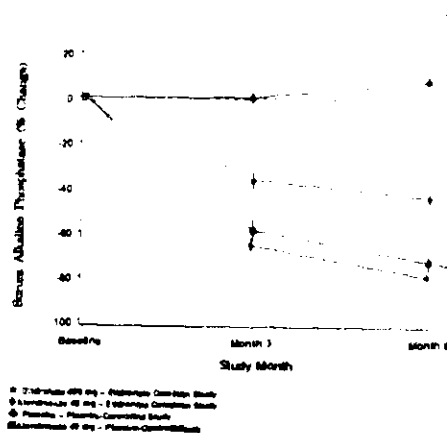
Comparison Study In the placebo group, there was a small increase in serum alkaline phosphatase

Table VIII Serum Alkaline Phosphatase (U/L) Analysis of Percent Change From Baseline at Month 6 Intention-to-Treat Approach

Daily Treatment	N	Mean	Mean	Adjusted 84% CI	Between Groups
Dose-Ranging Study (015)^a					
ALN 20 mg	6	-29.5	-29.5	(-40.6, -18.4)	
ALN 40 mg	7	-50.4	-50.4	(-60.6, -40.1)	
ALN 80 mg	5	-68.1	-68.1	(-80.2, -55.9)	p = 0.011 ^a
Treatment Duration Study (024)					
ALN 40 mg 3 month	11	-55.4	-59.5	(-68.1, -50.9)	p = 0.806 ^b
ALN 40 mg 6 month	14	-62.8	-61.5	(-68.8, -54.2)	
ALN 80 mg 3 month	12	-62.4	-63.2	(-72.8, -53.5)	p = 0.090 ^b
ALN 80 mg 6 month	14	-79.1	-79.1	(-87.9, -70.3)	
Etidronate Comparison Study (056)^c					
ETD 400 mg	47	-43.9	-45.2	(-52.2, -37.2)	
ALN 40 mg	41	-79.0	-79.3	(-82.1, -76.1)	p < 0.001 ^c
Placebo-Controlled Study (059)^d					
Placebo	27	8.0	16.8	(-1.8, 39.0)	
ALN 40 mg	27	-72.5	-70.8	(-75.2, -65.6)	p < 0.001 ^d
^a Patients received treatment with alendronate (ALN) for only 3 months ^b Percent change from baseline expressed as geometric mean. ^c Test for difference in means among dose levels 20, 40, and 80 mg. ^d Test for difference in means between 6- and 3-month regimens within the 80 mg dose cohort. ^e Test for difference in means between 6- and 3-month regimens within the 40 mg dose cohort. ^f Test for difference in means between etidronate (ETD) and alendronate (ALN) ^g Test for difference in means between placebo and alendronate (ALN)					

Figure 3 graphs the mean percent change from baseline serum alkaline phosphatase at Months 3 and 6 for the Phase III Studies. The graph strongly suggests that the percent decrease from baseline in response to alendronate increased with time

Figure 3 Mean Percent Change From Baseline in Serum Alkaline Phosphatase (U/L) by Timepoint Phase III Studies Geometric Mean $\pm$ SE



In the two studies that contained patients who received 40 mg/day for three months, the mean decrease in serum alkaline phosphatase was approximately 50% (50.4% and 55.4% in the Dose-Ranging Study and the Treatment Duration Study, respectively). In contrast, in the three studies that included a six-month 40 mg alendronate group, this regimen produced a decrease in alkaline phosphatase of approximately 70% (62.8, 79, and 72.5% in the Treatment Duration Study, Etidronate Comparison Study, and Placebo-Controlled Study, respectively). These studies indicate that the six-month 40 mg regimen induces more marked suppression of Paget's disease activity. Based on this efficacy and safety profile, this appears to be the optimum regimen for treatment of Paget's disease.

In summary, the decreases observed in serum alkaline phosphatase in patients treated with 40 mg of alendronate for six months, whether assessed relative to baseline, placebo, or etidronate, were highly significant. The decreases at Month 6 were very similar in the two Phase III Studies. This is true despite the fact that timing of dosing differed between these studies. In the Etidronate Comparison Study, alendronate was dosed at least two hours before breakfast (consistent with the dosing recommendations for etidronate), whereas in the Placebo-Controlled Study, patients took their alendronate 30 minutes or more before breakfast. This observation, although based on two different populations of patients consisting of small numbers of subjects, suggests that a 30-minute interval between dosing and ingestion of food and/or beverages (other than water) may be associated with efficacy comparable to that observed with a two-hour interval. Since the shorter interval is anticipated to be associated with better patient compliance, it is the one

recommended by the Sponsor for routine clinical use. A possible explanation for this observation is that despite the variability of absorption due to the different regimens of administration, the cumulative dose of the drug was sufficient to produce similar pharmacologic effects. The percent decreases seen in patients with less active disease (in the Treatment Duration Study) were somewhat smaller than those seen in the Phase III Studies, as expected based on the lower absolute levels of baseline serum alkaline phosphatase.

3) Month 3

Table IX reports the three-month mean percent change from baseline. The adjusted means resulting from the ANOVA model are also reported. While Month 3 was not the primary timepoint of the studies (with the exception of the Dose-Ranging Study), the data in this table provide evidence that there is a significant, albeit submaximal, reduction in serum alkaline phosphatase in alendronate-treated patients by Month 3. Placebo-treated patients showed no reduction and etidronate-treated patients showed significantly less reduction than the alendronate-treated patients ($p < 0.001$).

Table IX Serum Alkaline Phosphatase (U/L) Analysis of Percent Change From Baseline at Month 3 Intention-to-Treat Approach

Daily Treatment	N	Mean	Adjusted		Between Groups
			Mean	84% CI	
Dose-Ranging Study (015)					
ALN 20 mg	8	-29.8	-24.0	(-32.5, -15.4)	p = 0.007 ^a
ALN 40 mg	10	-44.0	-40.9	(-48.1, -33.7)	
ALN 80 mg	9	-52.6	-50.0	(-57.5, -42.5)	
Treatment Duration Study (024)					
ALN 40 mg 3 month	13	-53.6	-56.7	(-64.7, -48.8)	p = 0.508 ^c
ALN 40 mg 6 month [†]	15	-52.3	-51.8	(-58.9, -44.6)	p = 0.482 ^b
ALN 80 mg 3 month	14	-58.0	-61.2	(-69.5, -52.9)	
ALN 80 mg 6 month [†]	15	-66.2	-66.7	(-74.4, -59.1)	
Etidronate Comparison Study (056)[*]					
ETD 400 mg	47	-36.3	-37.4	(-43.8, -30.4)	p < 0.001 ^d
ALN 40 mg	41	-65.5	-66.0	(-69.6, -61.9)	
Placebo-Controlled Study (059)[*]					
Placebo	27	0.5	3.1	(-10.3, 18.5)	p < 0.001 ^e
ALN 40 mg	25	-58.7	-57.7	(-63.1, -51.4)	
[*] Percent change from baseline expressed as geometric mean ^a Test for difference in means among dose levels 20, 40, and 80 mg ^b Test for difference in means between 6- and 3-month regimens within the 80 mg dose cohort ^c Test for difference in means between 6- and 3-month regimens within the 40 mg dose cohort ^d Test for difference in means between etidronate (ETD) and alendronate (ALN) ^e Test for difference in means between placebo and alendronate (ALN) [†] Patients received 40 or 80 mg for 6 months. This table shows results after 3 months of treatment.					

4) Serum Alkaline Phosphatase--Responders and Normalizers

Table X reports the prevalence of responders (i.e., predefined as those patients in whom serum alkaline phosphatase entered the normal range or decreased by 60% from baseline) at Months 3 and 6 for the Phase III Studies. Figure 4 graphs the proportion of responders at Month 6 by treatment group. In the Etidronate Comparison Study, 87.8% (36 of 41) of the alendronate-treated patients responded at Month 6 compared with 29.8% (14 of 47) of those treated with etidronate. An 84% confidence interval for the proportion of responders at Month 6 in the alendronate group was (80.6, 95.0). The estimate of the odds ratio, adjusted for stratum, is 15.6 with a 95% confidence interval of (5.9, 41.5). Thus, the odds that alendronate patients will respond is about 16-fold greater than for etidronate patients ($p < 0.001$). In the Placebo-Controlled Study, 77.8% (21 of 27) of the alendronate-treated but none of the placebo-treated patients responded at Month 6, hence, an odds ratio could not be computed. In both of the Phase III Studies, all of the responders at Month 3 remained responders at Month 6, as predicted by the time course of change from baseline alkaline phosphatase, more patients were responders at six than at three months (see Table X). Overall, in the combined Phase III Studies (Table X), the proportion of responders at Month 6 among 40 mg alendronate-treated patients was 83.8% (57 of 68), versus 57.6% (38 of 66) at Month 3.

Table X Prevalence of Responders (Decrease of 60% From Baseline or Normalization of Serum Alkaline Phosphatase [U.L.]) by Timepoint Phase III Studies Intention-to-Treat Approach

Time	Daily Treatment	Percentage	84% CI	Between Group
Etidronate Comparison Study				
Month 3	ETD 400 mg	17.0 (8 of 47)	(9.3, 24.7)	$p < 0.001^a$
	ALN 40 mg	63.4 (26 of 41)	(52.8, 74.0)	
Month 6	ETD 400 mg	29.8 (14 of 47)	(20.4, 39.2)	
	ALN 40 mg	87.8 (36 of 41)	(80.6, 95.0)	
Placebo-Controlled Study				
Month 3	Placebo	0.0 (0 of 27)	--	$p < 0.001^b$
	ALN 40 mg	48.0 (12 of 25)	(34.0, 62.0)	
Month 6	Placebo	0.0 (0 of 27)	--	
	ALN 40 mg	77.8 (21 of 27)	(66.5, 89.0)	
In the combined Phase III Studies, the percent of responders in the ALN 40 mg group was 83.8% (57 of 68) at Month 6 and 57.6% (38 of 66) at Month 3				
^a Alendronate (ALN) vs etidronate (ETD)				
^b Alendronate (ALN) vs placebo				

Figure 4 Prevalence of Responders at Month 6 (Decrease of 60% From Baseline or Normalization of Serum

Alkaline Phosphatase (U/L)
Phase III Studies: Percentage With 84% Confidence Intervals

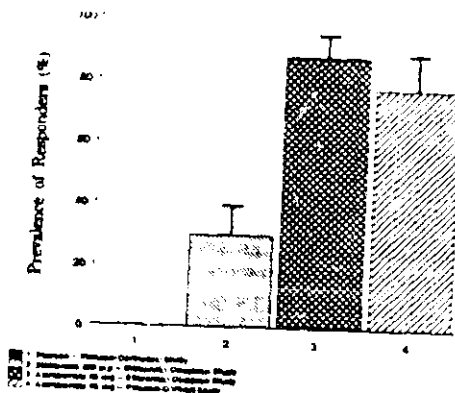


Table XI reports the prevalence of normalizers (i.e., those in whom serum alkaline phosphatase entered the normal range) at Months 3 and 6 for the Phase III Studies. Figure 5 graphs the proportion of normalizers at Month 6 by treatment group. In the Etidronate Comparison Study, 17.0% (8 of 47) of the etidronate-treated patients decreased serum alkaline phosphatase into the normal range at Month 6. The corresponding proportion of normalizers in the alendronate-treated group was 63.4% (26 of 41). The estimate of the odds ratio, adjusted for stratum, is 40.2 with a 95% confidence interval of (9.7, 166.7). Thus, the odds that alendronate-treated patients will respond is about 40-fold greater than those for etidronate-treated patients ($p < 0.001$). For patients treated with 40 mg of alendronate, normalization was consistent across strata. None of the etidronate-treated patients whose baseline serum alkaline phosphatase was above four times the ULN decreased their serum alkaline phosphatase into the normal range, whereas 41.7% of alendronate-treated patients in that stratum did so.

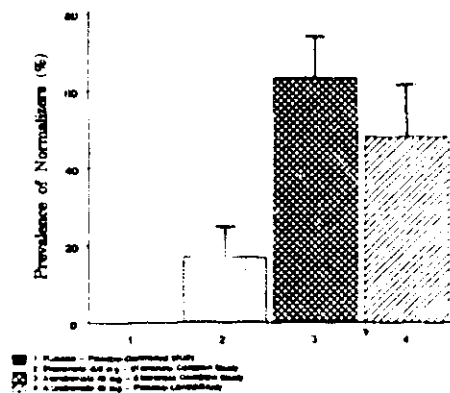
In the Placebo-Controlled Study, 48.1% (13 of 27) in the alendronate group decreased their serum alkaline phosphatase into the normal range at six months, whereas there were no normalizers in the placebo group, thus an odds ratio could not be computed. An 84% confidence interval for the proportion of normalizers at Month 6 in the alendronate group was (34.6, 61.7).

In the combined Phase III Studies, 57.4% (39 of 68) of alendronate-treated patients normalized their alkaline phosphatase at Month 6, versus 21.2% (14 of 66) at Month 3.

Table XI Prevalence of Normalizers of Serum Alkaline Phosphatase by Timepoint
Phase III Studies Intention-to-Treat Approach

Time	Daily Treatment	Percentage	84% CI	Between Groups
Etidronate Comparison Study				
Month 3	ETD 400 mg	10.6 (5 of 47)	(4.3, 17.0)	p = 0.049
	ALN 40 mg	26.8 (11 of 41)	(17.1, 36.6)	
Month 6	ETD 400 mg	17.0 (8 of 47)	(9.3, 24.7)	p < 0.001*
	ALN 40 mg	63.4 (26 of 41)	(52.8, 74.0)	
Placebo-Controlled Study				
Month 3	Placebo	0.0 (0 of 27)	--	p = 0.064
	ALN 40 mg	12.0 (3 of 25)	(2.9, 21.1)	
Month 6	Placebo	0.0 (0 of 27)	--	p < 0.001 ^b
	ALN 40 mg	48.1 (13 of 27)	(34.6, 61.7)	
In the combined Phase III Studies, the proportion of normalizers in the ALN 40 mg group was 57.4% (39 of 68) and 21.2% (14 of 66) at Month 6 and 3, respectively * = Alendronate (ALN) vs etidronate (ETD) ^b = Alendronate (ALN) vs placebo				

Figure 5 Prevalence of Normalizers at Month 6 - Phase III Studies: Percentage With 84% Confidence Intervals



b) Effects on Urinary Resorption Markers

Tables XII and XIII and Figures 6 and 7 depict the % changes from baseline in urinary resorption markers at Months 3 and 6. Both the tables and the figures suggest that both markers were substantially decreased at three months and continued to decrease with time in the alendronate groups.

In the Etidronate Comparison Study, at Month 6, the primary timepoint in the studies, the mean % change (adjusted for stratum) from baseline in urinary deoxypyridinoline was -75.5% in the alendronate group and -51.8% in the etidronate group. The mean % changes from baseline deoxypyridinoline in alendronate-treated patients were consistent across the three strata of prior bisphosphonate use and baseline levels of serum alkaline phosphatase. In the etidronate group, the decrease in deoxypyridinoline was significantly less ($p < 0.001$) than that observed in the alendronate group (Table XII). In the Placebo-Controlled Study at Month 6, the mean % change (adjusted for center) from baseline in urine NTX was -84.6% in the alendronate group and 8.3% in the placebo group (Table XIII).

Table XII Urinary Deoxypyridinoline (pmol/mol Creatinine)
Analysis of Percent Change From Baseline
Intention-to-Treat Approach

Time	Daily Treatment	N	Geometric Mean	Adjusted	
				Geometric Mean	84% CI
Etidronate Comparison Study					
Month 3	ALN 40 mg	41	-66.2	-66.8	(-70.6, -62.5)
	ETD 400 mg	47	-46.5	-47.1	(-52.8, -40.6)
Month 6	ALN 40 mg	41	-75.1	-75.5	(-78.4, -72.3)
	ETD 400 mg	47	-51.0	-51.8	(-57.1, -45.8)
ALN = Alendronate ETD = Etidronate					

Table XIII Urine N-Telopeptide (nmol BCE/mmol Creatinine)
Analysis of Percent Change From Baseline
Intention-to-Treat Approach

Time	Daily Treatment	N	Geometric Mean	Adjusted	
				Geometric Mean	84% CI
Placebo-Controlled Study					
Month 3	Placebo	26	-8.7	-1.1	(-21.0, 23.9)
	ALN 40 mg	26	-77.9	-76.6	(-81.1, -70.9)
Month 6	Placebo	26	-7.9	8.3	(-16.3, 40.2)
	ALN 40 mg	26	-86.4	-84.6	(-88.0, -80.3)
ALN = Alendronate					

Figure 6 Mean % Change From Baseline in Urinary Deoxypyridinoline (pmol/umol Creatinine) by Timepoint Etidronate Comparison Study - Geometric Mean $\pm$ SE

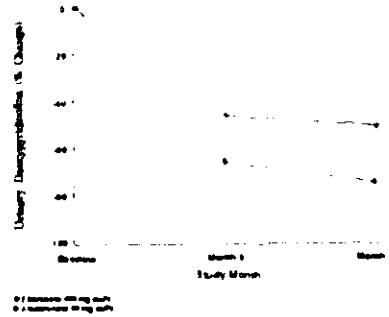
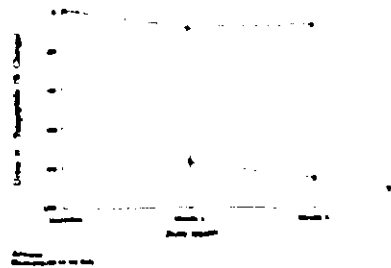


Figure 7 Mean % Change From Baseline in Urine N-Telopeptide (umol BCE/mmol Creatinine) by Timepoint Placebo-Controlled Study - Geometric Mean $\pm$ SE



The mean % changes in urinary resorption markers between Month 3 and Month 6. Results are shown in Tables XIV and XV. In the Etidronate Comparison Study, urinary deoxypyridinoline decreased by 26.5% during this period in the alendronate group ($p < 0.001$) as opposed to a nonsignificant 8.4% decrease in the etidronate group. In the Placebo-Controlled Study, the urinary excretion of NTX decreased by 38.7% between Month 3 and Month 6 ($p < 0.001$), whereas no significant changes were seen in the placebo group.

Table XIV Analysis of Percent Change From Month 3 at Month 6 Urinary Deoxypyridinoline (pmol/mol Creatinine) Intention-to-Treat Approach

Daily Treatment	N	Mean*	95% CI	Within Groups
Etidronate Comparison Study				
ETD 400 mg	47	-8.4	(-17.2, 1.3)	$p = 0.095^{**}$
ALN 40 mg	41	-26.5	(-36.1, -15.5)	$p < 0.001^{**}$
* Percent change from Month 3 expressed as geometric mean				
** Test for mean difference equal to 0				

Table XV Analysis of Percent Change From Month 3 at Month 6 Urine N-Telopeptide (micromol BCE/mmol Creatinine) Intention-to-Treat Approach

Daily Treatment	N	Mean*	95% CI	Within Groups
Placebo-Controlled Study				
Placebo	26	0.8	(-10.7, 13.9)	$p = 0.894^{**}$
ALN 40 mg	26	-38.7	(-49.2, -26.0)	$p < 0.001^{**}$
* Percent change from Month 3 expressed as geometric mean				
** Test for mean difference equal to 0				

The marked decreases in urinary resorption markers confirm that alendronate suppresses the abnormal bone turnover that underlies Paget's disease of bone. The decreases observed at Month 3 and Month 6 in both resorption markers in patients treated with alendronate 40 mg/day were highly significant relative to baseline, placebo, and etidronate. The continued decrease from Month 3 to Month 6 cannot be explained by a lag effect since effects of bisphosphonates on resorption are immediate and cease upon treatment withdrawal. This additional suppression of -38.7 and -26.5% seen during the second three months of therapy further supports the selection of a six-month course of 40 mg/day of alendronate in the treatment of Paget's disease. Of note, in a Phase II Osteoporosis Study, in which patients received alendronate 40 mg/day for six weeks, the urinary resorption markers did not continue to decline after treatment withdrawal. Thus, treatment with alendronate for six months is required to achieve optimal suppression of bone resorption.

c) Effects on Pain Score

A pain score analysis was done on the 111 patients (of a total of 144) who completed the baseline Brief Pain Inventory and reported having pain at baseline: 70 from the Etidronate Comparison Study and 41 from the Placebo-Controlled Study. The baseline characteristics for these 111 patients did not differ meaningfully from those of patients in the intention-to-treat analysis for the biochemical endpoints. The range of the mean pain score is 0 to 10. In Etidronate Comparison Study, the baseline mean pain scores were 3.4 and 3.1 in the alendronate and etidronate groups, respectively. In the Placebo-Controlled Study, the baseline mean pain scores was 2.48 and 2.0 in the alendronate and placebo groups, respectively.

Table XVI reports the means and other summary statistics for the change from baseline in pain scores at Month 6. Figure 8 graphs the unadjusted mean change from baseline in pain intensity versus time. In the Etidronate Comparison Study, the mean change from baseline at Month 6 in the alendronate group was -0.67, indicating an improvement in pain intensity. However, in the etidronate group the mean change at Month 6 was 0.21, indicating a nonsignificant mean increase in pain intensity. The difference between the two groups was marginally significant (p = 0.07).

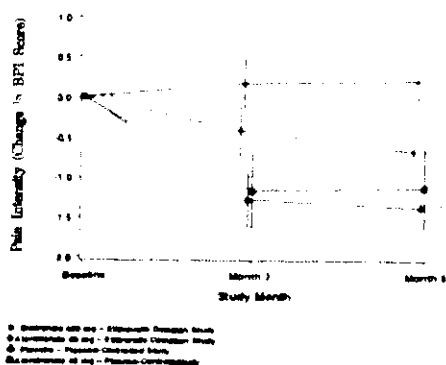
Table XVI Pain Intensity--Mean Change From Baseline in Pain Scores at Month 6 in Patients With a Score >0 at Baseline: Phase III Studies, Intention-to-Treat Approach

Daily Treatment	N	Mean Change	Adjusted	
			Mean Change	84% CI
Etidronate Comparison Study				
ETD 400 mg	36	0.21	0.19	(-0.30, 0.67)
ALN 40 mg	34	-0.67	-0.69	(-1.16, -0.22)
Placebo-Controlled Study				
Placebo	19	-1.38	-1.71	(-2.39, -1.03)
ALN 40 mg	22	-1.13	-1.50	(-2.14, -0.87)
Phase III Studies Combined				
ALN 40 mg	56	-0.85	-0.90	(-1.30, -0.50)*
ETD = Etidronate ALN = Alendronate * 95% Confidence Interval				

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Figure 8 Mean Change in Pain Intensity by Timepoint
Phase III Studies - Mean Change $\pm$ SE



In the Placebo-Controlled Study, the change in pain scores of -1.38 and -1.13 in the placebo and alendronate groups, respectively, at Month 6 indicated equal improvement in both groups. The relative shortness of the observation period (six months) may account, at least partially, for the inability to detect a difference between alendronate and placebo. The intrinsic difficulty in interpreting pain in pagetic patients may have also contributed to this finding. A 95% confidence interval, derived from the pooled alendronate data, did not overlap 0 (-1.30, -0.50), indicating slight but significant decreases in the pain score in alendronate-treated patients. For patients treated with 40 mg of alendronate, the mean decrease from baseline in the pain scores was similar in the two studies. However, the difference between the two groups was not significant ($p = 0.73$). Within each protocol, the difference in analgesic consumption between the treatment groups was not significant.

d) Effects on Functional Impairment

The range for mean functional impairment score is 0 to 10. In the Etidronate Comparison Study, the baseline mean scores were 3.3 and 2.4 in the alendronate and etidronate groups, respectively. In the Placebo-Controlled Study, the baseline mean scores were 2.06 and 1.7 in the alendronate and placebo groups, respectively. This analysis was based on the 105 of 144 patients who reported some functional impairment at baseline: 69 from the Etidronate Comparison Study and 36 from the Placebo-Controlled

Study. In the former there was a nonsignificant decrease of -0.32 in the alendronate group and a nonsignificant increase of 0.20 in the etidronate group at Month 6. The difference between the groups was also not significant ($p = 0.22$). In the Placebo-Controlled Study there were significant decreases in the functional impairment scores at Month 6 versus baseline in both treatment groups (-2.29 and -2.10 in the placebo and alendronate group, respectively) but the difference between the two groups was not significant.

e) Radiologic Changes in Osteolytic Lesions

Comparison of paired baseline and Month 6 x-rays were performed on 114 of the 144 patients in the Phase III Studies: 68 in the Etidronate Comparison Study and 46 in the Placebo-Controlled Study. Comparisons were done in patients who had at least one osteolytic lesion at baseline. Baseline characteristics for age, gender, weight, and serum alkaline phosphatase of these patients were not meaningfully different from those of all the patients in the two studies. All x-rays were read at the same center by the same expert radiologist, blinded to sequence and treatment, assuring consistency in readings.

The data were analyzed in two ways. In the first method, the average radiologic score, which could range from 1 to 5 for each patient, was analyzed as a continuous variable. In the second method, the average scores were partitioned using three categories: those with scores less than three were classified as improving, those with scores of three were classified as having no change, and those with scores greater than three were classified as worsening. The improvement category includes definitely better and probably/marginally better. The worsening category includes definitely worse and probably/marginally worse.

In the Phase III Studies, 22 of 57 (38.6%) of the evaluable patients treated with alendronate showed improvement in the degree of osteolysis, whereas 3 patients (5.3%) experienced a worsening. Improvement was observed in 9 of 34 (26.5%) etidronate-treated patients and in 1 of 23 (4.3%) receiving placebo (Table XVII). Worsening was observed in 14.7% (5 of 34) of patients receiving etidronate and none of the patients receiving placebo.

In the Etidronate Comparison Study, the scores in the alendronate group ranged 1 to 5 versus 2 to 5 in the etidronate group. Five patients in the alendronate group were classified as definitely better, but none in the etidronate group was so classified. There was little difference in osteolysis between the alendronate group and the etidronate group with respective mean scores of 2.7 and 3.0, the difference between the groups did not achieve statistical significance, $p = 0.13$.

In the Placebo-Controlled Study, the maximum average score was three for the patients in both treatment groups. None of the patients in either treatment group worsened. The median score was also three, indicating that the majority of the patients in both treatment groups had no change in

osteolysis. The minimum scores were 2.83 and 1 (indicating definite radiologic improvement) in the placebo and alendronate groups, respectively. A test for the difference between the mean change in osteolysis between the two groups was significant ($p = 0.020$).

Table XVII and Figures 9 and 10 show the proportion of patients who worsened, improved or showed no change for each treatment group. In the Etidronate Comparison Study, 9 of 34 (26.5%) of the etidronate patients improved, compared with 11 of 34 (32.4%) alendronate patients. Five of the 11 patients that showed improvement in the alendronate group had at least one bone that was definitely improved. However, none of the nine improved patients in the etidronate group were definitely improved. In the Placebo-Controlled Study, 11 of 23 (47.8%) of the alendronate patients showed improvement. Four of these 11 patients had at least one bone that was classified as definitely better. The patient in the placebo group showing improvement was classified as probably/marginally better.

In summary, alendronate was effective in improving osteolysis in comparison to placebo. The similarity of the results for the alendronate groups in both Phase III Studies provides further evidence that alendronate is associated with radiologic improvement of pagetic osteolytic lesions.

Table XVII Degree of Osteolysis at Month 6 Compared With Baseline. Phase III Studies, Intent-to-Treat Approach

Change From Baseline	Daily Treatment	Percentage
Etidronate Comparison Study		
Improvement	ETD 400 mg	26.5 (9 of 34)
	ALN 40 mg	32.4 (11 of 34)
No Change	ETD 400 mg	58.8 (20 of 34)
	ALN 40 mg	58.8 (20 of 34)
Worsened	ETD 400 mg	14.7 (5 of 34)
	ALN 40 mg	8.8 (3 of 34)
Placebo-Controlled Study		
Improvement	Placebo	4.3 (1 of 23)
	ALN 40 mg	47.8 (11 of 23)
No Change	Placebo	95.7 (22 of 23)
	ALN 40 mg	52.2 (12 of 23)
Worsened	Placebo	0.0 (0 of 23)
	ALN 40 mg	0.0 (0 of 23)
Phase III Studies Combined		
Improvement	ALN 40 mg	38.6 (22 of 57)
No Change	ALN 40 mg	56.1 (32 of 57)
Worsened	ALN 40 mg	5.3 (3 of 57)
ETD = Etidronate ALN = Alendronate		

Figure 9 Degree of Osteolysis at Month 6 Compared With Baseline Eudronate Comparison Study
Percent by Degree of Improvement

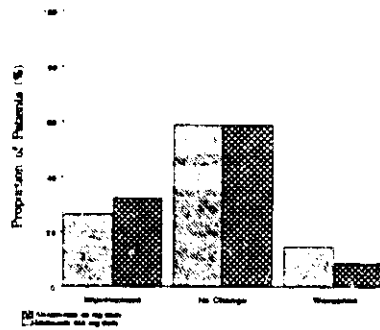
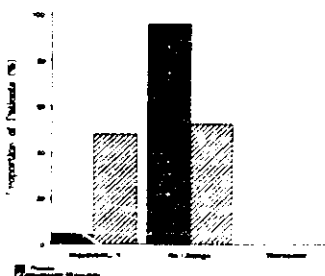


Figure 10 Degree of Osteolysis at Month 6 Compared With Baseline Placebo-Controlled Study
Percent by Degree of Improvement



f. Effects on Calcium Metabolism

Table XVIII and Figure 11 show the change from baseline in serum calcium over time in the Phase III Studies. In the Etidronate Comparison Study, there was an initial small decrease at Month 1 in the alendronate group, followed by a gradual return to baseline by Month 6. In the etidronate group, there were no significant changes in serum calcium.

In the Placebo-Controlled Study, was a slight nonsignificant decrease in serum calcium in the alendronate group at Month 3, which abated at Month 6. In the placebo group, slight positive changes from baseline were seen at Month 3 and Month 6.

Table XVIII. Summary of Change From Baseline Over Time in Serum Calcium (mg/dL)
Phase III Studies Intention-to-Treat Approach

Time	Daily Treatment	N	Mean	SE	Median	Range
Etidronate Comparison Study						
Month 1	ETD 400 mg	47	-0.03	0.04	0.00	(-0.65 to 0.80)
	ALN 40 mg	41	-0.45	0.06	-0.50	(-1.20 to 0.15)
Month 3	ETD 400 mg	47	-0.05	0.05	0.00	(-0.60 to 0.80)
	ALN 40 mg	41	-0.37	0.06	-0.35	(-1.10 to 0.30)
Month 6	ETD 400 mg	47	0.10	0.05	0.15	(-0.55 to 1.30)
	ALN 40 mg	41	-0.11	0.06	-0.15	(-0.85 to 0.80)
Placebo-Controlled Study						
Month 3	Placebo	27	0.18	0.10	0.11	(-0.67 to 1.28)
	ALN 40 mg	25	-0.11	0.09	0.01	(-1.10 to 0.84)
Month 6	Placebo	27	0.17	0.07	0.21	(-0.44 to 0.81)
	ALN 40 mg	27	0.03	0.06	0.04	(-0.61 to 0.81)
Phase III Studies Combined						
Month 3	ALN 40 mg	66	-0.27	0.05	-0.19	(-1.10 to 0.84)
Month 6	ALN 40 mg	68	-0.05	0.04	-0.07	(-0.85 to 0.81)
ETD = Etidronate						
ALN = Alendronate						

Figure 11 Mean Change From Baseline in Serum Calcium (mg/dL.) by Timepoint
Phase III Studies: Mean Change $\pm$ SE

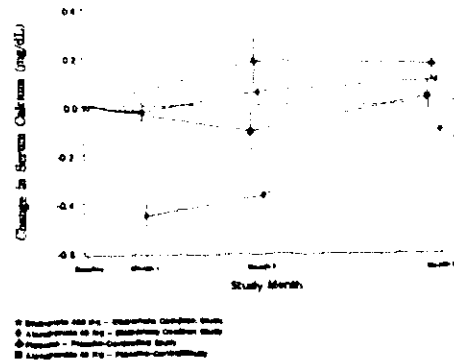


Table XIX and Figure 12 show the change from baseline in serum phosphate in the Etidronate Comparison and Placebo-Controlled Studies. In the Etidronate Comparison Study, serum phosphate decreased initially in the alendronate group, but, like serum calcium, returned toward baseline. In contrast, etidronate-treated patients showed a marked highly significant increase at Month 1 that increased further through Month 6.

In the Placebo-Controlled Study, mean change from baseline was negative in the alendronate group, whereas no significant change was observed in the placebo group.

Table XIX Summary of Change From Baseline Over Time in Serum Phosphate (mg/dL)
Phase III Studies Intention-to-Treat Approach

Time	Daily Treatment	N	Mean	SE	Median	Range
Etidronate Comparison Study						
Month 1	ETD 400 mg	46	0.66	0.09	0.52	(-0.50 to 2.55)
	ALN 40 mg	41	-0.47	0.07	-0.40	(-1.45 to 0.30)
Month 3	ETD 400 mg	47	0.96	0.12	0.85	(-0.50 to 3.50)
	ALN 40 mg	41	-0.34	0.07	-0.25	(-1.10 to 0.80)
Month 6	ETD 400 mg	47	1.02	0.13	0.95	(-0.60 to 3.50)
	ALN 40 mg	41	0.01	0.07	0.00	(-0.80 to 0.85)
Placebo-Controlled Study						
Month 3	Placebo	27	-0.05	0.06	-0.01	(-0.65 to 0.85)
	ALN 40 mg	25	-0.32	0.09	-0.34	(-1.18 to 0.58)
Month 6	Placebo	27	-0.02	0.07	-0.01	(-0.66 to 0.95)
	ALN 40 mg	27	-0.30	0.10	-0.28	(-1.20 to 0.91)
Phase III Studies Combined						
Month 3	ALN 40 mg	66	-0.33	0.06	-0.30	(-1.18 to 0.80)
Month 6	ALN 40 mg	68	-0.11	0.06	-0.10	(-1.20 to 0.91)
ETD = Etidronate						
ALN = Alendronate						

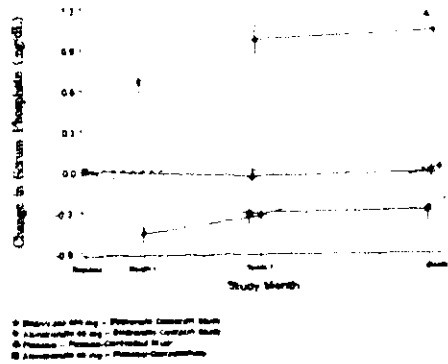


Figure 12 Mean Change From Baseline in Serum Phosphate (mg/dL) by Timepoint Phase III Studies Mean $\pm$ SE

The lower values for serum calcium and phosphate observed in the alendronate group were consistent with the expected positive skeletal balance due to the inhibition of bone resorption. The changes were small and not associated with symptoms. In contrast, consistent with its effect to decrease bone mineralization, etidronate did not decrease serum calcium.

In addition, because etidronate increases renal tubular reabsorption of phosphate, serum phosphate levels were characteristically increased. It has been postulated that this increase may be directly related to the effect of etidronate to impair skeletal mineralization.

Table XX Prevalence of Responders by Timepoint (Decrease of $\geq 60\%$ From Baseline or Normalization of Serum Alkaline Phosphatase [U/L])*

Time**	Daily Treatment	Percentage
Treatment Duration Study (#24)		
Month 6	ALN 40 mg for 3 months	77.8 (7 of 9)
	ALN 40 mg for 6 months	91.7 (11 of 12)
	ALN 80 mg for 3 months	81.8 (9 of 11)
	ALN 80 mg for 6 months	100.0 (14 of 14)
Month 12	ALN 40 mg for 3 months	90.0 (9 of 10)
	ALN 40 mg for 6 months	100.0 (11 of 11)
	ALN 80 mg for 3 months	100.0 (14 of 14)
	ALN 80 mg for 6 months	100.0 (14 of 14)
*No data were carried forward, so only patients with data at Month 6 or Month 12 are included in this analysis		
** From study start		

5. Duration of Response Following Withdrawal of Treatment

No relapses were observed in patients treated with 40 mg alendronate for either three or six months during the following six- to nine-month follow-up period in the Phase II Treatment Duration Study. This is consistent with previous studies showing that, unlike calcitonin, the biochemical (and clinical) response to bisphosphonates is maintained after cessation of treatment for some time. Ongoing extension studies will collect data to establish the actual duration of response.

Nevertheless, since similar responses to alendronate were observed in patients who had received prior therapy with other bisphosphonates and those who had not, retreatment with alendronate may be considered, following a six-month posttreatment evaluation period, both in patients who relapse (as assessed by an increase in serum alkaline phosphatase) and in those who fail to normalize their serum alkaline phosphatase.

6. Efficacy in Relation to Demographic and Other Parameters

Subgroup analyses were performed on pooled data from the Eudronate Comparison Study the Placebo-Controlled Study on the basis of race, gender, baseline age, height, weight, serum creatinine, alkaline phosphatase, prior use of bisphosphonates and concomitant medications at anytime during the study.

The subgroups are: age (<65, ≥ 65 years), age (<75, ≥ 75 years); gender; race (white, non-white); height (<65.9, ≥ 65.9 inches), height (<63, ≥ 63 inches), lowest tertile versus upper tertiles, height (<65.9, ≥ 65.9 inches), weight (<169, ≥ 169 pounds), weight (<153, ≥ 153 pounds), lowest tertile versus upper tertiles, serum creatinine (<1.19, ≥ 1.19 mg/dL), lower tertile versus highest tertiles, serum alkaline phosphatase (<4 x ULN, ≥ 4 x ULN), prior use of bisphosphonates; and use of concomitant medication (non-u-

ser/user) at any time during the study, including beta blockers, calcium channel blockers, cardiac glycosides, aspirin-containing medications, nonsteroidal anti-inflammatory drugs, anticonvulsants, thiazides, and glucocorticoids. The mean and 95% confidence interval for percent changes in serum alkaline phosphatase from baseline at Month 6 were determined for each subgroup. No formal statistical hypothesis testing within the subgroups was performed. The estimates and confidence intervals reported must be interpreted cautiously because of both type I and type II errors. Differences between the subgroups should be interpreted with caution.

a. Age

Two age-based analyses were performed on alendronate-treated patients. The standard cutoff of 65 years was used to distinguish "younger" (<65 years) from "elderly" (≥ 65 years) patients. Of the 68 patients, 53 (78%) were elderly. Because most patients were older than 65, a second analysis was performed with a cutoff of 75 years. The estimates and confidence intervals for the subgroups are reported in Table XXI and Figure 13. As seen in Figure 13, there is considerable overlap in the confidence intervals in each of the subgroup analyses. Both the table and the figure confirm the lack of importance of age as a determinant of the efficacy of alendronate.

b. Gender

Twenty-seven patients were women and 41 men as shown in Table XXI and Figure 13. Men had a slightly lower response due to one man (AN 1204 in Protocol 059, Study 059003) with an increase in serum alkaline phosphatase at Month 6. However, both estimates are well within the confidence interval for all patients treated with alendronate and there is considerable overlap in the confidence intervals for men and women. Thus gender is not an important determinant of the efficacy of alendronate.

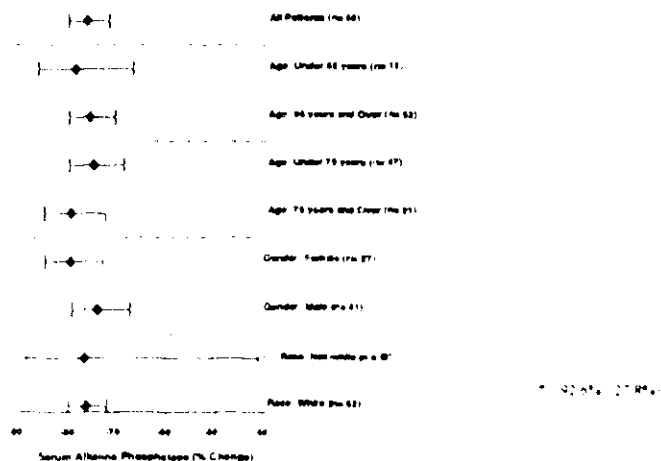
c. Race

Almost all patients in the Phase III Studies were white (62 of 68 alendronate-treated patients). This is likely to reflect a representative population of patients with Paget's disease as this condition is known to be much more common in individuals of European extraction than among non-white races. Table XXI and Figure 13 indicate that there is no difference in alendronate efficacy between these groups.

Table XXI Percent Change From Baseline in Serum Alkaline Phosphatase (U/L) at Month 6--Patients Treated With Alendronate (40 mg) (Age, Gender, and Race) - Phase III Studies Combined Intention-to-Treat Approach

Baseline Covariate	N	Geometric Mean	95% CI
All Patients	68	-76.6	(-80.5, -72.0)
Age			
<65 years	15	-78.9	(-86.5, -67.1)
≥65 years	53	-75.9	(-80.2, -70.7)
<75 years	47	-75.1	(-80.1, -68.8)
≥75 years	21	-79.7	(-85.1, -72.5)
Gender			
Female	27	-79.7	(-84.8, -72.9)
Male	41	-74.3	(-79.6, -67.6)
Race			
Non-white	6	-77.0	(-92.6, -27.8)
White	62	-76.6	(-80.3, -72.2)

Figure 13 Mean Percent Change From Baseline in Serum Alkaline Phosphatase (U/L) at Month 6--Only Patients Treated With Alendronate (40 mg) (Age, Gender, and Race) Phase III Studies Geometric Mean With 95% Confidence Intervals



d Height and Weight

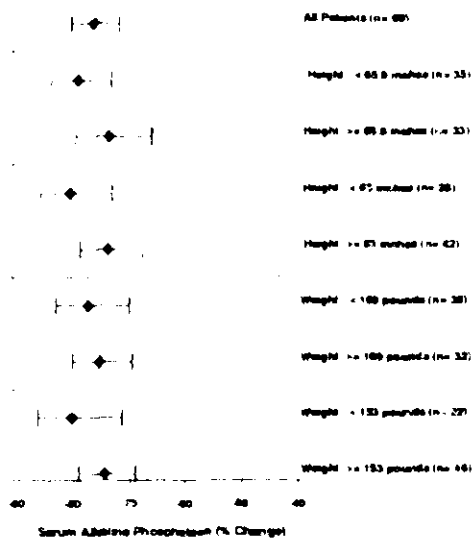
Patients with a lower body weight will receive a higher dose of alendronate per unit body weight than those who are heavier. Therefore, the lowest 33% (lowest tertile) was selected as the cut point for weight to assess if larger body size would reduce the positive effects on serum alkaline phosphatase. The effect, if any, of height was assessed also by comparing the alkaline phosphatase

tase response in the lowest tertile with that in the two upper tertiles. The cut points for height and weight were 63 inches and 153 pounds. The median height and weight were 65.9 inches and 169 pounds. Although the mean response was slightly greater in lighter or shorter patients, this difference was not clinically meaningful. See Table XXII and Figure 14. Thus, there is no evidence that alendronate dosing needs to be adjusted on the basis of weight or height.

Table XXII Percent Change From Baseline in Serum Alkaline Phosphatase (U/L) at Month 6-- Patients Treated With Alendronate (40 mg) (Height and Weight) Phase III Studies Combined Intention-to-Treat Approach

Baseline Covariate	N	Geometric Mean	95% CI
All Patients	68	-76.6	(-80.5, -72.0)
Height			
<65.9 inches (Below Median)	35	-79.3	(-83.7, -73.6)
≥ 65.9 inches (At and Above Median)	33	-73.5	(-79.8, -65.2)
<63 inches (Lowest Tertile)	26	-80.3	(-85.5, -73.1)
≥ 63 inches (Upper Tertiles)	42	-74.0	(-79.2, -67.6)
Weight			
<169 pounds (Below Median)	36	-77.5	(-83.1, -70.1)
≥ 169 pounds (At and Above Median)	32	-75.6	(-80.3, -69.6)
<153 pounds (Lowest Tertile)	22	-80.3	(-86.4, -71.3)
≥ 153 pounds (Upper Tertiles)	46	-74.6	(-79.2, -69.1)

Figure 13 Mean Percent Change From Baseline in Serum Alkaline Phosphatase (U/L) at Month 6-- Only Patients Treated With Alendronate (40 mg) (Height and Weight) - Phase III Studies - Geometric Mean With 95% Percent Confidence Intervals



e Renal Function Serum Creatinine

Serum creatinine was used as an indicator of renal function. Creatinine clearance was not assessed directly in any of the Paget's disease clinical studies. However, patients with significant impairment of renal function at screening were excluded. An increase in creatinine (indicating a decline in renal function) should lead to a greater uptake of alendronate from the circulation into the skeleton, since alendronate is neither metabolized nor excreted by any other route besides the kidneys. The upper 33% (highest tertile) of concentrations was selected as the point to assess whether elevated serum creatinine would increase the effect of alendronate on alkaline phosphatase.

As seen in Table XXIII and Figure 14, the upper tertile for serum creatinine was 1.19 mg/dL. Patients in the lower tertiles responded similarly to patients in the upper tertile. Therefore, within the range of renal function of patients enrolled in these studies, renal function appears unimportant in determining alendronate efficacy.

f Baseline Serum Alkaline Phosphatase

Table XXIII and Figure 14 show the mean percent change from baseline for the two subgroups $<4 \times \text{ULN}$ and $\geq 4 \times \text{ULN}$. Patients with greater baseline serum alkaline phosphatase had a greater percent decrease, a difference more apparent in the Placebo-Controlled Study than in the Etidronate Comparison Study. This difference in percent decrease may be explained by either "regression to the mean" effect or the nonsuppressible component of serum alkaline phosphatase that is derived from the liver and other sources. Therefore, the closer the pretreatment serum alkaline phosphatase is to the normal range, the smaller the percent suppression that can be expected in response to effective therapy.

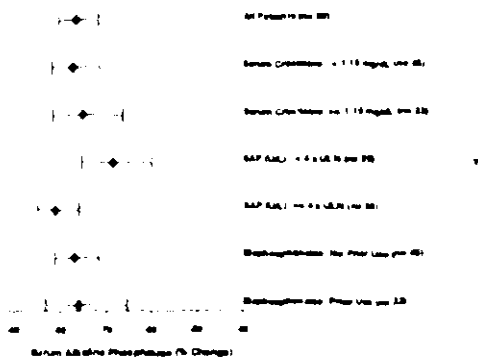
g Prior Use of Bisphosphonates

The percent change from baseline in serum alkaline phosphatase at Month 6 for patients reporting no prior treatment with any bisphosphonate was -77.0%. The corresponding change for patients reporting prior bisphosphonate use was -76.0%. Both Table XXIII and Figure 14 confirm the lack of importance of prior bisphosphonate use as a determinant of the efficacy of alendronate.

Table XXIII Percent Change From Baseline in Serum Alkaline Phosphatase (U/L) at Month 6 in the Patients Treated With Alendronate (40 mg) (Serum Creatinine, Serum Alkaline Phosphatase, Prior Bisphosphonate Use) Phase III Studies Combined - Intention-to-Treat Approach

Baseline Covariate	N	Geometric Mean	95% CI
All Patients	68	-76.6	(-80.5, -72.0)
Serum Creatinine (mg/dL)			
<1.19 mg/dL (Lower Two Tertiles)	45	-77.3	(-81.9, -71.5)
≥1.19 mg/dL (Upper Tertile)	23	-75.3	(-81.8, -66.5)
Serum Alkaline Phosphatase (U/L)			
<4 x Upper Limit of Normal	29	-68.6	(-75.4, -60.1)
≥4 x Upper Limit of Normal	39	-81.2	(-85.2, -76.1)
Bisphosphonates			
No Prior Use	45	-77.0	(-81.2, -71.7)
Prior Use	23	-76.0	(-83.3, -65.4)

Figure 14 Mean Percent Change From Baseline in Serum Alkaline Phosphatase (U/L) at Month 6--Only Patients Treated With Alendronate (40 mg) (Serum Creatinine, Serum Alkaline Phosphatase, Prior Bisphosphonate Use) - Phase III Studies
Geometric Mean With 95% Confidence Intervals



h Concomitant Medications

To assess the influence of concomitant medications on the effect of alendronate to decrease serum alkaline phosphatase, the mean percent change in serum alkaline phosphatase was compared for the different types of medications for "users" versus "non-users." Data were combined from the Phase III Studies. A medication "user" is defined as anyone who used a medication regardless of dose, route, or duration during the study. The information is summarized in Tables XXIV, XXV, and XXVI, and Figures 15, 16, and 17. No analyses are presented for subgroups of five or fewer patients. Both the response to treatment and the subgroups are based on post randomization effects and thus all results require cautious interpretations.

The medication groups selected for assessment included:

- (1) those in which any treatment group had at least a 5% experience with the medication (beta blockers, calcium channel blockers, and cardiac glycosides);
- (2) medications known or believed to affect bone metabolism (anticonvulsants, thiazides, and glucocorticoids);
- (3) medications with known gastric effects that might conceivably influence oral bioavailability (aspirin-containing compounds and nonsteroidal anti-inflammatories).

(1) As Tables XXIV and XXV and Figures 15 and 16 illustrate, the number of users of each medication in groups (1) and (2) above was relatively small, and both users and non-users had comparable responses in serum alkaline phosphatase. In group (3) (Table XXVI and Figure 17), where the number of non-users was relatively larger, comparable responses in serum alkaline phosphatase were observed in users and non-users of nonsteroidal anti-inflammatory drugs. The only group in which a small difference was observed was aspirin-containing medications (see below).

Table XXIV Percent Change From Baseline in Serum Alkaline Phosphatase (U/L) at Month 6--All Patients Treated With Alendronate (40 mg) (Beta Blockers, Calcium Channel Blockers, Cardiac Glycosides) - Phase III Studies Combined - Intention-to-Treat Approach

Baseline Covariate	N	Geometric Mean	95% CI
All Patients	68	-76.6	(-80.5, -72.0)
Beta Blockers			
Non-user	59	-77.4	(-81.2, -72.9)
User	9	-70.5	(-84.9, -42.5)
Calcium Channel Blockers			
Non-user	57	-76.3	(-80.6, -71.0)
User	11	-78.2	(-85.8, -66.6)
Cardiac Glycosides			
Non-user	60	-75.9	(-80.1, -70.8)
User	8	-81.4	(-89.7, -66.3)

Figure 15 Mean Percent Change From Baseline in Serum Alkaline Phosphatase (U/L) at Month 6--Only Patients Treated With Alendronate (40 mg) (Beta Blockers, Calcium Channel Blockers, Cardiac Glycosides) - Phase III Studies - Geometric Mean With 95% Confidence Intervals

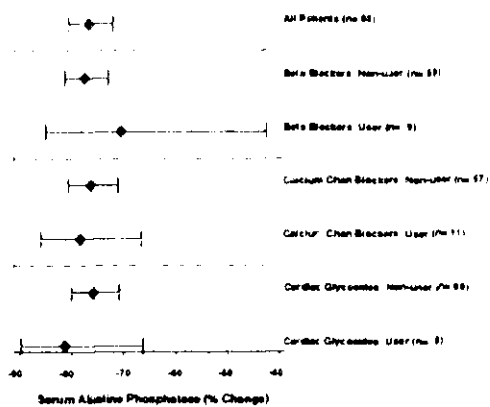
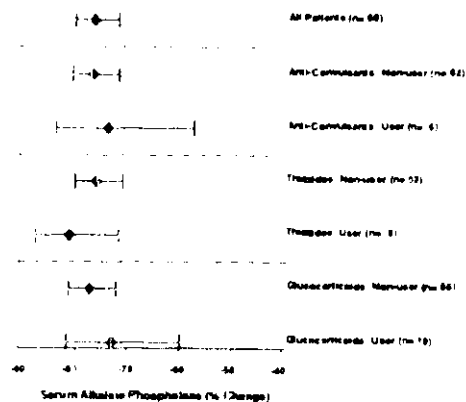


Table XXV Percent Change From Baseline in Serum Alkaline Phosphatase (U/L) at Month 6--All Patients Treated With Alendronate (40 mg) (Anticonvulsants, Thiazides, Glucocorticoids) Phase III Studies Combined - Intention-to-Treat Approach

Baseline Covariate	N	Geometric Mean	95% CI
All Patients	68	-76.6	(-80.5, -72.0)
Anticonvulsants			
Non-user	62	-76.9	(-81.0, -71.9)
User	6	-73.9	(-84.0, -57.4)
Thiazides			
Non-user	62	-76.1	(-80.3, -71.0)
User	6	-81.3	(-87.7, -71.7)
Glucocorticoids			
Non-user	58	-77.2	(-81.4, -72.1)
User	10	-72.9	(-81.7, -59.9)

Figure 16 Mean Percent Change From Baseline in Serum Alkaline Phosphatase (U/L) at Month 6--Only Patients Treated With Alendronate (40 mg) (Anticonvulsants, Thiazides, Glucocorticoids) Phase III Studies - Geometric Mean With 95% Confidence Intervals



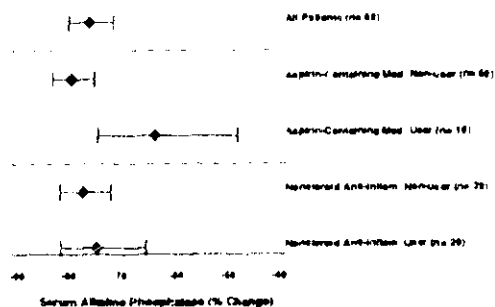
3) Aspirin-Containing Medications

Table XXVI and Figure 17 illustrate that the response in the aspirin-containing medication user group (n = 18) was lower than the non-users' (n = 50) response. Upper gastrointestinal irritation caused by aspirin would, if anything, be expected to increase bioavailability of alendronate and therefore, a greater rather than lesser effect in this patient subpopulation might have been considered likely. No difference was observed between users and non-users of nonsteroidal anti-inflammatory agents. Since these agents have gastrointestinal effects similar to aspirin, the prototype of the class, one would expect to see a difference for them as well. This also suggests that the difference between aspirin users and non-users is only apparent and not a real, biologically meaningful, phenomenon.

Table XXVI Percent Change From Baseline in Serum Alkaline Phosphatase (U/L) at Month 6--All Patients Treated With Alendronate (40 mg) (Aspirin-Containing Medications, Nonsteroidal Anti-Inflammatories) - Phase III Studies Combined - Intention-to-Treat Approach

Baseline Covariate	N	Geometric Mean	95% CI
All Patients	68	-76.6	(-80.5, -72.0)
Aspirin-Containing Medications			
Non-user	50	-80.0	(-83.5, -75.7)
User	18	-64.1	(-75.0, -48.4)
Nonsteroid Anti-Inflammatories			
Non-user	39	-77.7	(-82.0, -72.3)
User	29	-75.1	(-81.9, -65.8)

Figure 17 Mean Percent Change From Baseline in Serum Alkaline Phosphatase (U/L) at Month 6--Only Patients Treated With Alendronate (40 mg) (Aspirin-Containing Medications, Nonsteroidal Anti-Inflammatories) - Phase III Studies - Geometric Mean With 95% Confidence Intervals



The different subgroup analyses indicate that alendronate was similarly effective irrespective of baseline patient characteristics, including alkaline phosphatase and prior use of other bisphosphonates. The independence from baseline alkaline phosphatase indicates that alendronate is effective in suppressing bone turnover even in those patients with the most severe elevations, reflecting more severe disease. Moreover, the response to alendronate does not appear to be diminished by the previous use of other agents of the same class.

VI. EFFICACY

The clinical efficacy studies provide evidence that treatment with oral alendronate suppresses bone turnover in pagetic patients. Serum alkaline phosphatase was decreased by treatment, this effect was independent of baseline patient characteristics, such as age, gender, race, height, weight, renal function, and concomitant medications. In addition, alendronate was effective in patients previously treated with other bisphosphonates. Similar response rates were seen in patients with mild or marked elevations in baseline alkaline phosphatase.

In the Phase III Studies, daily oral alendronate 40 mg for six months produced a decrease from baseline alkaline phosphatase of approximately 70 to 80%. This response was greater than that seen with currently available therapies such as etidronate and calcitonin, which usually reduce alkaline phosphatase on average by 40 to 50%. In the Etidronate-Comparison Study, the decrease of serum alkaline phosphatase in patients receiving 400 mg etidronate for six months was 44%. A majority (approximately 84%) of alendronate-treated patients in the Phase III studies responded to treatment at Month 6 using as definition of therapeutic response either normalization of serum alkaline phosphatase or a decrease from baseline by 60%, whereas only 30% of patients who received etidronate did so. A majority (57%) of alendronate-treated patients normalized alkaline phosphatase by Month 6 in the combined Phase III Studies. This was in contrast to the responses seen with etidronate (17%) and placebo (0%).

Other markers of bone turnover (of resorption rather than formation), including urinary hydroxyproline and pyridinium cross links, are also increased in Paget's disease. In untreated patients, these markers rise

proportionately to markers of bone formation, reflecting the preserved coupling between resorption and formation. Alendronate decreased the urinary excretion of these markers at three months, with evidence for continued, albeit less marked, declines at six months.

A majority of the alendronate-treated patients showed small and transient decreases in serum calcium and phosphate, consistent with the effect of the drug to decrease bone resorption. These expected and small changes occurred in the absence of any associated clinical signs or symptoms. In contrast, a majority of the etidronate-treated patients showed an increase in serum phosphate, a known consequence of etidronate therapy. No significant effects on serum calcium were observed in the etidronate group. This is consistent with results of previous studies. In the Placebo-Controlled Study, no meaningful differences were seen between alendronate and placebo in their effects on serum calcium or phosphate, although data were not collected at Month 1, when those effects may be maximal.

Bone pain is probably the most common presenting complaint in Paget's disease, but its cause is often heterogeneous and difficult to characterize. The mechanism of true pagetic pain is obscure; it may be caused by periosteal stretching, increased intramedullary pressure, or by microfractures, which tend to occur frequently in weight-bearing pagetic long bones. Pagetic pain may be difficult to distinguish from the pain due to coincidental osteoarthritis or to arthritis secondary to Paget's disease, resulting from altered mechanical stress on bones and joints. In addition, it has been generally observed that, in the case of bisphosphonates, pain relief is ordinarily slow and may not be observed until several months after the start of treatment. In the Etidronate Comparison Study, alendronate-treated patients showed a decrease in their pain score between Month 1 and Month 3, with a further decrease between Month 3 and Month 6. In contrast, patients receiving etidronate experienced a progressive increase over time in the pain score. Although the effects of alendronate approached significance compared with etidronate, this may have been because the etidronate group had higher baseline pain scores. In the Placebo-Controlled Study, both alendronate- and placebo-treated patients showed a significant decline in pain score over six months, but no differences were observed between the two groups.

A variety of radiological changes can be seen in Paget's disease but the typical radiographic picture is most commonly characterized by an advancing lytic front behind which lie mixed areas of focal bone resorption and formation in a disorderly pattern. Osteolytic lesions are radiolucent and generally correspond to the osteolytic resorption fronts observed histologically. They tend to predominate in the early stages of the disease and are followed by mixed or osteosclerotic lesions due to new bone formation. In the Phase III Studies, a majority of patients showed no change in the degree of osteolysis in response to treatment over the six-month period of evaluation, which may have been too brief to show a definite change in all patients. However, a greater proportion of patients receiving alendronate (39% in the Phase III Studies combined) showed radiologic improvement than did placebo-treated patients (4%). In view of the natural history of the untreated disorder, which does not remit spontaneously, this observation is consistent with the effect of alendronate to decrease bone resorption. Alendronate may halt the progression of the resorption fronts in approximately 40% of patients versus only 5% in placebo-treated patients. These findings are consistent with the observation that alendronate can normalize the bone microstructure from woven to lamellar in pagetic patients.

In summary, the results presented show that alendronate is an effective treatment for Paget's disease. The degree of response observed after six months of treatment with 40 mg alendronate across studies exceeds the results generally obtained with other currently available therapies. In particular, etidronate, the most widely used bisphosphonate, generally decreases alkaline phosphatase by no greater than 40 to 50%, a similar magnitude of response was observed in the Etidronate Comparison Study. In addition, etidronate use is limited by its propensity to induce defective bone mineralization at clinically useful doses, which

may lead to the development of pathological fractures. Other available agents, including the calcitonins and plicomycin are either only partially effective or have very poor tolerability.

Efficacy Conclusions

Oral alendronate 40 mg/day for six months is:

- a. An effective treatment for Paget's disease of bone
- b. Similarly effective in all patient subgroups studied, including age (<65 or ≥65), gender, race, renal function, concomitant medication, prior use of other bisphosphonates, or baseline alkaline phosphatase.
- c. Associated with radiologic improvement of pagetic osteolytic lesions relative to placebo
- d. Demonstrates greater efficacy than etidronate.

VII. SAFETY

A. Introduction

Alendronate sodium is distributed selectively to bone as compared to other organs. In over 2000 postmenopausal women, the safety and tolerability profile, at doses up to 20 mg/day for two years followed by 5 mg/day for one year or 10 mg/day for up to three years is similar to that seen in patients receiving placebo. In patients with Paget's disease, the safety and tolerability profile of alendronate, at doses up to 80 mg/day for up to six months, is also favorable, but because higher doses were used, demonstrated some adverse events.

B. Overall Population

The safety profile of alendronate is derived from three main sources: Phase II and III Paget's Disease Studies, Clinical Pharmacology Studies, and studies in "other patient populations." Only serious adverse experience data are provided for "other patient populations." An overview of the study populations described in this Safety Summary is shown in Table XXVII.

Table XXVII Study Population

Type of Study	Number of Studies	Patients Enrolled
Paget's Disease	4	235
Clinical Pharmacology	17	368
Other Patient Populations		
Core Osteoporosis Studies	8	2661
Other Osteoporosis Studies	9	8332
Other MRL Studies	17*	750
Non-MRL Studies	41	1298
Total Enrolled		13,644
* Includes one Paget's Disease Study designed and conducted by Istituto Gentili		

These studies involved different alendronate doses, routes of administration, durations of treatment, and patient populations. A description of each source follows.

1. Paget's Patients

a. Paget's Clinical Studies

Four Paget's Disease Studies were conducted, two Phase II and two Phase III Studies. The duration of alendronate therapy in these studies was three to six months. One Phase II Study, the Dose-Ranging Study (Protocol 015) (Table XXVIII), had three treatment arms, two of which involved crossover to or from placebo. The other Phase II Study, the Treatment Duration Study (Protocol 024), compared two doses (40 and 80 mg) and two durations (three months and six months) (see Table XXIX). Each of these studies was conducted as a single center study.

Table XXVIII Design of the Paget's Disease Dose-Ranging Study (With Highlighted Off-Alendronate Periods)

Alendronate (20, 40, 80 mg) 12 weeks		Placebo 8 Weeks	Posttreatment Surveillance 24 Weeks
Placebo 8 Weeks	Alendronate (20, 40, 80 mg) 12 Weeks		Posttreatment Surveillance 24 Weeks
Alendronate (80 mg) 12 Weeks		Posttreatment Surveillance 32 Weeks	

Table XXIX Design of the Paget's Disease Treatment Duration Study (With Highlighted Off-Alendronate Periods)

Alendronate (40, 80 mg) 6 Months		Posttreatment Surveillance 6 Months
Alendronate (40, 80 mg) 3 Months	Placebo 3 Months	Posttreatment Surveillance 6 Months

The Phase III Studies had virtually identical study designs, patient populations, and six-month durations of treatment, however, one study was placebo-controlled (Protocol 059) whereas the other study compared alendronate to etidronate (Protocol 056). These latter studies provide the major experience with the 40 mg dose.

b. Clinical Pharmacology Studies

Seventeen Clinical Pharmacology Studies provide experience with either the intravenous (IV) formulation of alendronate in patients with postmenopausal osteoporosis, Paget's disease, metastatic bone disease, or in healthy volunteers or the oral formulation in patients with osteoporosis, Paget's disease, or in healthy volunteers. In these studies, the longest period of treatment was six weeks.

Table XXX shows the Paget's Disease and Clinical Pharmacology Studies

Table XXX Study Design of Paget's Disease and Clinical Pharmacology Studies

Study Name (Protocol No.)	Total Dose Duration	ALN Doses (mg)	ALN	Patients Enrolled		Total
				PBO/Comparative Agent	Patients Enrolled*	
Paget's Disease Studies						
Dose-Ranging Study (015)	12 weeks	All oral 20, 40, 80	24*	7**		31
Treatment Duration Study (024)	3 or 6 months	40, 80	60***	30		60
Etidronate Comparison Study (056)	6 months	40	42	47 ETD		89
Placebo-Controlled Study (059)	12 months†	40	27	28		55
Total			153	112		235
Clinical Pharmacology Studies						
Pharmacokinetics and Pharmacodynamics (007, 008A, 008B, 010, 013, 014, 017, 023, 032, 039, 048, 049, 053, 060, 065, 066, 069)	1 day to 6 weeks	0 125 to 10 IV‡ 0.5 to 100 oral	255# (oral)	128# (IV)		368

* Actual patients counted once

† Counts include patients who received alendronate (ALN) for 12 weeks followed by placebo (PBO) for 8 weeks

** Counts include patients who received PBO for 8 weeks followed by ALN for 12 weeks

*** Counts include patients who received ALN for three months followed by PBO for three months.

† A six-month interim analysis is presented, at this time

‡ Includes patients who received multiple IV doses up to 10 mg/day for five consecutive days.

These values include patients who received both IV and oral formulations of ALN, or both ALN and PBO.

2. Other Patient Populations

Thirty-four (34) studies of alendronate were conducted by MRL and include safety data for the treatment and prevention of osteoporosis in postmenopausal women using the oral formulation (eight core osteoporosis studies, nine other osteoporosis studies). 17 studies of the treatment of other bone diseases (hypercalcemia of malignancy, metastatic bone disease, periodontal disease and Paget's disease) utilized the IV or oral formulations of alendronate. One study in Paget's disease (Protocol 003) was not included in the Paget's disease population because it was designed, initiated, and executed by the principal investigator in collaboration with [redacted]. Data were assembled into case report forms and analyzed retrospectively by MRL for informational purposes. A different formulation of alendronate (free acid) was provided by [redacted] as compared to the alendronate sodium formulation used in the MRL Paget's Disease Studies. In this study, 45 patients received intravenous alendronate and 9 patients received either 30 or 60 mg of oral alendronate. Forty-one non-MRL studies were conducted by collaborating organizations.

The safety data derived from the Paget's Disease Studies and Clinical Pharmacology Studies are discussed separately. The IV and oral formulations of alendronate in the Clinical Pharmacology Studies are presented separately within each table in all Clinical Pharmacology tables and displayed by route of administration. To maximize the number of patients from which safety information is available, the adverse experiences from the four Paget's Disease Studies have been combined, although the study designs and durations are different. The Phase III Studies are also discussed separately because these studies represent the major experience with the 40 mg dose and because they have similar designs and durations, allowing for more meaningful comparisons. For all tables, selected percentages were chosen, where appropriate, to facilitate presentation of the data.

C. Rationale for Safety Evaluations in Clinical Studies

The rationale for selection of safety parameters in clinical studies of alendronate was based on the potential risks described in published literature involving both clinical and animal studies of other bisphosphonates as well as results from preclinical studies of alendronate. As described in the Clinical Pharmacology Section, alendronate localizes to bone, metabolism of alendronate is negligible or nonexistent and it is eliminated, unchanged, exclusively through renal excretion. Therefore, alendronate was predicted to have a favorable safety profile. Extensive nonclinical toxicity studies were performed to identify potential risks of alendronate therapy in clinical studies. Although animal toxicity was identified with high doses of alendronate in several organ systems, no findings were observed at doses 3.5 times the intended 40 mg oral dose for treatment of Paget's disease (a 40 mg oral dose in a 70 kg individual is equal to 0.6 mg/kg/day).

The parameters utilized for safety assessment are presented by body system. In addition to routine clinical and laboratory parameters, a number of special evaluations were performed in clinical studies.

1. Body as a Whole (Systemic)

A systemic syndrome characteristic of an acute-phase response may occur when aminobisphosphonate therapy is initiated. This usually occurs after intravenous administration and rarely occurs with the second or subsequent doses. Doses of oral pamidronate

in excess of 150 mg have also been associated with the acute-phase response. Symptoms are usually mild and include fever and malaise one to two days after dosing. Transient laboratory findings typical of this acute-phase response may occur in the absence of pyrexia and may include decreases in leukocytes, lymphocytes and serum zinc levels and increases in C-reactive protein. Relatively high systemic exposure to drug, such as after intravenous administration, is required to precipitate an acute-phase response.

In animal studies, no bisphosphonates, including alendronate, are known to produce responses analogous to the acute-phase response in humans.

In clinical studies with alendronate, specific evaluations to detect signs or symptoms of an acute-phase response included serial temperature measurements (up to twice daily) and clinical and laboratory assessments.

In addition, routine evaluations at clinic visits were performed to detect systemic adverse experiences and included cardiopulmonary, abdominal, musculoskeletal and neurologic examinations as well as vital signs, weight and oral temperature. Laboratory test results were utilized to assess and confirm systemic adverse experiences.

2. Musculoskeletal

a. Fractures and Bone Histomorphometry

Etidronate, a nonselective bisphosphonate, was first used to inhibit mineralization of ectopic bone in the treatment of myositis ossificans. However, inhibition of mineralization is undesirable in the treatment of Paget's disease and etidronate treatment may induce osteomalacia and fractures in humans. In patients with Paget's disease, continuous etidronate treatment with doses up to 18 mg/kg/day orally for 18 to 30 months was associated with increased skeletal pain and spontaneous fractures of bones not associated with Paget's disease. A 5 mg/kg daily oral dose, when administered for six months in patients with Paget's disease, is associated with significant focal osteomalacia in many patients. Osteomalacia was also reported in patients with moderate decreases in renal function receiving very high doses of oral etidronate, 18 mg/kg/day for 18 to 30 months.

Long-term (one- to two-year) studies of etidronate treatment in dogs revealed that even doses as low as 0.1 mg/kg/day given subcutaneously produced modest reductions in new-bone mineralization. At a 0.5 mg/kg/day subcutaneous dose, several spontaneous fractures were observed in treated dogs. Higher doses (2 to 20 mg/kg/day) totally blocked mineralization activity, increased osteoid thickness and greatly increased spontaneous fracture incidence.

There is also a report of mineralization defects and/or osteomalacia in biopsies of patients with Paget's disease treated with intravenous pamidronate at cumulative doses of 180 or 360 mg over periods ranging from six to nine weeks up to one year. No adverse clinical effects were observed in any of the patients. The report did not indicate whether the osteomalacia was due to metabolic abnormalities (i.e., hypocalcemia and hypophosphatemia due to remineralization of pagetic bone) or to a direct toxic effect on bone mineralization as with etidronate.

Alendronate is a highly potent inhibitor of bone resorption. In contrast to etidronate, the antiresorptive selectivity of alendronate is very high relative to inhibition of bone formation. In rat studies utilizing the Schenk assay, the estimated ratio of the dose required to inhibit bone mineralization to the dose that inhibits resorption is 6000:1. With etidronate inhibition of bone mineralization occurs at the same dose that inhibits bone resorption (ratio 1:1). In studies of rats, a parenteral dose of alendronate 2.5 mg/kg/day was required before inhibition of mineralization was observed. This parenteral dose corresponds to a daily oral dose of approximately 25,000 mg in a 70 kg patient (based on approximately 0.7% absorption). The ratio between this estimated 25,000 mg oral dose and the 40 mg oral Paget's disease treatment dose is 625, which provides a very large margin of safety. Thus, alendronate-induced osteomalacia should not occur clinically.

Alendronate produced no detrimental effects on bone strength or fracture rates during long-term toxicity studies in animals. Alendronate treatment increased bone mass and bone strength with normal histomorphometry in animal models of estrogen deficiency bone loss. Based on these observations, the bone formed during alendronate treatment of Paget's disease should be of normal quality.

Fracture healing is an important consideration in the treatment of Paget's disease. Etidronate impairs radiolar fracture callus strength in dogs treated with 0.5 mg/kg/day subcutaneously. Radiographic non-union was observed at higher doses. Impaired fracture healing in animals treated with etidronate is due to impaired mineralization.

A study of fracture healing in dogs receiving 2 mg/kg/day of oral alendronate before and/or after fracture occurrence showed that strength of the bone at the healed fracture site was normal in alendronate-treated animals. Thus, the bone toxicity observed with etidronate is not predicted to occur with alendronate treatment in patients with Paget's disease.

In clinical studies with alendronate, clinical fractures and complications with fracture healing were identified and recorded as clinical adverse experiences. Additionally, bone histomorphometry was performed to provide data on mineralization, turnover, lamellar architecture and other qualitative measures of bone structure. A bicortical, transiliac biopsy after demeclocycline or tetracycline labeling was performed on subgroups of consenting patients. Evaluation of the specimen included measurement of trabecular osteoid volume, osteoid thickness, mineralizing surface, and qualitative assessment.

A second mechanism-related animal toxicity of bisphosphonates that was observed with alendronate is retention of the primary spongiosa. Bone that forms under growth plates is normally resorbed during bone growth in young animals. Linear growth of bones in alendronate-treated growing animals was not affected, and no apparent adverse effects on the health of these rats resulting from the altered long bone morphology were noted. Although this retention of the primary spongiosa was seen only in growing animals, it may be relevant in adults treated with alendronate for conditions associated with rapid bone formation.

b Pain

Following treatment with etidronate and pamidronate, patients with Paget's disease may have initially increased bone pain at pagetic and previously asymptomatic sites. This pain is seen in 5 to 20% of etidronate patients and may resolve with continued therapy. The actual mechanism is not known. In clinical studies with alendronate, data on musculoskeletal pain were derived mainly by query of the patient for any adverse experience and physical examination at each visit. In addition, assessment of levels and types of pain as a secondary efficacy parameter was done in the Phase III Paget's Disease Studies using a pain questionnaire, the Brief Pain Inventory.

3 Digestive System

The most frequent gastrointestinal adverse experiences reported at therapeutic doses with oral bisphosphonates are symptoms of upper gastrointestinal mucosal irritation with nausea, vomiting, epigastric pain, or dyspepsia. These symptoms are relatively unusual with clodronate but are a feature of both etidronate and pamidronate therapy. A dose relationship has been established for pamidronate with few or no upper gastrointestinal side effects observed with a daily oral dose less than 150 mg. Gastrointestinal toxicity was the limiting factor in oral alendronate dosing in rats. Affected animals exhibited anorexia with typical gastric findings of distention, mucous cell hyperplasia, gastritis, and rare mucosal erosions or ulcers. There was a clear dose relationship with reactions occurring only at very high oral doses (5 mg/kg/day).

In clinical studies with alendronate, data on upper gastrointestinal adverse experiences were derived mainly by questioning the patient about any adverse experience and by physical examination at each visit. There were no clinical trials that included specific direct assessment (e.g., routine endoscopy in asymptomatic patients) of the effects of alendronate on the upper gastrointestinal system. However, if an upper gastrointestinal adverse experience occurred, further investigation through endoscopy was recommended, as deemed clinically appropriate by the investigator.

4 Urogenital System

Large intravenous doses of bisphosphonates, best described for etidronate but also observed with tiludronate and clodronate, are associated with acute impairment of renal function. This is related to the rate of infusion and is possibly due to precipitation of calcium and/or magnesium bisphosphonate complexes. There is a recent report with oral clodronate of acute renal insufficiency in eight patients, seven of whom were also taking nonsteroidal anti-inflammatory agents (NSAIDs). In five patients, the reaction occurred within two months of treatment. A small number of renal biopsies showed proximal tubular necrosis. Although the mechanism of these adverse renal effects is unknown, there are no published reports of renal toxicity in clinical studies with other oral bisphosphonates.

In preclinical studies with alendronate, histologic evidence of renal toxicity was observed at high doses in dogs. This was manifested by mild focal nephritis detected microscopically only. This finding was not associated with functional renal impairment at doses as high as 1 mg/kg/day intravenously or 8 mg/kg/day orally (the latter corresponds to a daily oral dose of 560 mg in a 70 kg patient), and was reversible with cessation of treatment. Dogs are the species most sensitive to nephrotoxicity and, given the high dose required

for the microscopic findings, the potential for nephrotoxicity in humans is minimal.

In order to assess renal function in both IV and oral alendronate studies, laboratory tests were conducted at specified intervals and included creatinine clearance, serum BUN and creatinine levels, and urinalysis (protein and microscopy). Urinary N-acetylglucosaminidase activity (NAG), a specific marker of renal tubular damage, was measured in patients in one Clinical Pharmacology Study, following repeated daily intravenous dosing.

5. Hematologic

One patient receiving pamidronate treatment for Paget's disease developed chronic idiopathic thrombocytopenic purpura. Because the condition responded to glucocorticoids, it was considered an autoimmune disorder rather than marrow suppression. Transient decreases in white blood cell counts (without clinical sequelae) have been reported with oral pamidronate by the same investigator.

There are anecdotal reports of acute and chronic leukemia associated with clodronate treatment. These events have not been reported in detail, and no causal effect has been established between the development of acute or chronic leukemia and therapy with any bisphosphonate. As described previously, transient hematologic changes may be observed as a manifestation of aminobisphosphonate acute-phase reaction.

No hematologic toxicity was observed in preclinical studies with alendronate. Also, there were no treatment-related increases in tumor incidence in 105- and 91-week studies of rats and mice. In clinical studies with alendronate, laboratory safety tests of hematology were conducted and assessed at baseline and at subsequent visits during treatment.

6. Skin

Pamidronate has been associated with rashes, with a 1 to 2% incidence reported by one group of investigators. A sulfur-containing bisphosphonate, tiludronate, has been associated with a severe rash with features of toxic epidermal necrolysis in one patient. At the time of the report, it was the only known severe cutaneous reaction to tiludronate among approximately 1500 treated patients. Vasculitis and erythema multiforme were reported after a single dose of radiolabeled sodium diphosphonate (methylene bisphosphonate, 0.5 mg) used for a bone scan.

In clinical studies with alendronate, cutaneous reactions were assessed by questioning the patient for adverse experiences and through physical examination at visits that included a clinical evaluation. Skin biopsies were performed when considered clinically indicated by the investigator.

7. Metabolic

The pharmacologic effects of bisphosphonates on inhibition of osteoclast-mediated bone resorption are known to produce secondary effects on calcium and phosphate homeostasis, such as decreases in serum calcium and phosphate. Other mechanism-of-action-related effects of etidronate include increases in parathyroid hormone and 1,25-dihydroxyvitamin D, and decreases in serum and urine markers of bone turnover, alkaline phosphatase and hydroxyproline. Similar changes may be anticipated with alendronate. Etidronate is unusual in that an increase (rather than a decrease) in serum phosphate may

occur with its use

The only metabolic toxicity observed in animals treated with oral alendronate 5 mg/kg/day was severe hypocalcemia and dystocia observed in pregnant female rats during parturition. This toxicity was prevented by treatment with calcium supplementation, intravenously.

Biochemical changes in animals treated with alendronate include decreases in serum calcium, serum phosphorus, and serum alkaline phosphatase. Such changes are anticipated to occur with a selective inhibitor of bone resorption without evident signs of toxicity.

In clinical studies with alendronate, secondary effects on calcium and phosphate homeostasis were assessed through serum and urine chemistry tests. These tests were usually conducted at each visit in conjunction with other laboratory safety tests. Clinical evaluation for signs and symptoms of metabolic disorders, including those other than ones related to bone and mineral metabolism, was made at each visit. Patients with normal calcium-regulating hormonal function and adequate dietary calcium and vitamin D should not be at risk for clinical hypocalcemia during therapy with alendronate. Patients with greatly accelerated bone turnover, such as patients with extensive Paget's disease, are at increased risk of hypocalcemia and hypophosphatemia during bisphosphonate therapy due to the rapid influx of mineral into bone which accompanies effective antiresorptive therapy. Therefore, patients in the Phase III Studies and the Phase II Dose-Ranging Study (Protocol 015) received oral calcium supplements.

In addition, patients with hypocalcemia or metabolic conditions causing hypocalcemia (e.g., vitamin D deficiency or hypoparathyroidism) are at risk for exacerbation of hypocalcemia and they were excluded from clinical studies of alendronate.

8 Special Senses

Acute hearing loss was reported in two patients who received oral pamidronate for several years. Both patients had active stapedial otosclerosis and sensorineural hearing loss when they began treatment, and neither had any further deterioration of hearing during the first year of therapy. Uveitis, episcleritis, and scleritis have been reported in patients following intravenous pamidronate and once after oral risedronate.

In clinical studies with alendronate, safety data derived for special senses were obtained through routine clinical examination or query of the patient for adverse experiences at each visit. Because no special sense toxicity was found in preclinical studies, there were no special examinations in any of the clinical trials to assess specific senses.

C Description of Statistical Methods for Clinical and Laboratory Adverse Experience Evaluation

The analysis of safety data is a screening experiment, with both the number of, and the specific hypotheses being tested, a data driven post hoc exercise. Thus statistical significance or the lack thereof can serve as useful bench marks but should not by themselves be definite.

1 Predefined Limits of Change

Predefined limits of change (from baseline) were established for laboratory safety

parameters that were conservative and included values consistent with normal health. The number and percentage of patients in each treatment group with changes outside the predefined limits for these laboratory parameters were provided for each treatment group. In order to obtain better estimates of the incidence of these changes, data from the patients treated with alendronate in the Phase III Studies were pooled. All patients treated with alendronate were compared with placebo and with patients treated with etidronate. Treatment comparison of clinically important increases and clinically important decreases were made using Fisher's Exact Test.

2. Count of Patient-Months for Paget's Disease Studies

The Paget's Disease Studies had several different durations for different treatment groups. Therefore, a calculation of patient-months was performed to provide comparable values between therapy groups, which otherwise cannot be appreciated by reviewing the tables which do not provide duration information. The process of calculating time on treatment makes use of a data listing containing information on each patient's compliance to their assigned treatment. This listing consists of an observation per treatment period with a series of dates describing the beginning and end of each period which are then converted to relative start and stop days for each treatment interval.

The six-month limit is 220 days for the Phase III Studies, 182 days for the Dose-Ranging Study (Protocol 015), and 225 days for the Treatment Duration Study (Protocol 024). These are the periods of time for which patient counts were performed. The number of days on each treatment (the difference between the start and stop days) was summed for each patient. Off-drug periods were not counted. Then the days were summed by treatment assignment and protocol. In addition, the total days on any amount of alendronate and the days on placebo were summed. These counts were converted into a number of person-months by dividing the days by 30, and rounding to the nearest month.

3. Overall Extent of Exposure of the Study Population

Six hundred and three (603) patients were entered into the Paget's Disease and Clinical Pharmacology Studies (Table XXXI). The number of months patients received treatment and the total number of patients who received each treatment in the Paget's Disease and Clinical Pharmacology Studies are presented for patients treated with IV alendronate (N = 128), oral alendronate (N = 415), placebo (N = 121), or oral etidronate (N = 56). The number of months patients received treatment is based on actual days that the patient took medication and does not include interruptions in treatment or missed doses. Therefore, the "months on treatment" is usually slightly less than the actual duration of the treatment period. A patient who received more than one drug or alendronate dose may appear more than once in a table under different treatments (alendronate, placebo, or etidronate) or dose. Hence, the sum of the numbers of patients in each treatment group or dose for Paget's Disease Studies (N = 289) for example, is greater than the number of patients enrolled in the studies (N = 235).

In the Paget's Disease Studies, 160 patients were treated with oral alendronate, 82 with oral placebo and 47 with oral etidronate 400 mg daily. Of the 160 patients

who received oral alendronate, 142 (88.8%) were treated for at least three months. The longest duration of treatment with oral alendronate in these studies was 198 days. Only 50 of 82 patients (61.0%) in the placebo group received placebo for at least three months. The number of patients who received placebo in these studies is approximately half the number of patients who received alendronate. The number of patients who received etidronate (N = 47) is also small.

In the Clinical Pharmacology Studies, 60 patients were treated with IV alendronate, 255 patients were treated with oral alendronate, 68 patients received both formulations, 9 patients were treated with oral etidronate, and 39 patients were treated with placebo (oral and IV formulations). Patients in the Clinical Pharmacology Studies received IV doses of alendronate up to 10 mg/day for five consecutive days. This parenteral dose corresponds to a daily oral dose of approximately 1400 mg/day (based on an approximate 0.7% absorption).

Table XXXI Number of Patients on Study Drug by Dose and Actual Months of Treatment
Paget's Disease and Clinical Pharmacology Studies

Months	1	1 to 3	3 to 6	>6	Total
Paget's Disease Studies					
ALN Oral					
Any Combination of Doses†	5	13	57	85	160
20 mg	0	2	6	0	8
40 mg	5	5	27	73	110
80 mg	0	6	24	12	42
PBO Oral	3	29	26	24	82
ETD 400 mg Oral	3	3	3	38	47
Clinical Pharmacology Studies					
ALN IV					
Any Combination of Doses	128	0	0	0	128
0.125 mg	46	0	0	0	46
0.25 mg	22	0	0	0	22
5 mg	1	0	0	0	1
7.5 mg	21	0	0	0	21
10 mg	39	0	0	0	39
ALN Oral					
Any Combination of Doses	207	48	0	0	255
0.5 mg	1	0	0	0	1
5 mg	42	16	0	0	58
10 mg	149	0	0	0	149
20 mg	24	16	0	0	40

Table XXXI (Cont.) Number of Patients on Study Drug by Dose and Actual Months of Treatment
Paget's Disease and Clinical Pharmacology Studies

Months	1	1 to 3	3 to 6	>6	Total
ALN Oral (Cont.)					
25 mg	17	0	0	0	17
40 mg	48	16	0	0	64
50 mg	25	0	0	0	25
75 mg	5	0	0	0	5
80 mg	15	0	0	0	15
100 mg	12	0	0	0	12
PBO Oral and IV	22	17	0	0	39
ETD 400 mg Oral	9	0	0	0	9
This table displays the number of patients receiving each dose by the actual length of time the dose was received (based on actual days drug was taken). Each month equals 27 days based on an assumed compliance rate of 90%.					
Note: an individual patient may be counted multiple times if during the course of study the patient's daily dosage was changed. However, a patient is counted only once for each daily dose level received during the study.					
† Any Combination of Doses: In this row, each patient is counted once by the total months the patient has been on drug.					

Table XXXII presents a summary of the number of days patients in the Paget's Disease Studies received treatment for all oral alendronate doses and for comparative agents. Patient exposure to oral alendronate in the Paget's Disease Studies ranged from treatment for six days to approximately six months. The duration of treatment with placebo was two-thirds that of treatment with alendronate. The mean number of days on study drug was approximately 136.2, 103.2, and 158.9 for alendronate, placebo and etidronate, respectively, among the studies of 12 weeks to six months duration. The median number of days on study drug was approximately 168, 84, and 182 for alendronate, placebo, and etidronate, respectively. In addition, the number of patients who received placebo exclusively was small (N = 28).

Table XXXII Days Patients Received Treatment Paget's Disease Studies

	ALN Oral	PBO Oral	ETD Oral
Total number of patients	160	82	47
Range of days on drug	6 to 198	4 to 194	3 to 212
Mean number of days on drug	136.2	103.2	158.9
Median number of days on drug	168.0	84.0	182.1

In the Phase II Dose-Ranging Study (Protocol 015), patients received alendronate for 12 weeks as compared to placebo for 8 weeks. In the Phase II Treatment Duration Study (Protocol 024), two groups received alendronate for the full six months while two groups received alendronate for three months followed by placebo for three months. Only one of the two Phase III Studies had a placebo group (Protocol 059). Therefore, because of the varied study design, amongst the four studies, a marked imbalance of patient-month experience between alendronate and placebo groups occurred. 726 alendronate-patient months versus 282 placebo-patient months (Table XX). In one Phase III Study (Protocol 056), there was a 249 patient-month experience for etidronate.

Table XXXIII Summary of Patient Exposure to Treatment
(Intention-to-Treat Approach)
Paget's Disease Studies

Protocol	Daily Treatment	Patient-Months
Phase II		
015	PBO	49
	ALN 20 mg	23
	ALN 40 mg	30
	ALN 80 mg	34
024	PBO	75
	ALN 40 mg	123
	ALN 80 mg	125
Phase III		
056	ALN 40 mg	231
	ETD 400 mg	249
059	PBO	158
	ALN 40 mg	162
All	PBO	282
	ALN	726
	ETD	249

Based on lower mean duration of exposure to placebo, the total incidence of adverse experiences in the placebo group may be an under-representation of the adverse experiences that would occur for a duration of treatment comparable to that of the alendronate group. Data from the Phase III Studies employing comparable study design and duration provide a better evaluation of the relationships between drug and adverse experiences.

D Demographic and Other Characteristics of the Study Population

Baseline demographics for the study population enrolled in the Paget's Disease and Clinical

Pharmacology Studies are outlined in Tables XXXIV and XXXV respectively. Patients who received more than one treatment (e.g., crossover treatments with IV alendronate, oral alendronate, or placebo) are counted in these tables under the heading of each treatment received (i.e., patients may be counted more than once).

The number of males and females were approximately equal in the alendronate and placebo groups. There were more males (66%) than females (34%) in the etidronate group. The mean age of patients in the Paget's Disease Studies was 69.3 years, with a range from 43 to 87 years. 94.5% were Caucasian and 4.5% were black. A somewhat higher proportion of etidronate patients (17.0%) in Paget's Disease Studies were black as compared to the alendronate (3.1%) and placebo groups (0%). Otherwise, demographic characteristics of the patients in the Paget's Disease Studies were similar across studies. These demographic characteristics are consistent with the epidemiology of Paget's disease.

Table XXXIV Baseline Patient Demographics
Paget's Disease Studies

	ALN (N = 160)	PBO (N = 82)	ETD (N = 47)
	N (%)	N (%)	N (%)
Sex			
Female	75 (46.9)	39 (47.6)	16 (34.0)
Male	85 (53.1)	43 (52.4)	31 (66.0)
Age in Years			
40 to 49	3 (1.9)	2 (2.4)	1 (2.1)
50 to 59	19 (11.9)	10 (12.2)	5 (10.6)
60 to 69	51 (31.9)	26 (31.7)	14 (29.8)
70 to 79	74 (46.3)	35 (42.7)	24 (51.1)
80 to 89	13 (8.1)	9 (11.0)	3 (6.4)
Mean	69.5	69.0	69.4
SD	8.2	8.8	8
Median	71.0	70.0	71.0
Range	43-85	48-87	45-84
Racial Origin			
Caucasian	154 (96.3)	81 (98.8)	38 (80.9)
Black	5 (3.1)	0 (0.0)	8 (17.0)
Other	1 (0.6)	1 (1.2)	1 (2.1)

Table XXXV Baseline Patient Demographics
Clinical Pharmacology Studies

	ALN IV (N = 128)	ALN Oral (N = 255)	PBO (Oral and/or IV) (N = 39)	ETD (N = 9)
	N (%)	N (%)	N (%)	N (%)
Sex				
Female	95 (74.2)	232 (91.0)	27 (69.2)	9 (100)
Male	33 (25.8)	23 (9.0)	12 (30.8)	0 (0.0)
Age in Years				
20 to 29	4 (3.1)	4 (1.6)	0 (0.0)	0 (0.0)
30 to 39	1 (0.8)	1 (0.4)	0 (0.0)	0 (0.0)
40 to 49	5 (3.9)	15 (5.9)	3 (7.7)	2 (22.2)
50 to 59	43 (33.6)	128 (50.2)	18 (46.2)	2 (22.2)
60 to 69	44 (34.4)	84 (32.9)	13 (33.3)	3 (33.3)
70 to 79	30 (23.4)	23 (9.0)	5 (12.8)	2 (22.2)
80 to 89	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Mean	61.2	58.1	59.8	59.6
SD	11.1	8.7	8.6	10.7
Median	61.0	57.0	58.0	60.0
Range	21-80	21-76	42-76	45-77
Racial Origin				
Caucasian	109 (85.2)	210 (82.4)	38 (97.4)	9 (100)
Black	1 (0.8)	2 (0.8)	0 (0.0)	0 (0.0)
Other	18 (14.1)	43 (16.9)	1 (2.6)	0 (0.0)

Secondary Diagnoses

A secondary diagnosis is defined as any diagnosis that a patient had at any time prior to initiation of the study. This includes current diagnoses, as well as any diagnoses for conditions the patient had in the past that are no longer active. The number (%) of patients with secondary diagnoses (incidence 5%) in the four Paget's Disease Studies are presented in Table XXXVI. The number of patients included in each treatment category are the number who actually received that treatment. Thus, patients randomized to alendronate who crossed over to and received placebo are counted twice. The prevalence of secondary diagnoses was >95% for alendronate and placebo groups, all etidronate-treated patients had secondary diagnoses. The most common medical conditions were hypertension, hearing loss, and osteoarthritis. Hearing loss and osteoarthritis are common in Paget's disease patients. Prior surgical procedures were also equally common in the three groups. A prior history of musculoskeletal pain was reported equally in alendronate- and placebo-treated patients (11 and 10%, respectively), but was more frequent in the etidronate-treated patients (36%).

Table XXXVI Number (%) of Patients With Secondary Diagnoses by Body System (Incidence $\geq$ 5% in Any Treatment Group)†

	ALN (N = 160)	PBO (N = 82)	ETD (N = 47)
Number (%) of patients with any secondary diagnoses	153 (95.6)	81 (98.8)	47 (100.0)
Body as a Whole/Site Unspecified	31 (19.4)	15 (17.4)	14 (29.8)
Hemorrhaphy	14 (8.7)	5 (6.1)	5 (10.6)
Trauma	0	0	3 (6.4)
Cardiovascular System	70 (43.8)	40 (46.5)	31 (66.0)
Murmur, heart	3 (1.9)	0	6 (12.8)
Heart failure	3 (1.9)	5 (6.1)	1 (2.1)
Angina pectoris	13 (8.1)	7 (8.5)	6 (12.8)
Atherosclerosis, coronary	1 (0.6)	0	3 (6.4)
Hypertension	28 (17.5)	18 (22.0)	7 (36.2)
Myocardial infarction	10 (6.3)	5 (6.1)	1 (2.1)
Digestive System	70 (43.8)	36 (41.9)	26 (55.3)
Constipation	4 (2.5)	3 (3.7)	3 (6.4)
Dyspepsia	2 (1.2)	0	3 (6.4)
Acid regurgitation	10 (6.3)	4 (4.9)	5 (10.6)
Surgery, biliary	12 (7.5)	6 (7.3)	6 (12.8)
Appendectomy	24 (15.0)	17 (20.7)	6 (12.8)
Dentures	9 (5.6)	3 (3.7)	6 (12.8)
Ulcer, peptic	8 (5.0)	3 (3.7)	1 (2.1)
Endocrine	15 (9.4)	5 (5.8)	5 (10.6)
Hemic and Lymphatic	13 (8.1)	3 (3.5)	8 (17.0)
Anemia	6 (3.7)	0	5 (10.6)

	ALN (N = 160)	PBO (N = 82)	ETD (N = 47)
Metabolic, Nutritional, Immune	19 (11.9)	8 (9.3)	13 (27.7)
Hyperlipidemia	2 (1.2)	0	4 (8.5)
Hypercholesterolemia	7 (4.4)	2 (2.4)	7 (14.9)
Musculoskeletal	78 (48.8)	41 (47.7)	33 (70.2)
Prosthesis, hip	13 (8.1)	8 (9.8)	4 (8.5)
Arthritis	10 (6.3)	5 (6.1)	4 (8.5)
Osteoarthritis	22 (13.7)	3 (3.7)	9 (19.1)
Osteoarthritis, hip	6 (3.7)	5 (6.1)	2 (4.3)
Osteoarthritis, knee	5 (3.1)	5 (6.1)	1 (2.1)
Osteotomy	6 (3.7)	5 (6.1)	0
Spondylosis	5 (3.1)	0	4 (8.5)
Pain, musculoskeletal	17 (11.0)	8 (10.0)	17 (36.0)

Nervous System and Psychiatric	38 (23.7)	22 (25.6)	14 (29.8)
Headache	2 (1.2)	4 (4.9)	3 (6.4)
Depression	9 (5.6)	6 (7.3)	1 (2.1)
Respiratory System	21 (31.1)	16 (18.6)	11 (23.4)
Skin and Skin Appendage	27 (16.9)	16 (18.6)	15 (31.9)
Special Sense	71 (44.4)	16 (18.6)	30 (63.8)
Hearing loss	46 (28.7)	25 (30.5)	5 (10.6)
Surgery, corneal	0	0	4 (8.5)
Eyeglasses	6 (3.7)	0	8 (17.0)
Glaucoma	4 (2.5)	0	3 (6.4)
Cataract	14 (8.7)	8 (9.8)	7 (14.9)

	ALN (N = 160)	PBO (N = 82)	ETD (N = 47)
Special Sense (Cont.)	71 (44.4)	16 (18.6)	30 (63.8)
Surgery, lens	5 (3.1)	4 (4.9)	5 (10.6)
Myopia	5 (3.1)	0	5 (10.6)
Presbyopia	5 (3.1)	0	5 (10.6)
Urogenital System	64 (40.0)	31 (36.0)	21 (44.7)
Urolithiasis	7 (4.4)	0	5 (10.6)
Surgery, ovary	7 (4.4)	7 (8.5)	2 (4.3)
Hysterectomy	14 (8.7)	5 (6.1)	3 (6.4)
Benign prostatic hypertrophy	10 (6.3)	3 (3.7)	8 (17.0)
Surgery, prostate	9 (5.6)	6 (6.1)	4 (8.5)
† Derived from Table of All Patients With Secondary Diagnoses by Body System [Ref. D-74]			
Note: Patients with more than one secondary diagnosis in a body system are counted only once in that body system total and that overall total			

E. Concomitant Therapy

The number (%) of patients receiving concomitant therapy in the Paget's Disease Studies is presented in Table XXXVII. Approximately 91, 88, and 100% of the alendronate-, placebo-, and eudronate-treated patients, respectively, received concomitant therapy in these studies.

A wide range of other therapeutic classes was used as concomitant therapies in the Paget's Disease Studies including: central nervous system agents (includes acetaminophen, aspirin, benzodiazepines), anti-infectives (includes amoxicillin, cefaclor, erythromycin, penicillin, sulfamethoxazole/trimethoprim, tetracycline), vitamins and minerals (ascorbic acid, multivitamins, vitamin B-complex, D and E), anti-inflammatories (diclofenac sodium, ibuprofen, piroxicam, naproxen), and gastrointestinal drugs (aluminum/magnesium hydroxide, meclizine hydrochloride).

All patients in the Phase II Dose-Ranging Study (Protocol 015) and the Phase III Paget's Disease Studies were prescribed calcium carbonate as a nutritional supplement and for this reason it is

excluded from concomitant therapy tabulations. Approximately 60% of etidronate-treated patients were also treated with anti-infective agents compared with 44 and 40% of alendronate- and placebo-treated patients, respectively. This included treatment per protocol with demeclocycline for labeling of bone biopsies. A higher percentage of patients treated with etidronate (~47%) received cardiovascular drugs compared with patients treated with alendronate or placebo (~33 and ~37%, respectively). Approximately 45% of patients treated with etidronate received anti-inflammatory agents compared with approximately 16% of patients treated with either alendronate or placebo. Only 6.1% of the placebo-treated patients received hormones or synthetic substitutes compared with 15.6 and 17% of alendronate- and etidronate-treated patients, respectively.

Table XXXVII Number (%) of All Patients Receiving Any Concomitant Therapies

	ALN (N = 160)	PBO (N = 82)	ETD (N = 47)
Number (%) of patients with any concomitant therapy	145 (90.6)	72 (87.8)	47 (100.0)
Antihistamines	3 (1.9)	2 (2.4)	3 (6.4)
Anti-infective agents	70 (43.8)	33 (40.2)	28 (59.6)
Anti-inflammatories	26 (16.2)	13 (15.9)	21 (44.7)
Antineoplastic agents	0	0	1 (2.1)
Antiparkinsonian agents	1 (0.6)	2 (2.4)	1 (2.1)
Antitussives	15 (9.4)	7 (8.5)	2 (4.3)
Autonomic drugs	23 (14.4)	12 (14.6)	9 (19.1)
Blood formation/coagulation agents	7 (4.4)	4 (4.9)	1 (2.1)
Cardiovascular drugs	53 (33.1)	30 (36.6)	22 (46.8)

	ALN (N = 160)	PBO (N = 82)	ETD (N = 47)
Central nervous system drugs	93 (58.1)	46 (56.1)	27 (57.4)
Cold remedies	1 (0.6)	0	1 (2.1)
Electrolyte/caloric/water balance agents	27 (16.9)	18 (22.0)	5 (10.6)
Enzymes/enzyme inhibitors	0	1 (1.2)	0
Expectorants	3 (1.9)	2 (2.4)	1 (2.1)
Gastrointestinal drugs	33 (20.6)	13 (15.9)	7 (14.9)
Hormones/synthetic substitutes	25 (15.6)	5 (6.1)	8 (17.0)
Immunologic substances	4 (2.5)	0	2 (4.3)
Local anesthetics	3 (1.9)	1 (1.2)	1 (2.1)
Muscle relaxants	11 (6.9)	5 (6.1)	2 (4.3)
Ophthalmic preparations	2 (1.2)	0	1 (2.1)
Pharmaceutical adjuncts	4 (2.5)	2 (2.4)	0
Skin/mucous membrane preparations	4 (2.5)	1 (1.2)	1 (2.1)
Vitamins/minerals	75 (46.9)	35 (42.7)	47 (100.0)

Classification undetermined	1 (0.6)	0	1 (2.1)
Therapeutic procedures, noninvasive	1 (0.6)	1 (1.2)	0
Diagnostic procedures, noninvasive	1 (0.6)	0	0
Note: Patients with more than one concomitant therapy are counted only once in the overall total. Calcium carbonate has been excluded from the 'gastrointestinal drugs' category.			

F. Clinical Adverse Experiences

For each patient at clinic visits, investigators assessed the duration, severity, and relationship of adverse experiences to study therapy based on history and appropriate laboratory testing.

1. Paget's Disease Studies

a. Incidence of Clinical Adverse Experiences

Safety data from the Paget's Disease Studies are presented for patients who were studied for up to 12 months during Phase II Studies and up to 6 months in Phase III Studies. The number and percent of patients who had one or more clinical adverse experiences are summarized in Table XXVIII. The percentage of alendronate-, placebo- and etidronate-treated patients reporting at least one clinical adverse experience was 69.4%, 45.1%, and 76.6%, respectively. Adverse experiences considered by the investigator to be drug related (possibly, probably, or definitely) were reported in 28.1%, 12.2%, and 34.0%, respectively, of alendronate-, placebo-, and etidronate-treated patients.

The incidence of serious clinical adverse experiences was 3.1% in alendronate-treated patients, 2.4% in placebo-treated patients, and 12.8% in etidronate-treated patients. One alendronate-treated patient in the 40 mg alendronate group had two serious adverse experiences (esophagitis and esophageal dyskinesia) considered drug related by the investigator. Discontinuations due to clinical adverse experiences occurred in 5.6% and 2.4% of the alendronate- and placebo-treated patients, respectively, compared with 14.9% of etidronate-treated patients. Discontinuations due to drug-related adverse experiences were 2.5, 1.2, and 8.5% in the alendronate-, placebo-, and etidronate-treated groups, respectively. One death occurred in the etidronate group and none in the alendronate and placebo groups.

Table XXXVIII Summary of Clinical Adverse Experiences

	ALN (N = 160)	PBO (N = 82)	ETD (N = 47)
Number (%) of patients with one or more adverse experiences	111 (69.4)	37 (45.1)	36 (76.6)
with drug-related adverse experiences	45 (28.1)	10 (12.2)	16 (34.0)
with serious adverse experiences	5 (3.1)	2 (2.4)	6 (12.8)
with serious drug-related adverse experiences	1 (0.6)	0	0
withdrawn from therapy due to adverse experiences	9 (5.6)	2 (2.4)	7 (14.9)
withdrawn from therapy due to serious adverse experiences	3 (1.9)	0	3 (6.4)
withdrawn from therapy due to a drug-related adverse experience	4 (2.5)	1 (1.2)	4 (8.5)
withdrawn from therapy due to a serious drug-related adverse experience	0	0	0
Patients who died	0	0	1 (2.1)

The number and percent of patients from the Phase III Studies who had one or more clinical adverse experiences are summarized in Table XXXIX. In the Phase III Studies, which utilized the 40 mg dose of alendronate, the adverse experience profile of alendronate-treated patients more closely approximates that of the placebo-treated patients than is apparent in the overall adverse experience profile of the Paget's Disease Studies (Table XXXVIII). This is due in part to the lack of true placebo-only treatment arms in the Phase II Studies as found in the Placebo-Controlled Phase III Study (Protocol 059). The percentage of alendronate-, placebo-, and etidronate-treated patients reporting at least one clinical adverse experience was 78.3%, 64.3%, and 76.6%, respectively. Adverse experiences considered drug related (possibly, probably, or definitely) were reported in 27.5%, 28.6%, and 34% of alendronate-, placebo-, and etidronate-treated patients, respectively.

The incidence of serious clinical adverse experiences was 5.8% in alendronate-treated patients, 0% in placebo-treated patients, and 12.8% in etidronate-treated patients. Only one patient in the alendronate group had two serious adverse experiences (esophagitis, esophageal dyskinesia) considered drug related by the investigator. One death occurred in the etidronate group. Discontinuations due to clinical adverse experiences occurred in 8.7% and 3.6% of the alendronate- and placebo-treated patients, respectively, compared with 14.9% of etidronate-treated patients. Discontinuations due to drug-related adverse experiences were 2.9, 0, and 8.5% in the alendronate-, placebo-, and etidronate-treated groups, respectively.

In reviewing the combined data from the Phase III Studies, it is important to recognize that there were differences in the reported incidence of adverse

experience for alendronate between the two Phase III Studies. The incidence was higher in the Etidronate Comparison Study (Protocol 056) than in the Placebo-Controlled Study (Protocol 059). This may be due to potential observer bias of over-reporting when an active treatment control is employed. Furthermore, the number of patients in the Placebo-Controlled Study was smaller so that firm conclusions may not be drawn.

Table XXXIX Summary of Clinical Adverse Experiences
Phase III Paget's Disease Studies

	ALN 40 mg (N = 69)	PBO (N = 28)	ETD 400 mg (N = 47)
Number (%) of patients with one or more adverse experiences:	54 (78.3)	18 (64.3)	36 (76.6)
with drug-related adverse experiences	19 (27.5)	8 (28.6)	16 (34.0)
with serious adverse experiences	4 (5.8)	0	6 (12.8)
with serious drug-related adverse experiences	1 (1.4)	0	0
withdrawn from therapy due to adverse experiences	6 (8.7)	1 (3.6)	7 (14.9)
withdrawn from therapy due to a serious adverse experience	2 (2.9)	0	3 (6.4)
withdrawn from therapy due to a drug-related adverse experience	2 (2.9)	0	4 (8.5)
withdrawn from therapy due to a serious drug-related adverse experience	0	0	0
Patients who died	0	0	1 (2.1)

The number (%) of patients with a clinical adverse experience by dose (incidence = 2% for any treatment group) for the Paget's Disease Studies is presented in Table XI. The body systems with the highest frequency of adverse experiences were musculoskeletal, digestive, and body as a whole/site unspecified (mostly due to abdominal pain).

Collectively, adverse experiences were reported more frequently in alendronate-treated patients than in placebo-treated patients in several body systems. In etidronate-treated

patients, skin and special sense disorders occurred less frequently than in alendronate-treated patients, while digestive system disorders occurred with equal frequency. In all other body system categories, etidronate patients had more adverse experiences than alendronate patients. However, when the individual adverse experiences are examined the number of patients with adverse experiences is small, making it difficult to determine true differences in most instances.

The small number of patients who received 20 mg alendronate (N = 8) precludes any conclusions about dose trends using this group. In view of the disparity of the duration of patient exposure between the alendronate and placebo groups, the adverse experience profile of alendronate 20 to 80 mg daily was very similar to placebo. No difference in the incidence of clinical adverse experiences was observed between the 40 and 80 mg alendronate-treated patients. The adverse experiences of musculoskeletal pain, abdominal pain, headache and a few digestive system disorders were seen in more than 5% of alendronate-treated patients.

Headache occurred in 6.4% of 40 mg alendronate versus 2.4% of placebo-treated patients and 6.4% of etidronate-treated patients. No further increase was seen at the 80 mg dose. Paget's disease commonly involves the skull and can be manifested by headaches. The more serious and less common sequelae of skull involvement such as ataxia, vertigo, hydrocephalus, slurred speech, and cranial nerve dysfunction were not more common in alendronate-treated patients. Ataxia was seen in one etidronate patient.

Digestive system disorders as a whole were more frequent in the alendronate 40 and 80 mg patients (28.2 and 28.6%, respectively) and etidronate patients (25.5%) than in the placebo patients (11.0%). Frequently (5%) reported gastrointestinal (GI) adverse experiences included diarrhea, dyspepsia, flatulence, and nausea and occurred slightly more often with 40 mg oral alendronate than with placebo, only anorexia and vomiting were more frequent at the 80 mg dose. In the etidronate-treated patients, nausea was the most common digestive system disorder and occurred at an incidence of 10.6% versus 5.5% and 2.4% of alendronate- and placebo-treated patients, respectively. Diarrhea and flatulence were also slightly more common in etidronate patients compared to placebo. Gastritis and ulcers associated with gastrointestinal irritation and reported with other bisphosphonates were not seen in alendronate- or etidronate-treated patients in these studies. Esophagitis was reported in only one patient treated with alendronate who had been on chronic aspirin therapy.

Osteomalacia was reported in one patient treated with alendronate and one patient treated with etidronate.

In all other respects, the alendronate, placebo, and etidronate adverse experiences were similar.

Table XLNumber (%) of Patients With Clinical Adverse Experiences by Dose (Incidence $\geq 2\%$ in Any Treatment Group)[†]

	PBO (N = 82)	ALN 20 mg (N = 8)	ALN 40 mg (N = 110)	ALN 80 mg (N = 42)	ETD 400 mg (N = 47)
Body as a Whole/Site Unspecified	5 (6.1)	1 (12.5)	20 (18.2)	12 (28.6)	14 (29.8)
Asihemia/fatigue	1 (1.2)	0	5 (4.5)	2 (4.8)	2 (4.3)
Chills	0	0	0	1 (2.4)	0
Cold sensation	0	0	0	1 (2.4)	0
Death	0	0	0	0	1 (2.1)
Distention, abdominal	0	1 (12.5)	2 (1.8)	0	2 (4.3)
Edema/swelling	0	0	1 (0.9)	0	1 (2.1)
Fever	0	0	1 (0.9)	3 (7.1)	0
Hernia, abdominal	0	0	0	0	1 (2.1)
Malaise	0	0	2 (1.8)	0	2 (4.3)
Orthostatic effects	0	0	0	1 (2.4)	0
Pain	0	0	0	2 (4.8)	0
Pain, abdominal	2 (2.4)	0	10 (9.1)	5 (11.9)	4 (8.5)
Pain, chest	0	0	0	0	1 (2.1)
Pain, flank	0	0	0	0	2 (4.3)
Cardiovascular System	5 (6.1)	0	9 (8.2)	1 (2.4)	6 (12.8)
Angina pectoris	1 (1.2)	0	1 (0.9)	0	1 (2.1)
Arrhythmia	0	0	0	0	1 (2.1)
Hematoma	0	0	0	0	1 (2.1)
Hemorrhage	0	0	0	0	1 (2.1)
Hypertension, systolic	0	0	0	0	1 (2.1)
Murmur, heart	0	0	1 (0.9)	0	1 (2.1)
Palpitation	0	0	3 (2.7)	1 (2.4)	0
Tachycardia	0	0	0	0	1 (2.1)
Digestive System	9 (11.0)	1 (12.5)	31 (28.2)	12 (28.6)	12 (25.5)
Acid regurgitation	0	0	3 (2.7)	2 (4.8)	1 (2.1)
Anorexia	0	0	0	3 (7.1)	0
Cholecystitis	0	0	0	0	1 (2.1)
Cholelithiasis	0	0	0	0	1 (2.1)
Constipation	2 (2.4)	0	5 (4.5)	1 (2.4)	2 (4.3)
Diarrhea	3 (3.7)	0	7 (6.4)	2 (4.8)	2 (4.3)
Dyspepsia	2 (2.4)	0	6 (5.5)	0	1 (2.1)
Fecal abnormality	0	0	0	0	1 (2.1)
Flatulence	0	0	7 (6.4)	1 (2.4)	2 (4.3)
Hemorrhoids	0	1 (12.5)	1 (0.9)	0	0
Nausea	1 (1.2)	0	6 (5.5)	1 (2.4)	5 (10.6)
Neoplasm, gastric, malignant	0	0	0	1 (2.4)	0
Pancreatitis	0	0	0	0	1 (2.1)

Stomatitis, aphthous	0	0	0	1 (2.4)	0
Vomiting	0	0	2 (1.8)	2 (4.8)	1 (2.1)
Hemic and Lymphatic	0	0	1 (0.9)	0	0
Metabolic, Nutritional, Immune	0	0	3 (2.7)	0	3 (6.4)
Allergy	0	0	0	0	1 (2.1)
Osteomalacia	0	0	1 (0.9)	0	1 (2.1)
Weight loss	0	0	0	0	1 (2.1)
Musculoskeletal	11 (13.4)	3 (37.5)	40 (36.4)	11 (26.2)	18 (38.3)
Cramp, muscle	1 (1.2)	0	1 (0.9)	1 (2.4)	0
Fracture, vertebra	0	0	0	0	1 (2.1)
Myalgia	0	0	0	1 (2.4)	0
Pain, musculoskeletal	7 (8.5)	2 (25.0)	30 (27.3)	10 (23.8)	17 (36.2)
Sciatica	1 (1.2)	1 (12.5)	2 (1.8)	0	1 (2.1)
Stiffness	0	0	3 (2.7)	1 (2.4)	1 (2.1)
Swelling, joint	0	0	1 (0.9)	1 (2.4)	0
Weakness, muscle	0	0	0	0	1 (2.1)
Nervous System and Psychiatric	4 (4.9)	0	14 (12.7)	5 (11.9)	8 (17.0)
Abnormal sensation	0	0	0	0	1 (2.1)
Ataxia	0	0	0	0	1 (2.1)
Dizziness	0	0	2 (1.8)	1 (2.4)	1 (2.1)
Headache	2 (2.4)	0	7 (6.4)	2 (4.8)	3 (6.4)
Hypesthesia	0	0	0	0	2 (4.3)
Insomnia	0	0	0	0	1 (2.1)
Neuropathy, brachial	0	0	0	1 (2.4)	0
Paresthesia	1 (1.2)	0	2 (1.8)	1 (2.4)	0
Cough	0	0	0	0	1 (2.1)
Discomfort, pharyngeal	0	0	0	0	1 (2.1)
Dyspnea	1 (1.2)	0	0	1 (2.4)	0
Edema, pulmonary	0	0	1 (0.9)	0	1 (2.1)
Infection, respiratory, lower	3 (3.7)	0	1 (0.9)	1 (2.4)	0
Infection, respiratory, upper	2 (2.4)	1 (12.5)	4 (3.6)	0	5 (10.6)
Influenza	3 (3.7)	0	1 (0.9)	2 (4.8)	0
Pneumonia	0	0	0	0	1 (2.1)
Rales/rhonchi	0	0	3 (2.7)	0	0
Skin and Skin Appendage	2 (2.4)	0	10 (9.1)	4 (9.5)	1 (2.1)
Herpes zoster	0	0	0	2 (4.8)	0
Nodule, cutaneous	0	0	1 (0.9)	0	1 (2.1)
Pruritus	1 (1.2)	0	2 (1.8)	2 (4.8)	0
Special Sense	3 (3.7)	0	5 (4.5)	1 (2.4)	0
Conjunctivitis	0	0	2 (1.8)	1 (2.4)	0

Table XL (Cont.) Number (%) of Patients With Clinical Adverse Experiences by Dose (Incidence $\geq 2\%$ in Any Treatment Group)†

	PBO (N = 82)	ALN 20 mg (N = 8)	ALN 40 mg (N = 110)	ALN 80 mg (N = 42)	ETD 400 mg (N = 47)
Urogenital System	5 (6.1)	0	3 (2.7)	2 (4.8)	2 (4.3)
Dysuria	0	0	0	2 (4.8)	0
Hemorrhage, vaginal	0	0	0	0	1 (2.1)
Hot flashes	0	0	0	0	1 (2.1)
Infection, urinary tract	3 (3.7)	0	1 (0.9)	1 (2.4)	0
Urinary frequency	0	0	0	1 (2.4)	0
† Derived from Table of All Patients With Clinical Adverse Experiences by Dose Body system categories are presented at 0% incidence. Note: Patients with more than one clinical adverse experience in a body system are counted only once in that body system total.					

The number (%) of patients with a clinical adverse experience by body system (incidence $\geq 2\%$ in any treatment group) for the Phase III Studies was examined separately. As in the four combined studies, the body systems with the highest frequency of adverse experiences were musculoskeletal, digestive, and body as a whole/site unspecified systems. Nervous system and psychiatric and skin disorders were also more frequent in alendronate-treated patients. Musculoskeletal pain, headache, abdominal pain, asthenia/fatigue, and a few digestive system adverse experiences were seen more commonly in alendronate 40 mg and etidronate patients than in the placebo patients. Musculoskeletal pain occurred in 34.8% of the alendronate-treated patients versus 10.7% of patients who received placebo and 36.2% of patients who received etidronate. Abdominal pain occurred in 7.2% of the alendronate-treated patients versus 3.6% of patients who received placebo and 8.5% of patients who received etidronate.

Digestive system disorders were equally prevalent for alendronate, placebo, and etidronate treatment groups. The small number of patients precludes any conclusions regarding specific adverse experiences. Nausea was the most common digestive system disorder and occurred in 10.6% of etidronate-treated patients versus 5.8% of alendronate-treated patients and 3.6% of placebo-treated patients. Frequently ($>5\%$) reported adverse experiences included diarrhea, flatulence, and nausea and these occurred more often in the Phase III alendronate patients than in the placebo group, whereas constipation and dyspepsia were more frequent in the placebo group than in the alendronate patients.

For each clinical adverse experience, investigators were asked to assess drug causality by selecting one of five descriptions: definitely, probably, possibly, probably not, or definitely not. MRL includes the first three terms in classifying the adverse experiences as drug related.

Drug-related clinical adverse experiences that occurred in the Paget's Disease Studies are shown in Table XLI. The most common clinical adverse experience considered by investigators to be drug related was abdominal pain, 6.4% in 40 mg alendronate-, 0% in placebo-, and 8.5% in etidronate-treated patients. No further increase was seen at 80 mg. Other digestive system adverse experiences considered drug related occurred less

frequently (in alendronate 40 mg patients), at comparable rates in the etidronate group, and slightly less frequently in the placebo group. The most common drug-related digestive system disorders were nausea and diarrhea. Nausea occurred more frequently in the etidronate group than in the alendronate group (6.4 and 4.5%, respectively) and less in the placebo group (1.2%). Diarrhea occurred more frequently in alendronate-treated (4.5%) than placebo-treated patients (2.4%), and with equal frequency in the etidronate group (4.3%).

Drug-related musculoskeletal pain was reported in 5.5%, 1.2%, and 10.6% of 40 mg alendronate-, placebo-, and etidronate-treated patients, respectively. There were no reports of drug-related musculoskeletal pain in the 20 mg or 80 mg alendronate groups. Otherwise, the incidence of adverse experiences considered drug related was very similar among alendronate-, placebo-, and etidronate-treated patients.

Table XLI Number (%) of All Patients With Drug-Related Clinical Adverse Experiences by Dose

	PBO (N = 82)	ALN 20 mg (N = 8)	ALN 40 mg (N = 110)	ALN 80 mg (N = 42)	ETD 400 mg (N = 47)
Body as a Whole/Site Unspecified	1 (1.2)	0	10 (9.1)	4 (9.5)	5 (10.6)
Asthma/fatigue	0	0	1 (0.9)	0	0
Chills	0	0	0	1 (2.4)	0
Cold sensation	0	0	0	1 (2.4)	0
Distention, abdominal	0	0	1 (0.9)	0	1 (2.1)
Edema/swelling	0	0	0	0	1 (2.1)
Fever	0	0	1 (0.9)	1 (2.4)	0
Hernia, diaphragmatic	0	0	1 (0.9)	0	0
Infection, bacterial	1 (1.2)	0	0	0	0
Malaise	0	0	0	0	1 (2.1)
Pain, abdominal	0	0	7 (6.4)	2 (4.8)	4 (8.5)
Cardiovascular System	0	0	2 (1.8)	0	1 (2.1)
Palpitation	0	0	2 (1.8)	0	0
Tachycardia	0	0	0	0	1 (2.1)

Table XXLI (Cont.) Number (%) of All Patients With Drug-Related Clinical Adverse Experiences by Dose

	PBO (N = 82)	ALN 20 mg (N = 8)	ALN 40 mg (N = 110)	ALN 80 mg (N = 42)	ETD 400 mg (N = 47)
Digestive System	8 (9.8)	0	19 (17.3)	5 (11.9)	8 (17.0)
Acid regurgitation	0	0	3 (2.7)	2 (4.8)	1 (2.1)
Anorexia	0	0	0	1 (2.4)	0
Constipation	2 (2.4)	0	4 (3.6)	0	1 (2.1)
Diarrhea	2 (2.4)	0	5 (4.5)	1 (2.4)	2 (4.3)
Dyskinesia, esophageal	0	0	1 (0.9)	0	0
Dyspepsia	2 (2.4)	0	4 (3.6)	0	1 (2.1)
Esophagitis	0	0	1 (0.9)	0	0
Flatulence	0	0	3 (2.7)	1 (2.4)	1 (2.1)
Gastritis	1 (1.2)	0	0	0	0
Melena	0	0	1 (0.9)	0	0
Nausea	1 (1.2)	0	5 (4.5)	0	3 (6.4)
Ulcer, duodenal	1 (1.2)	0	0	0	0
Vomiting	0	0	2 (1.8)	1 (2.4)	0
Metabolic, Nutritional, Immune	0	0	2 (1.8)	0	1 (2.1)
Gout	0	0	1 (0.9)	0	0
Osteomalacia	0	0	1 (0.9)	0	1 (2.1)
Musculoskeletal	1 (1.2)	0	7 (6.4)	0	5 (10.6)
Cramp, muscle	0	0	1 (0.9)	0	0
Pain, musculoskeletal	1 (1.2)	0	6 (5.5)	0	5 (10.6)
Stiffness	0	0	1 (0.9)	0	0
Nervous System and Psychiatric	0	0	7 (6.4)	1 (2.4)	2 (4.3)
Depression	0	0	1 (0.9)	0	0
Dizziness	0	0	1 (0.9)	1 (2.4)	1 (2.1)
Headache	0	0	2 (1.8)	0	1 (2.1)
Paresthesia	0	0	2 (1.8)	0	0
Somnolence	0	0	1 (0.9)	0	0
Respiratory System	0	0	1 (0.9)	0	1 (2.1)
Discomfort, pharyngeal	0	0	0	0	1 (2.1)
Infection, respiratory, upper	0	0	1 (0.9)	0	0
Skin and Skin Appendage	1 (1.2)	0	5 (4.5)	0	0
Nail disorder	0	0	1 (0.9)	0	0
Nodule, cutaneous	0	0	1 (0.9)	0	0
Pruritus	1 (1.2)	0	2 (1.8)	0	0
Rash	0	0	1 (0.9)	0	0
Sweating	0	0	1 (0.9)	0	0
Special Sense	0	0	2 (1.8)	0	0
Conjunctivitis	0	0	1 (0.9)	0	0

Perversion taste	0	0	1 (0.9)	0	0
Urogenital System	0	0	1 (0.9)	0	0
Impotence	0	0	1 (0.9)	0	0
Note: Patients with more than one clinical adverse experience in a body system are counted only once in that body system total					

Clinical adverse experiences considered drug related by the investigators that occurred in the Phase III Studies examined separately. The most common of these were musculo-skeletal pain (reported in 8.7, 3.6, and 10.6% of 40 mg alendronate-, placebo-, and etidronate-treated patients, respectively) and abdominal pain (reported in 4.3%, 0, and 8.5% of 40 mg alendronate, placebo, and etidronate patients, respectively). Within the Digestive System category, a few adverse experiences (acid regurgitation, diarrhea, and nausea) occurred more frequently in the alendronate group, whereas others (constipation, dyspepsia, gastritis, and ulcer) occurred more frequently in the placebo group. Generally, the incidence of adverse experiences in the etidronate group was similar to that in the alendronate group. However, the incidences of abdominal pain and musculoskeletal pain were greater in the etidronate patients than in the alendronate patients.

In view of the small numbers of adverse experiences, meaningful conclusions regarding drug causality cannot be drawn. All other body systems showed no difference between 40 mg alendronate- and placebo-treated patients.

In summary, musculoskeletal pain and abdominal pain appeared to be the only clinical adverse experiences that were consistently increased in the 40 mg alendronate treatment group as compared with placebo. This was true for the Phase III Studies as well as the overall Paget's disease experience.

G. Serious Clinical Adverse Experiences

1. Deaths

In the Paget's Disease Studies, there was one death reported (AN 4961, Study 056008) that occurred in a patient treated with etidronate. The cause of death was pulmonary edema.

2. Nonfatal Serious Clinical Adverse Experiences

There were 12 patients with 16 nonfatal serious clinical adverse experiences reported for the Paget's Disease Studies. The respective incidence rates of patients with nonfatal serious clinical adverse experiences were 5 of 160 patients (3.1%) on oral alendronate, 2 of 82 patients (2.4%) on placebo, and 5 of 47 patients (10.6%) on etidronate.

There were two nonfatal serious adverse experiences in one 40 mg alendronate patient that were considered by the investigator to be possibly drug related. A 73-year-old woman with a history of esophageal spasm (AN 1226, Study 059001) was hospitalized for evaluation of chest pain 11 days after starting alendronate. Concomitant medications included aspirin, vitamin D, hydrochlorothiazide/amiloride, doxepin, and calcium. A gastroscopy revealed a small hiatal hernia with retained food in the distal esophagus,

suggestive of a motility disorder and minor distal esophageal erythema. A biopsy of the cardioesophageal junction showed findings consistent with acute esophagitis. Therapy with alendronate was interrupted and the dose of aspirin that the patient was taking decreased. The patient's symptomatology resolved approximately three weeks later. The patient resumed therapy with alendronate shortly after and did not experience a recurrence of symptoms during the rest of the study. The investigator considered these adverse experiences, esophageal dyskinesia and esophagitis, possibly drug related, but noted that concomitant therapy with aspirin had contributed to the adverse event, especially since the patient had been on alendronate therapy for only 11 days at the time of the adverse experience and developed no further symptoms when alendronate therapy was resumed.

H. Discontinuations Due to Clinical Adverse Experiences

Table XLII lists the clinical adverse experiences causing discontinuation of therapy from the Paget's Disease Studies. Nine of 160 (5.6%) alendronate, 2 of 82 (2.4%) placebo and 7 of 47 (14.9%) etidronate patients withdrew from therapy due to an adverse experience (Table XXXIII). Some patients discontinued for more than one adverse experience. With the exception of abdominal pain with vomiting, no more than one patient discontinued for any specific clinical adverse experience.

The most common reason for discontinuation of therapy among alendronate patients was abdominal pain in three of one hundred sixty alendronate patients (1.9%) with associated vomiting in two of these patients (AN 0017, Study 024001; AN 0049, Study 024001) and melena in one of these patient (AN 5008, Study 056012). One of the patients with vomiting received 40 mg alendronate while the second received 80 mg alendronate. The latter patient, (AN 0049, Study 024001), was diagnosed with carcinoma of the cecum two months later. All of these adverse experiences were considered drug related. One of 47 (2.1%) etidronate patients (AN 4936, Study 056006) discontinued for abdominal pain and abdominal distention.

An additional patient (AN 0019, Study 024001), had been off alendronate and on placebo for one month when he developed diarrhea; however, the investigator considered this adverse experience to be drug related.

Discontinuations also occurred for reasons other than an adverse experience. In the Paget's Disease Studies, one patient discontinued from the alendronate group due to a protocol deviation, and one patient each from the etidronate and placebo groups due to withdrawal of consent.

Table XI.II Listing of Patients Discontinued Due to Clinical Adverse Experiences

Study Number	AN	Sex/Age	Drug/Total Daily Dosage at Time of AE	Day AE/Discontinuation Study Drug/Discontinuation Study	Adverse Experience	Serious	Duration	Intensity	Drug Relation	Outcome
PBO'										
056001	1234	F/79	PBO/1 tablet	3/26/26	Apathy	No	24 days	Severe	Prob not	SP
			PBO/1 tablet	19/26/26	Epistaxis	No	8 days	Mild	Prob not	RFC
ALN 40 mg										
056001	4886	F/79	0.01 ALN 57 days/40 mg	176/119/176	Alzheimer's disease	Yes	1 day	Moderate	Prob not	SP
056005	4930	F/64	ALN/40 mg	5/6/17	Cramp, muscle ^a	No	2 days	Severe	Possibly	RFC
			ALN/40 mg	5/6/17	Cramp, muscle ^b	No	2 days	Severe	Possibly	RFC
			ALN/40 mg	5/6/17	Cramp, muscle ^c	No	2 days	Severe	Possibly	RFC
056005	4933	M/71	ALN/40 mg	91/97/228	Hepatitis C	No	27 days	Mild	Def not	RFC
056007	4956	M/66	0.01 ALN 54 days/40 mg	145/91/404	Dizziness	No	8 days	Moderate	Def not	RFC
			0.01 ALN 54 days/40 mg	145/91/404	Asthma/fatigue	No	8 days	Moderate	Def not	RFC
			0.01 ALN 54 days/40 mg	145/91/404	Pain, back	No	8 days	Moderate	Def not	RFC
056010	4994	F/85	ALN/40 mg	11/12/80	Myocardial infarction	Yes	70 days	Severe	Prob not	SP
056012	5008	M/77	ALN/40 mg	92/100/126	Pain, abdominal	No	35 days	Moderate	Possibly	RFC
			ALN/40 mg	95/100/126	Melena	No	32 days	Mild	Possibly	RFC

Table XLII (Cont) Listing of Patients Discontinued Due to Clinical Adverse Experiences

Study Number	AN	Sex/Age	Drug/Total Daily Dosage at Time of AE	Day AE/Discontinuation Study Drug/Discontinuation Study	Adverse Experience	Serious	Duration	Intensity	Drug Relation	Outcome
ALN 40 mg/PBO or PBO/ALN 40 mg										
024001	0017	M/69	ALN/40 mg	10/12/15	Pain, abdominal	No	4 days	Moderate	Probably	RI
			ALN/40 mg	10/12/15	Vomiting	No	4 days	Moderate	Probably	RI
024001	0019	F/76	PBO/1 tablet	124/124/148	Diarrhea	No	25 days	Severe	Definite	NRI
ALN 80 mg										
024001	0049	M/74	ALN/80 mg	69/72/78	Diarrhea	No	1 day	Moderate	Probably	NRI
			ALN/80 mg	69/72/78	Vomiting	No	7 days	Moderate	Probably	NRI
			ALN/80 mg	69/72/78	Pain, abdominal	No	10 days	Moderate	Probably	SP
ALN 80 mg/PBO or PBO/ALN 80 mg										
015001	0019	M/81	ALN/80 mg	64/71/71	Neoplasm, gastric, malignant	Yes	8 days	Severe	Def not	SP
ETD 400 mg										
056001	4875	F/72	ETD/400 mg	8/84/394	Fracture, vertebra, L5	Yes	77 days	Severe	Def not	SP
056006	4936	M/66	ETD/400 mg	29/91/169	Pain, abdominal	No	70 days	Moderate	Probably	RI C
			ETD/400 mg	29/91/169	Distention, abdominal	No	70 days	Moderate	Probably	RI C

Table XLII (Cont.) Listing of Patients Discontinued Due to Clinical Adverse Experiences

Study Number	AN	Sex/Age	Drug/Total Daily Dosage at Time of AE	Day AE/Discontinuation Study Drug/Discontinuation Study	Adverse Experience	Serious	Duration	Intensity	Drug Relation	Outcome
ETD-400 mg (Cont.)										
056006	4942	F/74	ETD/400 mg	10/10/28	Malaise	No	17 days	Moderate	Possibly	RF:C
			ETD/400 mg	10/10/28	Edema/swelling	No	17 days	Moderate	Possibly	RF:C
056008	4961	F/75	ETD/400 mg	10/10/28	Tachycardia	No	17 days	Moderate	Possibly	RF:C
056009	4975	M/72	ETD/400 mg	55/28/55	Edema, pulmonary	Yes	1 day	Severe	Prob not	RF:C
056010	4919	M/83	Off ETD 3 days/400 mg	2/3/36	Dizziness	No	7 days	Moderate	Possibly	RF:C
056012	5007	M/70	Off ETD 3 days/400 mg	26/23/66	Pain, chest	Yes	4 Hr	Moderate	Prob not	RF:C
			ETD/400 mg	109/122/294	Pain, leg	No	186 days	Severe	Possibly	RF:C
- a Muscle cramp, lower legs - b Muscle cramp thighs - c Muscle cramp, back										
- Outcome - NRE = No residual effects - RE = Residual effects - SP = Still present - RF:C = Recovered										

2. Clinical Pharmacology Studies

a. Incidence of Clinical Adverse Experiences

For the Clinical Pharmacology Studies, clinical adverse experience data were examined separately for the patients treated with IV (N = 128) and/or oral (N = 255) formulations within each table. The data for placebo-treated patients (N = 39) are pooled and represent thirty-two patients who received oral placebo, five patients who received IV placebo, and two patients who received both IV and oral placebo. The comparative oral etidronate control population consisted of only nine patients and is too small in number to make any valid comparisons of adverse experience incidences. Therefore, no safety data are presented here for etidronate-treated patients.

Only 6 of the 17 Clinical Pharmacology Studies were conducted as double-blind studies, while 10 of the studies were open-label and 1 was a single-blind study. This lack of blinding may have had an influence on adverse experience reporting. Overall, the clinical adverse experience data support the favorable safety profile of alendronate described above for patients in the Paget's Disease Studies.

In the Clinical Pharmacology Studies, 60 of 128 (46.9%) IV alendronate-treated patients had a clinical adverse experience. This was similar to the experience of oral alendronate-treated patients (137 of 255 or 53.7%) and placebo-treated patients, in which 21 of 39 (53.8%) reported having a clinical adverse experience.

There was a higher incidence of investigator rated drug-related adverse experiences in the IV alendronate (31.3%) and oral alendronate (25.9%) groups versus the placebo group (7.7%). Of these, only one patient (0.8%) was withdrawn from IV alendronate therapy due to an adverse experience (fever, chills, and malaise) that was considered drug related. One patient (0.4%) in the oral alendronate group was withdrawn from therapy due to a drug-related adverse experience (nausea and vomiting). There were no placebo-treated patients withdrawn due to a drug-related adverse experience.

There were three (2.3%) IV alendronate-treated and three (1.2%) oral alendronate-treated patients, versus two (5.1%) placebo-treated patients that had a serious adverse experience; none of these was considered drug related nor did they lead to patient discontinuation. There were no patients, in any of the groups, withdrawn from therapy due to a serious drug-related adverse experience, nor were there any patient deaths.

The body systems with the highest incidence of clinical adverse experiences in the IV alendronate-treated patients were body as a whole (20.3%) and nervous system/psychiatric (19.5%). The body systems with the highest incidence of clinical adverse experiences in the oral alendronate-treated patients were nervous system/psychiatric (34.9%), digestive system (16.1%), and musculoskeletal (12.2%). For placebo, the incidence of adverse experiences in these body systems was 25.6%, 17.9%, and 23.1%, respectively. However, the small number of placebo-treated patients for comparison precludes drawing any conclusions from these data.

The clinical adverse experiences with the highest incidence in the IV alendronate-treated group were headache (18.8%) and fever (14.8%). The incidence of these adverse events in placebo-treated patients was similar for headache (23.1%) and lower for fever (5.1%).

The relatively high incidence of fever may be a feature of the acute-phase responses known to occur with high doses of intravenous aminobisphosphonates. Twice daily oral temperature monitoring during the first week of a six-week oral alendronate (5, 20, or 40 mg/day) dosing study of early postmenopausal women revealed no drug-related elevations. Likewise, no febrile response was noted in a sequential, rising, multiple-dose study of oral alendronate (25, 50, and 100 mg/day each for five consecutive days) in pagetic patients. No subsequent study of oral alendronate in patients with Paget's disease has revealed any evidence of an acute-phase response with doses up to 80 mg.

The clinical adverse events with the highest incidence in the oral alendronate-treated group in the Clinical Pharmacology Studies were headache (31.8%), musculoskeletal pain (9.4%), and nausea (8.2%). The incidence of these adverse events in placebo-treated patients was lower for headache (23.1%), higher for musculoskeletal pain (20.5%), and similar for nausea (7.7%).

Of the IV alendronate-treated patients, 31.3% had clinical adverse experiences considered to be drug related versus 25.9% of oral alendronate patients and 7.7% of placebo patients. The most frequently reported drug-related adverse experiences by the investigator in patients receiving IV alendronate were fever (14.8%) and headache (10.9%). Headache (20.4%) and nausea (4.7%) were most commonly reported in the oral alendronate group. These rates differed from the placebo group that had an incidence of only 2.6% in each of these categories. This difference appears to have been the result of the occurrence of adverse experiences (mostly headaches) rated as "possibly" drug related in several open-label studies conducted without a placebo-control group. One investigator who participated in six of the Clinical Pharmacology Studies reported 35% (40 of 114) of all patient reports of headache, and 54% (36 of 67) of all drug-related headaches. Patients enrolled at this site made up 31% (113 of 368) of the entire Clinical Pharmacology population.

b Serious Clinical Adverse Experiences
Deaths

There were no deaths reported in the Clinical Pharmacology Studies.

Nonfatal Serious Clinical Adverse Experiences

In the Clinical Pharmacology Studies, 3 of 128 (2.3%) IV alendronate patients, 3 of 255 (1.2%) oral alendronate patients, and 2 of 39 (5.1%) placebo-treated patients had serious adverse experiences. None was considered drug related, and all but two of these events occurred during off-drug treatment follow-up periods of up to 696 days.

c. Discontinuations Due to Clinical Adverse Experiences

In the Clinical Pharmacology Studies, two patients treated with IV alendronate and one patient treated with oral alendronate were withdrawn due to non-serious clinical adverse experiences. AN 0114 (Study 023001), who received 7.5 mg IV alendronate once, was discontinued due to a moderate decrease in mental acuity which began on Study Day 1 after therapy. The adverse experience was considered probably not related to study drug and was attributed by the investigator to deterioration of the patient's preexisting Parkinson's disease. The patient recovered with no residual effects. AN 0001 (Study 008002) received a 10 mg IV dose of alendronate and was discontinued due to fever, chills and malaise which began on Study Day 2. The investigator rated this adverse experience as definitely drug related. AN 1137 (Study 053001), who received open-label 10 mg oral alendronate, was withdrawn due to intermittent nausea and vomiting which occurred on Study Day 15. This adverse experience was considered drug related.

Three patients in Clinical Pharmacology Studies of alendronate discontinued therapy for reasons other than adverse experiences including "lost to follow-up" (AN 6249, Study 065001), "patient withdrew consent" (AN 0006, Study 013001) and "withdrawn due to a protocol deviation" (AN 1593, Study 048001). None of the discontinuations suggested any adverse effects of alendronate.

I. Laboratory Safety Profile

In the Paget's Disease and Clinical Pharmacology Studies reported in this application, a large number of routine laboratory safety measurements were performed in laboratories throughout the world. In each study, a standard group of laboratory safety tests was performed in all patients. A central laboratory was commonly used for hematology and chemistry tests for most multicenter studies in the United States, while studies conducted outside the United States utilized local laboratories. In addition to standard laboratory tests performed at each visit, there were a number of laboratory tests that were performed in order to explain other clinical or laboratory findings.

Investigators reviewed laboratory results and determined if adverse experiences had occurred, if so, these were recorded on the case report form. The investigator evaluated all laboratory adverse experiences as to their seriousness, severity, relationship to study drug, action taken, and outcome. The reporting of any laboratory test abnormality as an adverse experience was based on the investigator's judgment of its clinical importance. Therefore, a laboratory value outside the normal range may have been considered an adverse event by some investigators and not by others.

In addition, the proportion of patients with laboratory test values outside predefined limits of change for the Phase III Studies was also determined. Predefined limits of change analyses for these studies may be found in the individual CSRs.

1. Paget's Disease Studies

a. Incidence of Laboratory Adverse Experiences

Table XLIII presents the laboratory adverse experience summary for the Paget's Disease Studies. Of the 242 patients receiving either alendronate or placebo, 35 (14.5%) had at least one laboratory adverse experience: 28 (17.7%) in the alendronate-treated group, and 7 (8.6%) in the placebo-treated group. Twenty-one patients had adverse experiences

considered possibly, probably, or definitely drug related by the investigator 18 (11.4%) in the alendronate-treated group and 3 (3.7%) in the placebo-treated group. Three alendronate-treated patients withdrew from therapy due to a laboratory adverse experience with associated clinical adverse experiences. One of these was considered serious and one was considered drug related by the investigator.

Table XLIII Summary of Laboratory Adverse Experiences

	ALN (N = 160)	PBO (N = 82)	ETD (N = 47)
Number of patients with at least one laboratory test post baseline	158	81	47
Number (%) of patients with one or more adverse experiences	28 (17.7)	7 (8.6)	6 (12.8)
with drug-related adverse experiences	18 (11.4)	3 (3.7)	1 (2.1)
with serious adverse experiences	1 (0.6)	0	0
with serious drug-related adverse experiences	0	0	0
withdrawn from therapy due to adverse experiences	3 (1.9)	0	0
withdrawn from therapy due to a serious adverse experience	1 (0.6)	0	0
withdrawn from therapy due to a drug-related adverse experience	1 (0.6)	0	0
withdrawn from therapy due to serious drug-related adverse experience	0	0	0
Patients who died	0	0	0

The laboratory adverse experience summary for the Phase III Studies were examined separately. Of the 97 patients receiving either alendronate or placebo, 21 (21.6%) had at least one laboratory adverse experience: 17 (25.0%) in the alendronate-treated group, and 4 (14.3%) in the placebo-treated group. Nine patients had adverse experiences considered possibly, probably, or definitely drug related by the investigator: 8 (11.8%) in the alendronate-treated group and 1 (3.6%) in the placebo-treated group. Two alendronate-treated patients withdrew from therapy due to a laboratory adverse experience with associated clinical

adverse experiences, one of which was considered drug related. No laboratory adverse experiences were serious. The laboratory adverse experiences reported in the Phase III Studies are comparable to those reported for the four Paget's Disease Studies combined.

Serum AST (aspartate aminotransferase) and ALT (alanine aminotransferase) were performed routinely as required by protocol in all of the Paget's Disease Studies. Serum GGT (γ -glutamyltransferase) was performed routinely in all but the Dose-Ranging Study (Protocol 015). The incidences of serum AST, ALT, and GGT increases were greater in the 80 mg group (9.5, 9.5, and 24.7%, respectively) than in the 40 mg group (1.9, 1.9, and 5.1%, respectively) which did not differ from placebo (0, 1.3, and 7.1%, respectively). Serum uric acid increase was seen in 3 of 78 (3.8%) of alendronate-treated patients. Gout is associated with Paget's disease and uric acid increases are not unexpected. With the exception of possible liver transaminase elevations for the 80 mg alendronate dose, there were no trends for dose-related effects for any other laboratory adverse experiences.

The Phase III experience is similar to the overall experience with a few exceptions. ALT and GGT increases occurred in 1.5 and 4.4%, respectively, of alendronate-treated patients and were less common than in the placebo-treated patients (3.6 and 7.1%, respectively). AST increases occurred in 1.6 and 0% of alendronate- and placebo-treated patients. Decreased lymphocytes occurred in 3 of 68 (4.4%) alendronate-treated patients compared to 0% of placebo-treated patients. Two of these patients had low pretreatment lymphocyte counts, and the third had a baseline lymphocyte count only slightly above the normal range. Decreased serum calcium and phosphate were infrequent (<5%) but expected because of the antiresorptive effect of the drug. Decreased hematocrit was seen in 4.4% of alendronate patients similar to the 3.6% incidence in the placebo patients. Increased uric acid was seen in 4.4% of alendronate patients compared to 0% of placebo patients. Gout is associated with Paget's disease and uric acid increases are not unexpected.

The investigator-rated drug-related laboratory adverse experiences that occurred in the Paget's Disease Studies are shown in Table XLIV. Increases in ALT, AST, and GGT were limited to the 80 mg group in the Paget's Disease Studies. Decreased hematocrit, lymphocytes, calcium, phosphate and guaiac positive stool were also considered drug related by the investigators and are discussed below. The incidences of these laboratory adverse experiences were minimally increased relative to placebo.

The adverse experience of decreased hematocrit was slightly more frequent in the 40 mg alendronate-treated patients (3 of 108; 2.8%) compared to placebo (0 of 78; 0.0%), but the patient number is small. None of these adverse experiences was serious. AN 5011 (Study 056012) had no clinical symptoms associated with the decreased hematocrit. AN 5008 (Study 056012) had abdominal pain and melena associated with the decreased hematocrit. AN 1231 (Study 059001) had no clinical symptoms associated with the decreased hematocrit.

Decreased lymphocytes adverse experiences were more common in the 40 mg alendronate-treated patients (3 of 108, 2.8%) than in the placebo-treated patients (0%). Two of these patients had low pretreatment lymphocyte counts and the third had a baseline lymphocyte count only slightly above the normal range.

One patient had an isolated decreased serum calcium (AN 4989, Study 056010). Another patient (AN 4895, Study 056002) had both decreased serum calcium and phosphate. None of the decreases was associated with clinical symptoms, but both were considered drug related by the investigator. However, the one patient with decreased serum calcium and phosphate developed a mineralization defect as a result of this decrease.

One alendronate patient (AN 4926, Study 056005), a 71-year-old male with a history of cholecystectomy and hemorrhoids, had a guaiac positive stool on Study Day 187. Subsequently, the patient had a normal endoscopy; however, a colonoscopy revealed a benign polyp and two bleeding hemorrhoids. The colon polyp and hemorrhoids were deemed to be definitely not drug related and it is unclear why the guaiac positive stool was considered possibly drug related. No action was taken.

With the exception of possible liver transaminase elevations for doses of alendronate through 80 mg, there were no trends for dose-related effects for any other laboratory adverse experiences.

Table XLIV Number (%) of All Patients With Drug-Related Laboratory Adverse Experiences by Dose

	PBO (N = 82)	ALN 20 mg (N = 8)	ALN 40 mg (N = 110)	ALN 80 mg (N = 42)	ETD 400 mg (N = 47)
Number of patients with any laboratory test post baseline	81	8	108	42	47
Number (%) of patients with any laboratory adverse experiences	3 (3.7)	0 (0.0)	10 (9.3)	8 (19.0)	1 (2.1)
Hematology					
Hematocrit decreased	0/78	0/8	3/108 (2.8)	0/42	1/47 (2.1)
Hemoglobin decreased	0/78	0/8	1/108 (0.9)	0/42	0/47
Lymphocytes decreased	0/78	0/8	3/108 (2.8)	0/42	0/47
Neutrophils decreased	1/78 (1.3)	0/8	1/67 (1.5)	0/42	0/0
Blood Chemistry					
ALT increased	0/78	0/8	1/108 (0.9)	4/42 (9.5)	0/47
AST increased	0/75	0/8	1/104 (1.0)	4/42 (9.5)	0/47
GGT increased	2/56 (3.6)	0/1	3/98 (3.1)	8/33 (24.2)	0/47
Calcium decreased	0/80	0/8	2/108 (1.9)	0/42	0/47
Phosphate decreased	0/80	0/8	1/108 (0.9)	0/42	0/47

Uric acid increased	0/50	0/8	1/78 (1.3)	0/12	0/47
Stool Analysis					
Guaiac positive	0/0	0/0	1/1 (100)	0/0	0/0
This table represents counts of patients having specific laboratory adverse experiences in the following format: number of patients with experience/number of patients tested (% of ratio)					
Note: Patients with more than one laboratory adverse experience are counted only once in the overall total					

The investigator-rated drug-related laboratory adverse experiences that occurred in the Phase III Paget's Disease Studies were examined alone.

Because the majority of drug-related laboratory adverse experiences occurred in the Phase III Paget's Disease Studies, the Phase III profile is similar to the overall Paget's disease experience. The only exception was the elevation of liver enzymes which occurred almost exclusively in the Phase II Studies.

b. Serious Laboratory Adverse Experiences

Deaths

There were no deaths associated with a laboratory adverse experience.

Nonfatal Serious Laboratory Adverse Experiences

One patient had a serious laboratory adverse experience in the 80 mg alendronate-treated group. The patient (AN 0019, Study 015001), an 81-year-old man with a history of bradycardia, had a decreased hemoglobin to 95 g/L (Normal range [NR] 115 to 150) on Day 64 from a baseline value of 142 g/L. The hematocrit also decreased to 0.29 (NR 0.37 to 0.47). The patient discontinued the study on Day 71. These events were reported as serious laboratory adverse experiences once the patient was diagnosed as having gastric cancer. The investigator felt that these adverse experiences were definitely not related to treatment with alendronate.

c. Discontinuations Due to Laboratory Adverse Experiences

Overall, 3 of 160 patients (1.9%) treated with alendronate in the Paget's Disease Studies were discontinued from treatment due to a laboratory adverse experience. Table XLV is a listing of these events. All three patients discontinued due to clinical adverse experiences with associated laboratory adverse experiences, one of which was considered drug related by the investigator and one which was considered serious, but not drug related.

Table XLV Listing of Patients Discontinued Due to Laboratory Adverse Experiences

Study Number	AN	Sex /Age	Drug /Total Daily Dosage at Time of AE	Day of AE/Discon Study Drug /Discon Study	Adverse Experience	Lab Value/Unit	Normal Range	Sero /Dru Relatu
ALN 40 mg								
056005	4933*	M/71	ALN/40 mg	91/97/228	GGT increased	272.0 U/L	15.0 to 85.0	No/Def1
			ALN/40 mg	91/97/228	AST increased	355.00 U/L	0.00 to 40.00	No/Def1
			ALN/40 mg	91/97/228	ALT increased	535.00 U/L	0.00 to 45.00	No/Def1
			Off ALN 8 days/40 mg	105/97/228	GGT increased	184.0 U/L	15.0 to 85.0	No/Def1
			Off ALN 8 days/40 mg	105/97/228	AST increased	214.00 U/L	0.00 to 40.00	No/Def1
			Off ALN 8 days/40 mg	105/97/228	ALT increased	371.00 U/L	0.00 to 45.00	No/Def1
056012	5008**	M/77	ALN/40 mg	91/100/126	Hematocrit decreased	41.40 %	42.00 to 52.00	No/Poss
ALN 80 mg/Placebo								
015001	0019***	M/81	ALN/80 mg	64/71/71	Hemoglobin decreased	95.00 g/L	115.00 to 150.00	Yes/Def
			ALN/80 mg	64/71/71	Hematocrit decreased	0.290 L/L	0.370 to 0.470	Yes/Def

* Associated clinical adverse experience Hepatitis C

** Associated clinical adverse experience Abdominal pain

*** Associated clinical adverse experience Gastric cancer

Drug Relation:

Def not = Definitely not

d Special Laboratory Evaluations

Values Outside of Predefined Limits of Change

Predefined limits of change from baseline were established for laboratory safety parameters to identify patients whose changes in laboratory values merited review and to estimate the numbers of patients in each treatment group who experienced such changes. Changes outside of the predefined limits of change may occur even within a normal, healthy population, on the basis of variability of laboratory analyses, diurnal and other causes of intra- and inter-individual variations. Nevertheless, predefined limits of change represent a rational tool for monitoring laboratory safety, allowing identification of individual changes and comparisons among treatment groups. In order to obtain better estimates of the incidence of these changes, data from the patients treated with alendronate in the two Phase III Studies that had similar designs, treatment duration, and patient characteristics were pooled. All patients treated with alendronate were combined and compared with those treated with placebo or etidronate. Patients were classified as "above limit" or "below limit" as defined in Treatment group comparisons of clinically important increases and decreases were made using the Fisher's Exact Test.

Analyses of three laboratory parameters (serum calcium, serum corrected calcium, and serum phosphate) revealed significant differences between the frequency of values outside predefined limits for alendronate-, placebo-, and etidronate-treated groups.

The frequency of serum calcium decreases to levels < 8.5 mg/dL and of serum corrected calcium decreases to levels $<$ lower limit of normal (LLN) in the alendronate group were statistically significant compared with placebo (19.1 versus 0%, $p < 0.017$ and 25.0 versus 0%, $p < 0.002$, respectively) and with etidronate (2.1%, $p < 0.007$ and 4.3%, $p < 0.004$, respectively). In general, the decreases were small, transient and occurred early on in the study. Greater decreases in serum calcium (values < 8.0 mg/dL) occurred in only one patient. Decreases in serum calcium were anticipated due to the pharmacological mechanism of action of alendronate resulting in positive skeletal balance and a net influx of calcium into bone. No signs or symptoms of hypocalcemia occurred in any patient.

Decreases in serum phosphate would also be anticipated due to the pharmacological mechanism of action of alendronate. Serum phosphate decreases (30% and to a level below the lower limit of normal) were seen in 11.8% alendronate versus 0% of placebo and etidronate patients. However, this was not significant.

Increased serum phosphate (30% and to a level above the upper limit of normal) were common in etidronate-treated patients (48.9%) and were not seen in the alendronate (0%, $p < 0.001$) or placebo patients (0%, $p < 0.001$). This is a well known effect of etidronate to increase serum phosphate by increasing renal tubular resorption (TmP/GFR). There is some evidence to suggest that this effect

of etidronate is related to its effect to inhibit mineralization of bone. Other bisphosphonates, such as alendronate, do not induce hyperphosphatemia at doses used clinically. To the contrary, serum phosphate tends to decrease both in response to the antiresorptive effect of alendronate and to the homeostatic increase in parathyroid hormone.

A transient decrease in circulating WBC and lymphocytes is seen after intravenous administration of alendronate. After oral administration, a decrease in WBCs (below the lower limit of normal) was seen in 13.2% of alendronate patients and was not significantly different from placebo (7.1%) or etidronate (4.3%). Decreases greater than 20% were seen in 4.4% of alendronate patients versus 3.6% of placebo patients and 2.1% of etidronate patients. Lymphocyte decreases greater than 20% were seen in 10.3% of alendronate patients and were not significantly different from placebo (3.6%) or etidronate (2.1%). No significant increases (greater than 50% and above the upper limit of normal) in AST, ALT, or GGT were seen in alendronate, placebo or etidronate patients. However, ALT and GGT increases were actually more frequent in placebo patients than in alendronate or etidronate patients.

2. Clinical Pharmacology Studies

a. Incidence of Laboratory Adverse Experiences

The overall percentages of alendronate- and placebo-treated patients with a reported laboratory adverse experience in the clinical pharmacology studies were generally similar to those seen in the clinical trials, allowing for the small number of placebo-treated patients. However, laboratory adverse experiences were greater in the IV (26.1%) versus oral (12.1%) alendronate patients, as were drug-related adverse experiences. There were no patients in these studies with serious laboratory adverse experiences. One patient discontinued due to a drug-related laboratory adverse experience in the alendronate IV group.

The most frequently reported laboratory adverse events in the IV alendronate-treated patients were increases in C-reactive protein (10 of 20, 50%), lymphocytes decreased (17 of 118, 14.4%), WBC decreased (12 of 118, 10.2%), and serum calcium decreased (9 of 119, 7.6%). The increase in C-reactive protein and the hematologic changes are typical of those observed with the acute-phase response associated with intravenous administration of aminobisphosphonates. The decrease in serum calcium would be an anticipated mechanism of the pharmacological-related effect of a bisphosphonate.

The most frequently reported laboratory adverse events in patients treated with oral alendronate were increases in parathyroid hormone (12 of 56, 21.4%) and increases in osteocalcin (3 of 56, 5.4%). The corresponding values in the placebo-treated group were (2 of 17, 11.8%) and (4 of 17, 23.5%), respectively. Additionally, the placebo-treated group had an

11.8% incidence (2 of 17) of increased urine calcium versus 2.1% (1 of 48) in the alendronate-treated groups. All of these differences may be anticipated as a result of alendronate's antiresorptive effect. None of these experiences was associated with a clinical adverse experience.

In the course of the sequential rising multiple-dose study of oral alendronate in patients with Paget's disease, there was a reversible reduction in the median estimated lymphocyte count of approximately 10 and 22% at the end of the first and second weeks of dosing (25 and 50 mg). This decrease was not progressive and was not observed while the patients continued to receive drug at the higher dose level. No other consistent significant changes occurred in any other hematologic parameter. At the end of the first week of alendronate dosing in the six-week study of early postmenopausal women (dose levels 0, 5, 20, and 40 mg), there were no differences from placebo for any hematologic parameter. No subsequent study of oral alendronate in patients with Paget's disease has revealed any evidence of an acute-phase response with doses up to 80 mg.

Drug-related laboratory adverse events reported in the alendronate IV population included decreased lymphocytes, neutrophils, WBC, and increased C-reactive protein, consistent with an acute-phase response. The incidence of serum calcium decrease considered drug related was 7.6% in patients treated with alendronate, which would not be unexpected in a population receiving an intravenous dose of a potent bisphosphonate. None of these patients with serum calcium decrease had a related symptomatic clinical adverse experience. ALT increases considered drug related were reported in 3 of 119 (2.5%) IV alendronate-treated patients versus 1 of 39 (2.6%) placebo patients.

Drug-related laboratory adverse events in patients treated with oral alendronate included increased parathyroid hormone (21.4%), which is anticipated as a physiologic response to alendronate's antiresorptive effect, decreased granulocytes (2.1%), decreased osteocalcin (1.8%), and urine RBCs increased (1.3%). In the placebo-treated patients, the most frequent drug-related laboratory adverse events were increased osteocalcin (5.9%) and increased parathyroid hormone (5.9%).

In summary, these laboratory adverse experiences were not associated with any clinical adverse experiences. Due to the small numbers of placebo patients present in these studies, no meaningful conclusions can be drawn from this comparison, although several observations (such as, decreased serum calcium) are consistent with the pharmacological effects of alendronate.

b Serious Laboratory Adverse Experiences

There were no deaths due to a laboratory adverse experience and there were no patients in the Clinical Pharmacology Studies who had a serious laboratory adverse experience.

c Discontinuations Due to Laboratory Adverse Experiences

One patient treated with IV alendronate was discontinued due to a laboratory adverse experience. AN 0001 (Study 008002) was a 64-year-old female who experienced the clinical adverse experiences of pyrexia, malaise, and rigor after receiving her first IV dose of alendronate. She recovered within 24 hours from these adverse experiences, but decided to withdraw from the study after Day 1. All clinical adverse experiences resolved without residual effects. On Day 2, the patient's lymphocytes decreased to $0.400 \times 10^9/L$ (NR 1.000 to 4.000) and her leukocytes decreased to $3.80 \times 10^9/L$ (NR 4.00 to 11.00) from baseline values of $1.900 \times 10^9/L$ and $7.7 \times 10^9/L$, respectively. These laboratory adverse experiences were considered drug related by the investigator.

J. Specific Safety Evaluations

1. Body as a Whole (Systemic)

In clinical studies with alendronate, routine evaluations to detect signs and symptoms of an acute-phase response included clinical adverse reports of fever, chills, flu-like illness, and malaise. The febrile acute-phase response observed with IV aminobisphosphonates or high-dose oral pamidronate was not observed with oral doses of alendronate up to and including 40 mg in the Paget's Disease and Clinical Pharmacology Studies. One patient treated with alendronate 80 mg (AN 0032, Study 024001), in the Treatment Duration Study, had a transient, asymptomatic drug-related fever on Day 2 of study therapy, consistent with an acute-phase response. In addition, two studies specifically monitored oral temperature. No other clinical adverse experiences potentially representing an acute-phase response were more common in patients treated with alendronate compared to placebo.

2. Musculoskeletal

a. Fractures

Fractures were captured as adverse experiences by the investigators in all Paget's Disease and Clinical Pharmacology Studies based on patient signs, symptoms, or history related by the patient or documented by an x-ray report. Fractures occurred rarely and there was no evidence for any treatment-related trends.

In the Paget's Disease Studies, no fractures occurred in patients while on alendronate therapy. One patient (AN 0045, Study 024001) treated with alendronate 80 mg for three months sustained an ankle fracture eight months after being off therapy. There was one patient (AN 4875, Study 056001) who experienced an L5 vertebral fracture while on etidronate.

In the Clinical Pharmacology Studies no fractures occurred in patients while on alendronate therapy. One ankle fracture, considered definitely not related to study drug, occurred in a patient treated with IV alendronate 7.5 mg for four consecutive days. This patient (AN 0002, Study 023001), had a CVA and fell 24 months after her last dose of study drug.

b. Bone Histomorphometry

Information concerning the quality of bone formed during alendronate treatment is available from preclinical and clinical histomorphometric studies as well as mechanical strength testing of bones from various animal models. The Alendronate Sodium Histomorphometry Report summarizes the preclinical data and discusses the clinical histomorphometry data. Evaluable data are available for 70 alendronate patients with iliac crest biopsies in Paget's Disease Studies for doses up to 80 mg. Additional data are available from studies in the osteoporosis population. Osteoid thickness (OTh) and osteoid volume (OV) and were measured in order to assess the effects of alendronate on the mineralization of newly formed bone. Mineralizing surface (MS) was measured to assess the effects of alendronate to decrease the rate of bone turnover, an expected consequence of inhibition of osteoclast-mediated bone resorption.

As described in more detail in the Histomorphometry Report and consistent with the preclinical data, no direct adverse effects of alendronate on mineralization were observed in the Paget's Disease Studies. OTh and OV decreased, meaning that a higher proportion of the total bone present was mineralized in alendronate-treated patients than in placebo-treated controls. These changes are the expected result of the decrease in the rate of bone turnover due to alendronate treatment and are opposite to those that would have been observed if alendronate caused osteomalacia. MS decreased dose-dependently up to 80 mg/day of alendronate, thereby confirming reduction in the rate of bone turnover. No qualitative abnormalities, such as woven bone or marrow fibrosis, occurred as a result of alendronate treatment.

In the Paget's Disease Studies, two patients (one on alendronate and one on etidronate) had evidence of defective mineralization, but to varying degrees. These cases are discussed below.

In the alendronate-treated patient (40 mg) (AN 4895, Study 056002), histomorphometry of bone taken from a pagetic site showed mean OTh of 14.5 μ m and an OV/BV of 6.3%. Although these values are moderately high for nonpagetic bone, they are not exceptional in pagetic bone. A review of the patient's laboratory data revealed definite changes in the indices of calcium homeostasis. In particular, serum calcium decreased from a prestudy value of 9.0 mg/dL to a value of 8.3 mg/dL at the first month and to 7.9 mg/dL at the third month of treatment (NR = 8.4 to 10.4 mg/dL), returning to normal range by the sixth month at which time the iliac crest biopsy was performed. Serum phosphate also decreased, from a prestudy level of 2.8 mg/dL to 2.3 mg/dL at the first month and 2.2 mg/dL at the third month (NR = 2.5 to 4.5 mg/dL), returning to normal by the sixth month. These decreases in calcium and phosphate are the expected consequence of the marked suppression of bone resorption and hence bone turnover (alkaline phosphatase 1148 and 121 U/L at baseline and six months, respectively), with subsequent positive skeletal mineral balance induced by alendronate. In fact, rather than an increase in unmineralized bone, the data from this patient suggest that the mineralization of bone actually improved during treatment (evidenced by the secondary decrease in calcium and phosphate). However, limited availability of calcium and phosphate prevented this remineralization process from progressing at an optimal rate.

In this patient, the reduced calcium times phosphate product, rather than any adverse, direct effect of alendronate is the most probable reason for the observed histomorphometric findings. In fact, if defective mineralization had been a direct effect, then the increased uptake of calcium and phosphate into bone and the observed decreased concentration of these ions in serum, would not have occurred.

The other patient (AN 4984, Study 056010) received etidronate 400 mg daily. The histomorphometric report following a bone biopsy on Day 189 indicated an OV/BV of 37%, signifying a major degree of osteomalacia. Unlike the alendronate-treated patient, serum calcium remained normal throughout the study, and serum phosphate increased, from a prestudy value of 3.7 mg/dL to a value of 6.0 mg/dL at the end of the sixth month. Thus, the osteomalacia observed in this patient was almost certainly a result of the known direct inhibitory effect of etidronate on bone mineralization, rather than a decrease in the calcium times phosphate product.

At pagetic bone sites, data from the Phase III Studies showed significantly higher values of OV and OTh in etidronate-treated patients versus those treated with alendronate. Based upon all of the available histomorphometric information from both the preclinical and the clinical studies, it is clear that alendronate at doses up to 80 mg/day for three months, 40 mg/day for six months in the Paget's Disease Studies, or 10 mg/day for three years, 20 mg/day for two years followed by 5 mg/day for a third year in the Osteoporosis Studies does not directly inhibit bone mineralization. All of the observed histomorphometric changes are those anticipated from the pharmacological action of alendronate as a potent inhibitor of bone resorption. Bone formed during alendronate treatment is qualitatively normal. In the rare cases of patients with Paget's disease and markedly increased bone turnover, in whom serum calcium and phosphate decline while on treatment, a slight lag in the rate of mineralization due to limited availability of calcium and phosphate have been noted.

c. Pain

Musculoskeletal pain was recorded as an adverse experience by the investigators in the Paget's Disease and Clinical Pharmacology Studies. It is one of the most common symptoms of Paget's disease. Because of the age of patients, however, it is often difficult to separate out pagetic bone pain from other causes of musculoskeletal pain (e.g., fracture, sarcoma, arthropathy, osteoarthritis).

In the Paget's Disease Studies, musculoskeletal pain was the most common clinical adverse experience occurring in 25.0, 27.3, and 23.8% of patients receiving alendronate 20, 40, and 80 mg daily as compared to 8.5% of placebo patients and 36.2% of etidronate patients. Only six (5.5%) 40 mg alendronate-treated Paget's disease patients had drug-related musculoskeletal pain as compared to one (1.2%) placebo patient and five (10.6%) etidronate patients. Musculoskeletal pain in these patients was typical of the early flare in pain seen with other bisphosphonates. There were no serious episodes of musculoskeletal pain on alendronate.

Generally, the pain on alendronate 40 mg was described as mild or moderate. Most of the patients first experienced pain within two months of starting alendronate, which is consistent with the phenomenon of increased or new pain associated with the initiation of treatment with other bisphosphonates. Recurrence of pain was rare and only one alendronate-treated patient, AN 4956 (Study 056007), discontinued due to back pain, dizziness and asthenia. Only two patients, one on alendronate 40 mg (AN 1247, Study 059002) and one on alendronate 80 mg (AN 0050, Study 024001), had joint swelling associated with their knee pain. These events were not considered drug related by the investigator. No other patients had clinical sequelae (e.g., fracture, sarcoma) associated with their pain.

The incidence of pain was similar in alendronate and etidronate patients versus the lower incidence in placebo patients. Again, back pain was the most common type of pain in alendro-

nate patients. Most of the patients experiencing pain did so within 45 days of initiating alendronate therapy. Pain was most common in the Phase III Etidronate Comparison Study. This may in part reflect bias be due to the anticipation of increased pain from initiation of etidronate therapy and because investigators and patients knew they were on a bisphosphonate for the duration of the study. In the Phase III studies, no difference in response to alendronate (decrease in alkaline phosphatase) was seen in patients with versus without musculoskeletal pain adverse experiences.

In the Phase III Studies, the incidence of drug-related musculoskeletal pain was 8.7% in alendronate versus 3.6% in placebo-treated patients.

In an effort to determine the effect of treatment on bone pain, an assessment of pain was made in the Phase III Paget's Disease Studies as a secondary efficacy endpoint using a questionnaire (Brief Pain Inventory). In the Etidronate Comparison Study, alendronate decreased pain whereas etidronate increased pain. In the Placebo-Controlled Study, a similar decrease was seen in both the alendronate and placebo groups. Moreover, patients in the alendronate group who reported musculoskeletal pain as an adverse experience did not differ in terms of change in pain score (Brief Pain Inventory) as compared to those patients without musculoskeletal pain. These data suggest that alendronate therapy does not increase pain as measured by this questionnaire.

In summary, clinical adverse experiences of musculoskeletal pain appear to be increased in alendronate-treated patients in the Paget's Disease Studies. This pain was not severe, rarely recurred and resulted in only one discontinuation. Although 27.3% of 40 mg alendronate-treated patients had musculoskeletal pain only 5.5% of 40 mg alendronate-treated patients had pain attributed to drug. When the pain questionnaire was used for assessment, no increase was documented in alendronate patients. In the osteoporosis population, no increase in musculoskeletal pain was seen. If musculoskeletal pain is truly the result of alendronate treatment, then it would appear to be specific to patients with Paget's disease. It has been suggested that initiation of bisphosphonates and the associated rapid decreases in bone turnover in patients with Paget's disease, as reflected by decreases in alkaline phosphatase, may result in a transient flare of pain which may herald subsequent clinical improvement and may in some way be related to the "healing" of pagetic lesions. However, the mechanism remains unknown. In the Phase III Studies, transient flares in musculoskeletal pain were seen as well as marked decreases in alkaline phosphatase. However, whether or not a patient had musculoskeletal pain, did not affect a patient's response as measured by a decrease in alkaline phosphatase.

3 Digestive System

a. Upper Gastrointestinal Adverse Experiences

As mentioned previously, the most frequent gastrointestinal adverse experiences reported for therapeutic doses of oral bisphosphonates are symptoms of upper gastrointestinal mucosal irritation, such as nausea, vomiting, epigastric pain or dyspepsia. For this reason, in the Paget's Disease Studies, a focused analysis of potential digestive system toxicity was performed by examining all adverse experiences listed under Body as a Whole/Site Unspecified (i.e., abdominal pain, abdominal distention, diaphragmatic hernia) or Digestive System Disorder, that may result from upper gastrointestinal mucosal irritation.

Table XLVI displays the summaries of these upper gastrointestinal adverse experiences for the Paget's Disease Studies. In these studies, 26 (23.6%) patients on 40 mg alendronate had at least one upper GI adverse experience, compared to six (7.3%) placebo patients. Although the patient numbers were small, no apparent dose trend was seen. Eighteen (16.4%) patients on 40 mg of

alendronate had investigator rated drug-related upper gastrointestinal adverse experiences compared to five (6.1%) patients on placebo. One patient in the 40 mg group described previously in detail, had serious, possibly drug-related adverse experiences of esophagitis and esophageal dyskinesia. Only two (1.8%) patients in the 40 mg group were withdrawn from alendronate therapy due to upper gastrointestinal adverse experiences (abdominal pain and vomiting, abdominal pain and melena), both were considered drug related.

Table XLVI Summary of Upper Gastrointestinal Adverse Experiences by Dose

	PBO (N = 82)	ALN 20 mg (N = 8)	ALN 40 mg (N = 110)	ALN 80 mg (N = 42)	ETD 400 mg (N = 47)
Number (%) of patients with one or more adverse experiences	6 (7.3)	1 (12.5)	26 (23.6)	10 (23.8)	10 (21.3)
with drug-related adverse experiences	5 (6.1)	0	18 (16.4)	5 (11.9)	9 (19.1)
with serious adverse experiences	0	0	1 (0.9)	0	0
with serious drug-related adverse experiences	0	0	1 (0.9)	0	0
withdrawn from therapy due to adverse experiences	0	0	2 (1.8)	1 (2.4)	1 (2.1)
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	2 (1.8)	1 (2.4)	1 (2.1)
withdrawn from therapy due to a serious, drug-related adverse experience	0	0	0	0	0
Patients who died	0	0	0	0	0

The number (%) of patients in the Phase III Studies who had one or more upper gastroin-

testinal adverse experiences are displayed in Table XLVII. Fourteen of 69 (20.3%) alendronate-treated patients had at least one upper gastrointestinal adverse experience compared to 5 of 28 (17.9%) placebo-treated patients. Only eight (11.6%) patients treated with alendronate had drug-related upper gastrointestinal adverse experiences compared to five (17.9%) patients treated with placebo. One patient had serious drug-related adverse experiences (esophagitis and esophageal dyskinesia). One patient on alendronate withdrew from therapy due to a drug-related adverse experience (abdominal pain and melena). Thus, in the six-month Phase III Studies, the upper gastrointestinal tolerability profile of alendronate 40 mg was virtually indistinguishable from that of placebo.

Table XLVII Summary of Upper Gastrointestinal Adverse Experiences
Phase III Paget's Disease Studies

	ALN 40 mg (N = 69)	PBO (N = 28)	ETD 400 mg (N = 47)
Number (%) of patients with one or more adverse experiences	14 (20.3)	5 (17.9)	10 (21.3)
with drug-related adverse experiences	8 (11.6)	5 (17.9)	9 (19.1)
with serious adverse experiences	1 (1.4)	0	0
with serious drug-related adverse experiences	1 (1.4)	0	0
withdrawn from therapy due to adverse experiences	1 (1.4)	0	1 (2.1)
withdrawn from therapy due to a serious adverse experience	0	0	0
withdrawn from therapy due to a drug-related adverse experience	1 (1.4)	0	1 (2.1)
withdrawn from therapy due to a serious drug-related adverse experience	0	0	0
Patients who died	0	0	0

In the Clinical Pharmacology Studies, the incidence of gastrointestinal adverse experiences in patients who received oral alendronate (16.1%) compared to the placebo (17.9%)

group was similar. In particular, abdominal pain was actually less common on oral alendronate (5.5%) than placebo (10.3%).

Table XLVIII shows the number (%) of patients with each upper gastrointestinal adverse experience by dose in the Paget's Disease Studies. In these studies, the most commonly reported adverse experiences in the 40 mg alendronate and placebo groups were abdominal pain (9.1 vs 2.4%), dyspepsia (5.5 vs 2.4%), nausea (5.5 vs 1.2%), and acid regurgitation (2.7 vs 0%), respectively.

Table XLVIII Number (%) of All Patients With Upper Gastrointestinal Adverse Experiences by Dose

	PBO (N = 82)	ALN 20 mg (N = 8)	ALN 40 mg (N = 110)	ALN 80 mg (N = 42)	ETD 400 mg (N = 47)
Number (%) of patients with one or more adverse experiences	6 (7.3)	1 (12.5)	26 (23.6)	10 (23.8)	10 (21.3)
Acid regurgitation	0	0	3 (2.7)	2 (4.8)	1 (2.1)
Anorexia	0	0	0	3 (7.1)	0
Distention, abdominal	0	1 (12.5)	2 (1.8)	0	2 (4.3)
Dyspepsia	2 (2.4)	0	6 (5.5)	0	1 (2.1)
Eructation	0	0	1 (0.9)	0	0
Esophagitis	0	0	1 (0.9)	0	0
Gastritis	1 (1.2)	0	0	0	0
Gastroenteritis	0	0	1 (0.9)	0	0
Hernia, diaphragmatic	0	0	1 (0.9)	0	0
Melena	0	0	1 (0.9)	0	0
Nausea	1 (1.2)	0	6 (5.5)	1 (2.4)	5 (10.6)
Pain, abdominal	2 (2.4)	0	10 (9.1)	5 (11.9)	4 (8.5)
Ulcer, duodenal	1 (1.2)	0	0	0	0
Vomiting	0	0	2 (1.8)	2 (4.8)	1 (2.1)
Note: Patients with more than one clinical adverse experience are counted only once in the overall total.					

In the Phase III Studies, the upper gastrointestinal tolerability profile of alendronate 40 mg is similar to that of placebo.

In all Paget's Disease Studies the number of patients who experienced drug-related abdominal pain was greater in the 40 mg alendronate group (7 of 110 (6.4%) versus 0 of 82 with placebo). No dose trend was observed between the 40 and 80 mg groups. Two patients (1.8%) in the 40 mg group and one patient (2.4%) in the 80 mg group with drug-related abdominal pain discontinued treatment. These events were not serious and were associated with other clinical gastrointestinal symptoms such as vomiting, diarrhea and melena. These cases are discussed below.

Alendronate 40 mg

AN 5008 (Study 056012), a 77-year-old male, treated with 40 mg alendronate, experienced abdominal pain on Study Day 92 and melena on Study Day 95 accompanied by a decreased hematocrit. The patient had a history of heartburn, and at the prestudy visit, complained of gassiness and intermittent abdominal discomfort. By Month 3, the gassiness and abdominal discomfort had worsened, and the patient's hematocrit had decreased to 41.4% from a baseline of 43.8% (NR = 42.0 to 52.0). The investigator believed that the decreased hematocrit and exacerbation of gastric distress were possibly drug related. Study drug therapy was discontinued on Day 100 and the patient's symptoms were much improved. Three follow-up tests for occult blood, gastrointestinal evaluations, and a D-xylose test to rule out malabsorption were all negative. Although the gastroenterologist did not feel that the patient's gastrointestinal symptoms were secondary to study drug therapy, the investigator did.

AN 0017 (Study 024001), a 69-year-old male, treated with 40 mg and with a history of angina, experienced abdominal fullness and discomfort on Study Day 6. Study therapy was continued at this time. On Study Day 10, he experienced abdominal pain and vomiting. Two days later, study therapy was discontinued, and he subsequently felt better. The investigator considered the adverse experience to be drug related.

Alendronate 80 mg

AN 0049 (Study 024001), a 74-year-old male treated with 80 mg and with a history of appendectomy and stomach disorders, entered the study with a GGT value of 50 U/L. On Day 9, he experienced nausea, vomiting, and abdominal pain. On Day 15, the patient's GGT increased to 74 U/L and subsequently decreased to 46 U/L on Day 29. Moderate abdominal pain persisted. On Day 69, he experienced diarrhea, upper abdominal pain, and vomiting that resulted in therapy discontinuation. On Day 78, while the patient was off therapy, his GGT and ALT increased to 101 and 82 U/L, respectively. The investigator rated the adverse experiences as drug related, however, two months later, carcinoma of the cecum was diagnosed.

Additional safety experience with 40 mg alendronate was obtained in studies of postmenopausal osteoporosis. Women with postmenopausal osteoporosis treated with 40 mg alendronate for up to one year, experienced a higher incidence of upper gastrointestinal adverse experiences, drug-related upper gastrointestinal adverse experiences and withdrawals due to upper gastrointestinal experiences, such as esophagitis and gastritis, compared with placebo and lower doses of alendronate.

In summary, alendronate at doses of 40 mg in patients with Paget's disease was generally well tolerated. Upper gastrointestinal adverse experiences did occur, although discontinuations were seen in only 1.8% of 40 mg alendronate patients and the incidence of these adverse experiences in the Phase III Studies was similar for the 40 mg alendronate

and placebo groups. Considering the overall Paget's disease and osteoporosis experience, upper gastrointestinal adverse experiences, such as abdominal pain, esophagitis, and gastritis, appear to be associated with 40 mg alendronate treatment and may cause discontinuation in some patients.

In all Paget's Disease Studies, patients were monitored for changes in liver function by monitoring liver enzymes and reporting clinical adverse experiences. ALT, AST, and GGT were performed routinely in the Phase III and the Treatment Duration Phase II Studies. Only ALT and AST were performed routinely in the Phase II Dose-Ranging Study (Protocol 024). In addition, predefined limits of change analyses were performed in the individual studies as well as collectively for the Phase III Studies. Group mean values, over time, for the liver enzymes are provided in the individual CSRs.

Across the four Paget's Disease Studies, AST, ALT, and GGT increases were not reported as laboratory adverse experiences more frequently in patients treated with 40 mg or in the Phase III Studies examined separately. The predefined limits of change analyses in the Phase III Studies did not identify a significant increase in AST, ALT, or GGT, defined as an increase $\geq 50\%$ and above the upper limit of normal. None of the Paget's Disease Studies showed any within group mean increases in the AST, ALT, or GGT values. However, AST, ALT, and GGT increases were reported as laboratory adverse experiences more commonly in patients treated with 80 mg alendronate (9.5, 9.5, and 24.2%) as compared with placebo-treated patients (0, 1.3, and 7.1%), respectively. All of the laboratory adverse experiences in the 80 mg alendronate group occurred in the Treatment Duration Study and were considered to be drug related by the investigator in this single center trial. For these patients, the increases in liver transaminases were small (<1.5 times the upper limit of normal) with the exception of one patient, AN 0049 (Study 024001) who was diagnosed with cecal carcinoma. No patients discontinued because of abnormal liver-associated enzymes alone. Many patients had single elevations that normalized while the patients were still on alendronate, and several of these patients had elevations prior to study treatment, during crossover placebo treatment or during the off-drug surveillance period. Several patients were also taking concomitant therapies that are known to increase liver-associated enzymes.

In a Phase IIb Osteoporosis Study (Protocol 026), in which patients received 40 mg alendronate for up to one year for the treatment of postmenopausal osteoporosis, the frequency of serum AST increases outside a predefined limit of change (increase $\geq 50\%$ and above the upper limit of normal) was significantly greater in the 40 mg/placebo group than in the placebo group (9/32 versus 1/30, respectively, $p = 0.013$). However, in three of the nine patients the AST increases occurred while the patients were receiving placebo in the second year crossover period. For all patients, changes in mean AST values from baseline were similar across all alendronate and placebo treatment groups in this study. Significant differences were not observed for increased ALT.

In the Clinical Pharmacology Studies, there was no appreciable difference in reported liver-associated enzyme adverse experiences in patients treated with alendronate compared with placebo, despite several of these studies utilizing intravenous doses of alendronate that results in a much higher systemic exposure compared with oral doses.

Therefore, laboratory studies showed no clear indication of adverse effects of alendronate

on serum liver-associated enzymes at oral doses up to 40 mg for up to one year. In one study, there was a higher incidence of increased liver-associated enzymes in patients treated with 80 mg alendronate for up to six months, however, a causal relationship was not established. Nonetheless, no persistent effects or evidence of clinical or biochemical hepatotoxicity are present for oral doses of alendronate up to 80 mg for up to six months.

4. Urogenital System

In order to assess the safety of alendronate with respect to renal adverse experiences, all urogenital adverse experiences were reviewed. In addition, standard renal function laboratory tests were performed.

The overall incidence of either clinical or laboratory renal function adverse experiences was not increased in patients treated with oral alendronate at any dose when compared to placebo in the Paget's Disease Studies. In the Clinical Pharmacology Studies there was no increase in renal adverse experiences in the oral or IV alendronate patients. Thus, there was no evidence to associate renal function abnormalities with alendronate therapy.

Two Clinical Pharmacology Studies included special evaluations of renal function in Paget's disease patients. The first study evaluated creatinine clearance (measuring mean percent change of serum creatinine values) following intravenous infusion of alendronate. The second study assessed glomerular filtration rate (using clearance of ^{51}Cr -EDTA), renal concentrating ability (using a water deprivation test), and proximal tubular injury (using urinary protein and N-acetylglucosaminidase excretion) following five repeated daily intravenous infusions of 10 mg alendronate (each equivalent to an oral dose approximately 1400 mg assuming oral bioavailability of 0.7%). No evidence of nephrotoxicity was disclosed through these specific laboratory evaluations of renal function.

5. Hematologic

Hematologic adverse experiences were evaluated at each visit by clinical assessment and performing specific laboratory tests. Patients treated with oral alendronate at doses of 80 mg or less did not show an increase in the incidence of clinical hematologic adverse experiences or laboratory hematological adverse experiences. Only three (2.8%) patients receiving 40 mg oral alendronate compared to zero patients receiving placebo in the Paget's Disease Studies had laboratory adverse experiences of decreased lymphocytes. Two of the three patients had pretreatment lymphocyte counts below the normal range and the third had a baseline lymphocyte count slightly above the lower limit of normal.

The predefined limits of change analyses in the Phase III Studies showed that there were more patients with lymphocyte reductions of at least 20% and below the lower limit of normal in the 40 mg alendronate-treated group compared with placebo. However, these differences were not statistically significant.

Although no laboratory adverse experiences were reported for decreased lymphocytes and WBCs in the Phase II Studies, mild decreases in lymphocytes and WBCs were identified in 80 mg patients in the predefined limits of change analyses in the Treatment Duration Study.

In the Clinical Pharmacology Studies, patients receiving IV alendronate had decreased lymphocytes, neutrophils, and WBCs compared to placebo patients, consistent with the

expected acute-phase response. Similar decreases in hematologic parameters were not seen in patients who received oral alendronate in the other Clinical Pharmacology Studies.

There were no reports of acute or chronic leukemia in any Paget's Disease or Clinical Pharmacology Studies.

In summary, no important hematologic safety problems were detected through extensive routine and special safety testing in the study population. Hematologic changes consistent with an acute-phase response may be seen with intravenous alendronate and rarely with oral alendronate 80 mg.

6. Skin

In the Paget's Disease Studies, the incidence of all skin adverse experiences or specific skin disorders such as rash, pruritus, or urticaria were infrequent and numerically slightly greater in the alendronate 40 mg (4 of 10; 3.6%) group than in the placebo (2 of 82; 2.4%) group. Severe rashes of the nature reported in one patient with tiludronate were not seen in this population. None of the rashes observed in alendronate-treated patients was rated as serious, and all tended to resolve spontaneously or after treatment discontinuation. No case was associated with bullous lesions, mucous membrane involvement, or any systemic symptoms such as laryngeal edema or wheezing.

In the Paget's Disease Studies, two 40 mg alendronate patients from the Treatment Duration Phase II Study experienced non-serious pruritus considered drug related by the investigator. These cases are discussed below:

Alendronate 40 mg

AN 0011 (Study 024001), a 75-year-old male with a history of angina and asthma, developed a skin rash (dermatitis) on both arms on Day 12 of treatment with 40 mg alendronate while also taking salbutamol and prochlorperazine. Alendronate therapy was interrupted for 15 days and the rash was treated with topical betamethasone. The rash was considered moderate and probably drug related by the investigator. On Day 29, one day after the completion of treatment for the rash, alendronate therapy was resumed. On Day 79, the patient developed pruritus, without a rash, on the right arm. The pruritus was again treated with topical betamethasone and lasted seven days. Although the pruritus was considered mild and drug-related therapy with alendronate was continued and, the patient remained in the study through Day 372 without recurrence.

AN 0028 (Study 024001), a 59-year-old male with a history of a left tibial nail and osteotomy, experienced pruritus of the left shin on Day 15 of treatment with 40 mg alendronate. The pruritus was considered mild and possibly drug related with residual effects. However, study therapy was continued.

In the Clinical Pharmacology Studies, there were three cases of

non-serious, drug-related rash or erythema. These cases are discussed below.

Alendronate 20 mg

AN 4456 (Study 049001), a 66-year-old female with a history of otosclerosis, depression, muscle cramps and back pain experienced a rash on Study Day 36 of treatment with 20 mg oral alendronate. The patient was concomitantly taking dothiepin, quinine and paracetamol/dextropropoxyphene. The rash lasted eight days and resolved spontaneously without treatment five days after discontinuation of alendronate therapy. The rash was considered moderate and possibly drug-related by the investigator.

Alendronate IV

AN 1061 (Study 039001), a 68-year-old female with a prestudy history of Reynaud's, arterial hypertension, arthritis, breast cancer, heart murmur, and facial erythema experienced an increase in intensity of her erythema on the same day of an infusion of 16 mg alendronate IV. The erythema lasted two and one-half hours and resolved spontaneously. The alendronate infusion was completed per protocol. The erythema was considered mild and possibly drug related by the investigator.

AN 0001 (Study 069001), a 62-year-old male with a history of eczema (impetigo as a child), renal calculus and low back pain experienced a rash on Study Day 16, two hours after the start of an intravenous alendronate infusion of 125 mcg. The rash lasted 20 minutes. The alendronate infusion was completed as per protocol and the rash spontaneously resolved without treatment. The rash appeared again two days after the infusion. This episode lasted two days. The rash was not treated and again spontaneously resolved. The first incidence of rash was considered mild and possibly drug-related by the investigator. The second incidence of rash was considered mild and probably not drug related by the investigator.

In summary, drug-related skin reactions appear to be an uncommon event in patients treated with alendronate. Because of the small number of events and resolution of rashes on therapy, a causal relationship was not clearly established.

7 Metabolic

At each visit, specific laboratory tests were performed to evaluate the effects of alendronate therapy on biochemical indices of calcium homeostasis.

A decrease in serum calcium was reported as a laboratory adverse event in 2 of 108 (1.9%) patients receiving 40 mg alendronate in the Paget's Disease Studies. These laboratory adverse experiences occurred within the first three months of therapy, were transient and resolved without therapy. In the predefined limits of change analyses in the

Phase III Studies, the incidence of decreased serum calcium (<8.5 mg/dL) was significantly increased in the 40 mg alendronate group compared with the placebo group (19.1 vs 0%, p = 0.017). However, the proportion of patients with greater decreases in serum calcium (<8 mg/dL) was not statistically significant. These decreases were usually transient occurring prior to three months of therapy and normalizing before six months.

In the Paget's Disease Studies, a decrease in serum phosphate was reported as an adverse experience in only one patient receiving 40 mg alendronate. This patient is the same patient that developed serum calcium <8 mg/dL and consequently had a mildly increased osteoid thickness and volume on bone biopsy. In the predefined limits of change analyses in the Phase III Studies, serum phosphate decreases ($\geq 30\%$ and to a level below the lower limit of normal) were seen in 11.8% of the 40 mg alendronate patients versus 0% in the placebo patients. However, this difference was not statistically significant (p > 0.20). In one of the Phase III Studies, a similar transient decrease of ~1% in serum phosphate was seen in the 80 mg group and ~0.5% in the 40 mg group which paralleled the decrease in calcium. This decrease in serum phosphate was maximum at around three months and normalized at six months. The phosphate findings are also mechanism of action-related to alendronate.

These transient and mild decreases in serum calcium and phosphate within the normal range are to be expected in patients treated with oral alendronate (as well as other inhibitors of bone resorption) as a result of positive skeletal calcium and phosphate balance.

8. Special Senses

The uveitis, episcleritis and scleritis associated with other bisphosphonates were not observed with oral or IV alendronate. In the Paget's Disease Studies, conjunctivitis occurred in 2 of 110 (1.8%) patients on 40 mg alendronate and 1 of 42 (2.4%) patients on 80 mg alendronate. One of these three events was considered drug related and is described below.

Alendronate 40 mg

AN 5008 (Study 056012), a 77-year-old male in the 40 mg group with a history of a cataracts and glaucoma, experienced a conjunctival hemorrhage of the left eye due to skewing of his contact lens. This was reported to the investigator on Study Day 31. Two months later on Study Day 84 he developed conjunctivitis in the same eye in which he experienced the conjunctival hemorrhage. This event was rated as possibly drug related by the investigator. However, study therapy was continued and the conjunctivitis resolved without further therapy.

In the Clinical Pharmacology Studies, one patient (AN 0015, Study 023001) experienced conjunctivitis on Day 5, one day after completing four daily infusions of 7.5 mg alendronate. This event was considered definitely not drug related by the investigator.

Although three of the above cases were temporally associated

with alendronate, other likely etiologies were present. Therefore, a causal relationship was unlikely.

K. Serious Adverse Experiences From Sources Other Than Case Report Forms

1. Overview

Following the case report form cutoff date for each individual study, serious adverse experiences for the 603 patients enrolled in the Paget's Disease and Clinical Pharmacology Studies were collected by the MRL Worldwide Adverse Experience System (WAES) and are presented here. The cutoff for the serious adverse experiences presented in this section is October 31, 1994. Serious adverse experience reports are included in WAES whether or not the reporter believes that a causal relationship exists between alendronate and the adverse event. The reported serious adverse events are collected in 'real time' so that the WAES database is dynamic, reflecting the most recent information. The WAES reports contain adverse experiences terminology that reflects the diagnosis or terminology used by the investigator. The reporter terminology is mapped to a Preferred Adverse Event Term using a MRL-developed dictionary. The WAES reports also contain narratives for all adverse events. The cutoff date for acquiring additional information about these experiences was November 21, 1994.

Serious adverse experiences contained in case report forms by the cutoff date for the 2661 patients in the Core Osteoporosis Studies are listed in the NDA Section for that indication. All other serious adverse experiences for the Core Osteoporosis Studies, for the 8332 patients in other osteoporosis studies and for the 2048 patients in the other MRL and non-MRL studies were collected into the WAES and are summarized below. These experiences are organized according to patient population and study number. The serious adverse experiences were typical for the respective patient populations, and no events or patterns were apparent that would alter the safety profile of alendronate provided from case report form data described earlier.

2. Serious Adverse Experiences Reported After the Case Report Form Cutoff Date and Through October 31, 1994

a. Paget's Disease Studies

Following the individual study case report form cutoff date for the Paget's Disease Studies, there were two deaths and 13 patients with 16 nonfatal serious adverse experiences reported into the WAES.

Deaths

The two patient deaths are presented in Table XLIX. None of the deaths was drug related.

Table XLIX Deaths Reported After the Case Report Form Cutoff Through October 31, 1994
Paget's Disease Studies

Study Number	AN	Sex	Age	WAES Number	Dose	Adverse Experience	Study Day	Rel	Cause of Death
ALN Oral									
015001	0015	M		91120245	80 mg	Death Trauma		No No	Trauma
059002	1262	M	52	94048778	40 mg	Neoplasm, Esophageal, Malignant Death	29* 61*	No No	Adenocarcinoma
* Study day of the protocol extension study. AN 1262 was randomized to placebo group in the original study. Study Day = Day on which adverse experience occurred									

Nonfatal Serious Adverse Experiences

There were 13 patients with 16 nonfatal serious adverse experiences reported after the individual study case report form cutoff date, none was considered drug related by investigators

One patient, AN 1238 (Study 059001) in the 40 mg alendronate treatment group from the Phase III Placebo-Controlled Study, had a nonfatal serious adverse experience, dyspepsia, for which the drug relationship was not provided by the investigator. The WAES report includes detailed information for this event.

b Clinical Pharmacology Studies

Following the case report form cutoff for the Clinical Pharmacology Studies, one patient (AN 0005, Study 023001) died and also had one nonfatal serious adverse experience reported into the WAES. This patient had a history of lumpectomy for breast carcinoma and she developed metastatic breast carcinoma causing her death approximately one and one-half years after receiving four consecutive daily doses of IV alendronate. The nonfatal serious adverse experience was benign uterine fibroids. Neither serious adverse event was considered drug related.

c Core Osteoporosis Studies

Serious adverse experiences contained in case report forms by the cutoff date for the 2661 patients in the Core Osteoporosis Studies are presented in that portion of the IND. There were 11 deaths and 286 patients with 465 nonfatal serious clinical adverse experiences in these studies. Alendronate and placebo groups did not differ in their overall rates of deaths and nonfatal serious clinical adverse experiences.

Following the case report form cutoff, there were six deaths and 86 patients with 119 nonfatal serious clinical adverse experiences reported into the WAES. None of these adverse experiences was considered to be drug related. These events are discussed in the Safety section of the osteoporosis part of the IND and were typical for the osteoporosis patient population; no events or patterns were apparent that would alter the safety profile of alendronate in patients with Paget's Disease.

3. Serious Adverse Experiences Reported Through October 31, 1994

a. Other Osteoporosis Studies

Serious adverse experiences for the 8332 patients enrolled in nine other osteoporosis studies are presented elsewhere. There were 45 deaths and 1335 patients with 1657 nonfatal serious clinical adverse experiences reported into the WAES through October 31, 1994. Twenty-five of these 1335 patients experienced 28 clinical adverse experiences considered by the investigator to be drug related. The treatment allocations for patients with serious adverse experiences in these studies were unblinded in the WAES only if considered drug related and unexpected (i.e., not a recognized or previously reported adverse effect attributed to alendronate). Otherwise, the events are reported in a blinded fashion for patients receiving alendronate or control.

Overall, the serious adverse experiences observed in the patients enrolled in these ongoing-blinded studies were typical for the respective patient populations.

Deaths

There were 45 patients deaths which were reported to the WAES through October 31, 1994. A listing of patient deaths are provided and the WAES reports providing detailed information are presented.

elsewhere. None of the deaths were considered drug related.

Nonfatal Serious Adverse Experiences

There were a total of 1335 patients with 1657 nonfatal serious clinical adverse experiences reported through October 31, 1994. Twenty-five of these 1335 patients experienced 28 clinical adverse experiences considered by the investigator to be drug related. Counts of patients with adverse experiences by body system and a patient listing of nonfatal serious adverse experiences are provided. WAES reports providing detailed information for all drug-related adverse experiences are also listed.

b. Other MRL Studies

Serious adverse experiences for the 750 patients in the Other MRL Studies were collected through October 31, 1994 by the WAES. These studies included one Periodontal Study (Protocol No. 042, 40 patients), one uncontrolled safety and pharmacodynamic study in patients with Paget's disease (Protocol No. 003, 54 patients) and 15 oncology studies (656 patients). No serious adverse experiences were reported into the WAES from Protocol Nos. 042 and 003. There were 268 deaths and 207 patients with 485 nonfatal adverse experiences in the oncology studies. Twelve of these 207 patients experienced 20 clinical adverse experiences considered by the investigators to be drug related.

Patients participating in the oncology clinical studies involving metastatic bone disease and hypercalcemia of malignancy had an established diagnosis of advanced cancer. In addition, these patients had multiple preexisting comorbid conditions; therefore, frequent serious clinical adverse experiences, including deaths, were not unexpected. It is established that patients with hypercalcemia of malignancy, for example, have a particularly poor prognosis with a median survival of 30 days despite intensive therapy for hypercalcemia. Therefore, the relatively large number of serious clinical adverse experiences, including deaths, was anticipated in conjunction with these studies. No particular pattern with respect to body system serious adverse experiences was identified.

Deaths

There were a total of 268 patient deaths from studies involving metastatic bone disease and hypercalcemia of malignancy were reported to the WAES through October 31, 1994. A listing of patient deaths is provided and WAES reports providing detailed information are presented.

In all cases, the deaths were a result of the patients' underlying malignancies or complications related to the underlying diseases, none was considered drug related.

Nonfatal Serious Adverse Experiences

There were a total of 207 patients with 485 nonfatal serious adverse experiences in trials involving metastatic bone disease and hypercalcemia of malignancy reported through October 31, 1994. A count of patients with adverse experiences by body system and drug relationship for nonfatal serious adverse experiences for metastatic bone disease and hypercalcemia of malignancy studies, respectively, is presented. For studies in metastatic bone disease, 128 patients had nonfatal serious adverse experiences, 7 of these patients had 11 adverse experiences which were considered drug related. For studies in hypercalcemia of malignancy, 79 patients had nonfatal serious adverse experiences, 5 of these patients had nine adverse experiences which were considered drug related. WAES reports providing detailed information for all drug-related adverse experiences are presented.

Body system counts by adverse experience term and a patient listing of nonfatal serious adverse experiences are provided. In the majority of cases, the serious adverse experiences were a result of the patients' underlying disease, complications related to their underlying disease, or complications of a

comorbid condition, and were considered probably not or definitely not drug related by the investigator. There were no new or unusual adverse experiences detected in this population.

c. Non-MRL Clinical Studies

Forty-one studies involving approximately 1298 patients were conducted by Gentili S.p.A., Teijin Limited, and Banyu Corporation. Study populations included patients with postmenopausal osteoporosis, Paget's disease, metastatic bone disease, hypercalcemia of malignancy, and hyperparathyroidism. The studies were open-label and included intravenous and oral formulations of alendronic acid or alendronate sodium or controls.

Deaths

There were 77 deaths reported into the WAES in non-MRL Clinical Studies through October 31, 1994. All deaths occurred in patients who were diagnosed with advanced cancer and were participating in studies of the safety and efficacy of alendronate in the treatment of hypercalcemia of malignancy, therefore, deaths were not unexpected. None of the 77 deaths reported was considered drug related. The investigators did not provide cause of death in six cases, and, in addition, the drug relationship was not provided for two of these deaths.

Nonfatal Serious Adverse Experiences

There were three patients with nonfatal serious adverse experiences in non-MRL Clinical Studies Reported into the WAES through October 31, 1994. This information was provided by Istituto Gentili S.p.A., Italy and by Teijin Limited, and Banyu Corporation, Japan, respectively, although specific criteria for evaluating seriousness were not provided. The serious adverse experiences were typical for the respective patient populations; no events or patterns were apparent that would alter the safety profile of alendronate in patients with Paget's disease.

Two of three patients had nonfatal serious adverse experiences reported that were considered drug related by the investigator. For the third patient, the drug relationship for the adverse experience was not provided by the investigator.

d. Marketed Use

There is a limited experience in Italy where alendronate 5 mg is marketed for the treatment of postmenopausal osteoporosis. Approximately 11.2 million tablets of alendronate 5 mg have been manufactured and/or distributed through October 31, 1994. Spontaneous reports of non-serious adverse experiences from countries in which alendronate is marketed are also reported to WAES. There was one such report of a patient who experienced a constellation of non-serious adverse events following a single 5 mg dose of alendronate that the reporting physician considered possibly related to drug. This patient, a female of unknown age with a history of drug allergies, developed extremity purpura, diffuse petechial suffusions, and polyarthritis in the evening following a morning dose of alendronate and concomitant levothyroxine sodium and lorazepam. No further alendronate was taken and the petechiae and joint swelling regressed the following day. One day later, she took her daily dose of levothyroxine, and the petechiae and swelling worsened. The patient was treated with cortisone and she subsequently recovered, although a papular rash appeared. No joint aspirations were performed and no laboratory data were provided. The reporting physician felt that the reaction might have been due to a drug interaction between alendronate and lorazepam and/or levothyroxine sodium. However, this assessment is entirely speculative, and there is no basis for suggesting the possibility for a drug interaction. No similar adverse experiences were noted in patients taking concomitant levothyroxine to suggest a drug interaction with alendronate. The patient's history of drug allergy, the clinical picture, consistent with an allergic purpura, and the exacerbation following rechallenge with levothyroxine sodium make it unlikely that alendronate caused

the events

In summary, reported deaths and serious adverse experiences in other osteoporosis studies, other MRL studies, non-MRL studies, and from marketed use were all typical and would not be unexpected in these populations. None of these events alter the safety profile of alendronate in patients with Paget's disease.

VIII. Response to Withdrawal of Treatment

In the Phase II Paget's Disease Studies, patients were randomized into different treatment subgroups of either alendronate, placebo/alendronate, or alendronate/placebo therapy, and were followed in a posttreatment surveillance period for 24 weeks in the Dose-Ranging Study (Protocol 015) or for six months in the Treatment Duration Study (Protocol 024). However, one subgroup in the Dose-Ranging Study was treated with 80 mg alendronate for 12 weeks, and was followed in a posttreatment surveillance period for 32 weeks.

Both studies contained subgroups previously treated with alendronate who were withdrawn from active therapy and switched to placebo prior to the posttreatment surveillance period. Patients in the Dose-Ranging Study were withdrawn from active therapy after 12 weeks and switched to placebo for eight weeks (total off-alendronate period of 32 weeks), and patients in the Treatment Duration Study previously treated with alendronate for three months were switched to placebo for three months (total off-alendronate period of nine months).

Patients in the Phase III Paget's Disease Studies are currently in crossover extension studies and data are not available.

Changes from active doses to placebo and/or follow-up during a posttreatment surveillance period were planned to observe clinical and laboratory safety parameters for the effects of alendronate withdrawal. There was no increased incidence nor any trend of any clinical or laboratory adverse experiences from withdrawal of alendronate treatment during the posttreatment surveillance period or post-alendronate placebo period. There were 6 patients with 7 nonfatal serious adverse experiences during the posttreatment surveillance and all were considered not drug related. No patients died during the posttreatment surveillance period.

In addition, patients were followed for alkaline phosphatase levels in one of the Phase II Studies. No relapses were observed within six months following the cessation of alendronate therapy.

In summary, withdrawal of treatment did not result in an increased incidence of any adverse experiences during the post-alendronate placebo period or the posttreatment surveillance period.

IX. Drug-Drug Interactions

The Sponsor claims that the pharmacological properties of alendronate make the possibility of drug interactions involving oral absorption, systemic disposition, metabolism, or elimination highly unlikely. Therefore, no formal drug interaction studies were performed with alendronate.

To confirm the absence of drug interactions resulting in adverse experiences, the frequency of adverse experiences in patients taking specified concomitant therapies (based on a minimum of 14 patients taking

a concomitant therapy) was examined for alendronate- and placebo-treated patients in the Phase III Studies. No conclusions could be drawn regarding specific drug-drug interactions because of the small numbers and limited exposure in the Paget's Disease Studies.

One clinical pharmacology study utilized IV ranitidine to determine the effect of elevated gastric pH on oral absorption of alendronate. In this study, a twofold enhanced bioavailability of alendronate was demonstrated in the presence of gastric pH 6. No increased adverse experiences due to alendronate were observed or are anticipated in the presence of disease (e.g., achlorhydria) or drug-induced elevated gastric pH. The present Reviewer believes additional data are needed, either from prospective studies or from carefully collected post-marketing experience to justify this conclusion.

The most extensive clinical trial experience has been in the treatment of osteoporosis in postmenopausal women, therefore, the comparison of alendronate and placebo groups with respect to concomitant therapy adverse experiences to identify potential drug interactions was performed in this population. These clinical adverse experiences were evaluated for the 991 patients who used concomitant therapies in the primary Phase III Osteoporosis Studies in which patients received either placebo, 5 or 10 mg alendronate for up to three years or 20 mg alendronate for up to two years followed by 5 mg in Year 3.

In summary, the adverse experience data from the Primary Phase III Osteoporosis Studies for all of the selected concomitant therapy groups reveals that only the incidence of upper gastrointestinal adverse experiences was increased in patients receiving concomitant therapy with aspirin-containing compounds and 20 mg alendronate. There were no other apparent drug interactions that increased the frequency of clinical adverse experiences in patients treated with oral alendronate for up to three years.

X Drug-Demographic and Drug-Disease Interactions

A. Age

The mean ages of the 160 alendronate-treated and 82 placebo-treated patients in the Paget's Disease Studies were 69.5 and 69.0 years, respectively. Nearly 70% of patients were >65 years of age.

Oral alendronate was generally well tolerated by patients both < and > age 65. In the Paget's Disease Studies, the most common clinical adverse experiences noted in the older group were the same as those noted among the younger group, although as expected because of age, at similar to somewhat higher incidences. However, the small number of patients <65 and the small number of events make meaningful conclusions difficult.

In patients < and > 65 years old, musculoskeletal pain adverse experiences were similarly increased in alendronate versus placebo patients (27.3 versus 10.3% and 29.3 versus 9.4%, respectively). In patients > age 65, the incidence of abdominal pain was more frequent in alendronate-patients (8.6%) compared to the placebo group (1.9%). In patients < age 65, a similar relationship was seen in alendronate-treated patients (11.4%) and in the placebo group (3.4%). Thus, the incidence of abdominal pain and musculoskeletal pain was similar in younger and older alendronate-treated patients, indicating that age does not appear to increase the risk of abdominal or musculoskeletal pain.

B. Race

In the Paget's Disease Studies, 94.5% of all patients were Caucasian, and 4.5% were black, in both the alendronate and placebo groups. This is not surprising since Paget's disease is uncommon in blacks. Only 1.3% belonged to other racial groups. Therefore, no comparisons of adverse experience incidences in racial subgroups were performed.

C. Renal Function

The potential effect of renal function impairment on the incidence of adverse experiences was examined through a review of the pooled clinical and laboratory adverse experience data in the Paget's Disease Studies. Adverse experience rates, by category, were compared between alendronate-, placebo-, and etidronate-treated patients whose serum creatinine fell into the upper tertile (1.11 mg/dL). Using the mean study age of 69 years and mean weight of 76 kg, the corresponding creatinine clearance, by the Cockcroft-Gault formula, is approximately 83 mL/min in males and 70 mL/min in females. Similar to the age analysis, no large differences were seen for adverse experiences based on renal function. Abdominal pain and musculoskeletal pain were the most common adverse experiences for both renal function groups.

Baseline serum creatinine values were available for 235 patients in the Paget's Disease Studies. The 95th percentile of the serum creatinine for these patients was 1.47 mg/dL , and the maximum serum creatinine was 2.05 mg/dL . The median serum creatinine for these patients was 1.02 mg/dL . Due to inadequate sample size, conclusions concerning the effect of more severe renal function impairment on the adverse effects of alendronate treatment cannot be made.

D. Gender

In the Paget's Disease Studies, oral alendronate was generally well tolerated by both male ($N = 85$) and female ($N = 75$) patients.

For both genders, the most common clinical adverse experiences included musculoskeletal pain and abdominal pain. In men, the incidence of musculoskeletal pain was more frequent in alendronate-treated patients (23.5%) compared to the placebo group (7.0%). Similarly in women, the incidences were 29.3% and 10.3%, respectively. The incidence of abdominal pain was higher in men among the alendronate-treated patients (11.8%) compared to the placebo group (2.3%). In women, the incidence was also higher, 6.7% and 2.6%, respectively.

In general, with the exceptions of abdominal pain and flatulence, the majority of gastrointestinal clinical adverse experiences were slightly higher in women than in men, however, the overall safety and tolerability profile of alendronate appears to be similar for men and women in the Paget's Disease Studies.

XI. Potential Risks Based Upon Animal Data

Alendronate has been evaluated extensively in a variety of preclinical animal toxicity studies. Potential toxicities affecting the skeleton, gastrointestinal mucosa, kidneys, and calcium homeostasis were identified in these studies.

Alendronate is a potent and selective inhibitor of bone resorption. In preclinical studies, mineralization defects are observed only at doses corresponding to approximately 25,000 mg oral alendronate per day (based on 0.7% absorption in a 70 kg patient). In Phase III Osteoporosis Studies, bone biopsies in 418 patients (on alendronate or placebo) showed no evidence of abnormal mineralization following treatment with doses up to 20 mg/day for two years, followed by 5 mg/day for a third year, or up to 10 mg for three years.

Likewise, bone biopsies in 99 patients (60 on alendronate) in Paget's Disease Studies also showed no evidence of abnormal mineralization following treatment with doses ranging from 20 to 80 mg/day for six months. The only case of a mineralization effect with alendronate occurred in a patient with Paget's disease, receiving 40 mg/day for six months because of unrecognized decreases in serum calcium and

phosphate, secondary to the positive skeletal balance for these minerals. No stress fractures have been reported either in animal studies or in clinical trials.

Related to its mechanism of action, alendronate caused retention of the primary spongiosa (bone formed under growth plates in young animals that is normally resorbed during bone growth). This morphological difference does not appear to affect the health of the growing rats and, in fact, is associated with an increased strength of the long bones. Moreover, since alendronate is not indicated in children and the phenomenon is growth related, retention of the primary spongiosa is not relevant for adults.

A published non-MRL preclinical study of the effects of a high parenteral dose (0.3 mg/kg/day) of alendronate on bone in tail suspended rats showed an increase in bone mass. Alendronate treatment also caused increased bone strength in the shaft; however, the authors suggested that alendronate-treated bone may not have the mechanical properties of normal bone. This conclusion did not take into account the differences in bone density changes at different sites (cancellous versus cortical bone) following short-term treatment that would not be expected to contribute to the strength measured in the shaft. Furthermore, many physiological changes result from tail suspension. Therefore, the only appropriate comparison from this study should be alendronate-treated and placebo-treated suspended rats. Instead, the authors made this conclusion comparing alendronate-treated suspended rats to placebo-treated unsuspended rats. Thus, the results from this study can not be interpreted to suggest any potential for human risk.

Other studies have shown that alendronate maintained or increased bone mass and bone strength in dogs, pigs, and baboons treated with doses equivalent to human (based on oral bioavailability of 0.7% in a 50 kg patient) oral doses of approximately 50 mg/day for three years, 50 mg/day for one year, and 130 mg/day for two years, respectively; therefore, increases in bone mass with alendronate are expected to increase bone strength and decrease fracture risk.

Microscopic reversible focal nephritis without impairment of renal function was observed in dogs, but at an oral human dose equivalent to approximately 400 mg per day. In clinical studies, there were no reports of acute renal failure or other severe renal disorders. One osteoporosis patient (AN 0192, Study 026009) who received 40 mg alendronate for 3 months followed by 2.5 mg daily developed nephrotic syndrome after 13 months of treatment with the latter dose. Focal segmental glomerulosclerosis and mild focal acute tubulointerstitial nephritis were found on biopsy; the adverse experience was not considered drug related. No clinical or laboratory renal adverse experiences were noted in other studies. The drug was as well tolerated in patients with mild to moderate renal insufficiency as in those with normal renal function. Due to a lack of clinical experience, alendronate is not recommended for patients with severe renal impairment.

Gastrointestinal toxicity was the dose-limiting factor in repeated dosing oral toxicity studies in rats. Mucosal erosions or ulcers were observed at high doses (5 mg/kg/day (250 mg/day in humans)). These findings were not unexpected as oral bisphosphonates have been associated with symptoms of increased upper GI irritation.

Gastrointestinal adverse effects were carefully monitored in clinical trials. Abdominal pain, usually mild and transient, was significantly increased at the 10 mg dose versus placebo in the Primary Phase III Osteoporosis Studies, but did not cause patient discontinuation more than placebo treatment. In the Paget's Disease Studies, abdominal pain, usually mild and transient, was increased at the 40 and 80 mg doses versus placebo. Certain upper GI disturbances likely due to mucosal irritation, (esophagitis, gastritis, odynophagia, dysphagia) appeared to be increased at the 40 mg dose compared to lower doses in

one osteoporosis study, but such increases in these adverse experiences were not apparent at the 40 or 80 mg dose in the Paget's Disease Studies. However, it is recommended that caution should be used when alendronate is given to patients with active upper gastrointestinal problems. Alendronate also should be taken with a full glass of water, consistent with the patient instructions in the clinical trials, to ensure proper delivery to the stomach.

During multiple-dose toxicity studies in rats, minor changes in liver-associated enzymes occurred. In a five-week intravenous toxicity study in rats, there were higher AST activities in the 0.25 and 1.0 mg/kg/day group compared to controls (up to 153 units). Most individual values were within the 95% spread of control values in the laboratory and these elevations were considered to be spurious values. These doses would be equivalent to an oral human dose of 2500 to 10,000 mg per day, assuming 0.7% absorption in a 70 kg patient. Liver enzymes including AST, ALT, and GGT were monitored during the clinical studies. As discussed elsewhere, there was a higher incidence of increased liver-associated enzymes in patients treated with 80 mg alendronate for up to six months in the Paget's Disease Treatment Duration Study (Protocol 024), however, a causal relationship was not established.

Consistent with its antiresorptive mechanism of action, alendronate caused decreases in serum calcium, phosphate, and alkaline phosphatase in animals. Similar changes for calcium and phosphate were seen in the clinical studies, but were mild and transient. No clinical symptoms were associated with biochemical changes.

In pregnant rats, severe hypocalcemia and dystocia were seen during parturition but could be prevented by calcium supplementation. This finding is of no clinical significance in women who are not pregnant.

Hypocalcemia should be corrected and other disturbances of calcium and mineral metabolism, such as vitamin D deficiency, should be effectively treated before initiating therapy with alendronate. Because of the positive bone balance occurring with alendronate, especially during the early months, adequate calcium and vitamin D nutrition should be maintained during a course of therapy.

XII. Pharmacologic Properties Other Than Inhibition of Bone Resorption

Alendronate sodium is a highly selective inhibitor of bone resorption. There are no other known pharmacologic properties of alendronate. Like other bisphosphonates, it may inhibit bone mineralization if administered at extremely high dosages. Studies in rats described in Nonclinical Pharmacology and Toxicology Documentation showed that a parenteral dose of alendronate 2.5 mg/kg/day was required before inhibition of mineralization was observed. A 2.5 mg/kg/day parenteral dose corresponds to the absorption of alendronate after an approximate 25,000 mg oral dose, based on 0.7% absorption, in a 70 kg patient. The ratio between this dose and the Paget's disease 40 mg oral treatment dose is 625, which provides a very large margin of safety. No inhibition of mineralization has been observed in human bone biopsies of osteoporotic patients treated with alendronate at doses up to 10 mg/day for three years or 20 mg/day for two years followed by 5 mg/day for one year. Likewise, no direct inhibition of mineralization has been observed in human bone biopsies of pagetic patients treated with alendronate at doses up to 80 mg/day for up to six months. One patient with concurrent asymptomatic hypocalcemia and hypophosphatemia consequently developed a mild mineralization defect. Because the anti-mineralization potency of alendronate is so low, there have been no studies of alendronate in the treatment of extraskeletal calcification. Indeed, there is no rationale for such studies.

Several bisphosphonates, including alendronate, were reported to inhibit squalene synthetase, an enzyme in the biosynthetic pathway of cholesterol. The *in vitro* IC_{50} for YM-175, the most potent bisphosphonate tested was 64 nM. Alendronate was >1500 times less potent with an IC_{50} >100 μ M. Therefore, the potency was so low that this pharmacologic property is not relevant to any current or potential clinical use.

Aminobisphosphonates, including alendronate, were reported to stimulate histidine carboxylase (HDC) activity in the bone marrow, spleen, lung, and liver of mice, resulting in an increase of histamine levels. The minimum doses ranged from 0.32 to 1.6 mol/kg/day (82 to 408 g/kg/day) x 4 days subcutaneously, whereas the minimum effective dose to inhibit bone resorption was considerably lower, 0.064 mol/kg/day (16 g/kg/day) x 4 days. For a 70 kg patient to absorb the minimum dose required to stimulate hepatic HDC in the rat, he or she would need to take 820 mg of alendronate daily based on 0.7% bioavailability. The clinical relevance of these findings is doubtful.

XIII. Safety Discussion

Safety data have been presented for four studies in Paget's disease, including one Phase III Etidronate Comparison Study (Protocol 056) and one Phase III Placebo-Controlled Study (Protocol 059). Also presented were safety data for 17 Clinical Pharmacology Studies and serious adverse experiences for other populations. In the Paget's Disease Studies, baseline demographics, secondary diagnoses and concomitant therapies in the alendronate and placebo groups were comparable. Because drug exposure (patient-months) for the placebo group was less than half that of the exposure on alendronate the number of adverse experiences in the placebo groups was generally less than with alendronate regardless of any potential influence of drug treatment on these events.

The safety and tolerability profile of alendronate, at doses up to 80 mg/day for up to six months, is favorable. This is a direct extension of the specificity and lack of metabolism of alendronate. The molecular structure of a P-C-P backbone creates a highly charged entity with high affinity for bone hydroxyapatite that does not easily cross cellular membranes resulting in low bioavailability and low extraskeletal tissue uptake, thereby localizing alendronate in bone. Alendronate is initially distributed to noncalcified tissues, and then rapidly redistributed into the circulation from which it is taken up by bone or excreted by the kidney. The overall distribution to noncalcified organs is less than 1%.

The overall adverse experience profiles of alendronate and placebo were similar in the Paget's Disease Studies. Total adverse experiences and drug-related adverse experiences appeared somewhat greater in alendronate- versus placebo-treated patients (69.4 versus 45.1% and 28.1 and 12.2%, respectively), possibly due to the unequal duration of exposure to drug in these groups. In the Phase III Studies, wherein both alendronate and placebo patients received drug for six months, the incidence of all clinical adverse experiences was slightly increased on alendronate (78 versus 64%), whereas drug-related adverse experiences were virtually identical (27.5 and 28.6%, respectively). Serious adverse experiences were infrequent (3.1%) in the alendronate and placebo groups as compared to the etidronate group (12.8%), and only one alendronate patient withdrew due to a serious drug-related adverse experience supporting the favorable tolerability of alendronate in patients with Paget's disease. The incidence of withdrawals due to clinical adverse experiences in the Paget's Disease Studies was less in the alendronate than in the etidronate group (5.6 versus 14.9%), and similar to that seen in the placebo group (2.4%). Only one to two patients in all groups withdrew for any single adverse experience at any dose. Withdrawals due to drug-related adverse experiences were also low and of similar frequency between the alendronate and placebo groups in the Paget's Disease Studies.

In the Paget's Disease Studies, musculoskeletal pain was the most common clinical adverse experience, regardless of causality, whose incidence was increased in the 40 mg alendronate group compared to placebo. Although 27.3% of 40 mg alendronate-treated patients had musculoskeletal pain in Paget's Disease Studies, only 5.5% had drug-related pain. This pain was not severe, with the majority of patients experiencing pain within the first two months of alendronate therapy. The pain rarely recurred and resulted in only one discontinuation. When a questionnaire was used for assessment of pain in the Phase III Studies, no increase in pain was documented in alendronate patients. Additionally, musculoskeletal pain adverse experiences were not increased in the osteoporosis population. If musculoskeletal pain is truly the result of alendronate treatment, then it would appear to be specific to Paget's disease.

Upper gastrointestinal adverse experiences were increased in 40 mg alendronate patients relative to placebo (23.6 versus 7.3%) overall, but there were few discontinuations (1.8%) and this increase was not seen in the Phase III Studies (20.3 versus 17.9%). The most common upper GI adverse experience was abdominal pain. Abdominal pain was generally mild and transient. In the Phase III Studies, the incidence of abdominal pain was somewhat greater in alendronate versus placebo patients. Other gastrointestinal adverse experiences such as diarrhea, flatulence, and nausea (incidence 5%) were only slightly more common in alendronate 40 mg patients than in placebo patients overall and in the Phase III Studies.

Fractures were reported as adverse experiences by investigators, and are a known complication of Pagetic bone disease. The only fracture to occur during study therapy was an ankle fracture in a patient on etidronate.

Concerns about bone quality with alendronate have arisen largely because of prior experience with etidronate, a non-selective bisphosphonate of low potency that has been shown both preclinically and clinically to induce mineralization defects with continuous dosing. MRL evaluated a large number of iliac bone biopsies from the patients in two Paget's Disease Studies. The findings clearly demonstrate the normal quality of bone formed during alendronate treatment, consistent with the preclinical studies and normal lamellar bone was seen without woven bone, marrow fibrosis, or evidence of cellular toxicity. The only exception was one case of a mild mineralization defect due to hypocalcemia and hypophosphatemia that had developed in the patient without the knowledge of the investigator. This is in contrast to the case of osteomalacia in a patient treated with etidronate that occurred in spite of normal serum calcium and phosphate levels as has been previously described in the literature. Therefore, alendronate at doses of up to 80 mg/day for up to six months does not directly cause osteomalacia.

Serious rash, as has been reported with tiludronate was not observed in the Paget's Disease Studies. Drug-related rash and/or pruritus was reported in only two patients in the Paget's Disease Studies. In the one instance, the rash recurred upon rechallenge, but then resolved while the patient remained on drug. In the second instance, therapy was never interrupted. Because of the small number of cases, it remains unclear if a true causal relationship exists. Nonetheless, rash may occur as a rare adverse experience of alendronate therapy.

Uveitis, scleritis, and episcleritis have been associated with pamidronate and risedronate. There was no evidence for these drug-related ophthalmologic adverse experiences in the Paget's Disease or Clinical Pharmacology Studies.

Laboratory studies showed no clear indication of adverse effects of alendronate on serum liver-associated enzymes at oral doses up to 40 mg for up to one year. In one study (Protocol 024), there was an increased

incidence of increased liver-associated enzymes (ALT, AST, GGT) in patients treated with 80 mg alendronate; however, a causal relationship has not been established. Nonetheless, no persistent effects or evidence of clinical or biochemical hepatotoxicity are present for oral doses of alendronate up to 80 mg for up to six months.

In the predefined limits of change analyses, reductions in serum corrected calcium (to 8.5 mg/dL and below the lower limit of normal) were increased. However, reduction in serum calcium to levels 8.0 mg/dL (2.0 mmol/L) occurred in only one alendronate patient who was asymptomatic. Similarly, reductions in serum phosphate (decrease 30% and below the lower limit of normal) were increased, but not significantly, in alendronate patients. These decreases were usually slight and transient, and are an expected result of the inhibition of bone resorption and induction of positive skeletal-mineral balance caused by alendronate.

Patients receiving IV alendronate had decreased lymphocytes, neutrophils and WBCs consistent with an acute-phase response as seen with other aminobisphosphonates. In some patients, mild, asymptomatic decreases in lymphocytes and WBCs were seen in some patients treated with oral alendronate at 80 mg.

There was only one patient in the Paget's Disease Studies treated with alendronate 80-mg who had a transient, drug-related fever consistent with an acute-phase response. Therefore, an acute-phase response may rarely be seen with the 80 mg oral dose.

One hundred percent of patients in the Phase III Paget's Disease Studies took some concomitant therapy during the six-month study period. Because of the small numbers in some groups and the differences in protocol design, it is difficult to draw meaningful conclusions concerning drug-drug interactions from these data. A lack of apparent drug interaction leading to adverse experiences is consistent with the pharmacokinetics of alendronate (low bioavailability, high concentration in bone, predicted plasma levels less than 5 ng/mL and lack of metabolism). In Osteoporosis Studies with a larger experience for up to three years, the only drug interaction seen was an increase in upper GI adverse experiences in patients receiving 20 mg alendronate and concomitant aspirin-containing compounds but this potential drug interaction was not observed for all nonsteroidal anti-inflammatory agents. Therefore, an increase in upper GI adverse experiences is possible in Paget's disease patients on 40 mg alendronate.

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

Alendronate appears to be equally well tolerated in all demographic subpopulations examined, although some of these subgroups (such as non-Caucasians) are small in number and tolerability cannot be formally analyzed. Subgroup analyses based on age, renal function, and gender showed similar safety and tolerability profiles for alendronate in young versus old, in patients with mild-to-moderate renal impairment versus those with normal renal function, and in men and women.

In summary, the adverse experience profile with 40 mg alendronate was similar to the experience with 10 mg alendronate in postmenopausal osteoporosis patients. However in the Paget's Disease Studies, there was an apparent increased incidence of musculoskeletal pain and of upper gastrointestinal adverse experiences with the 40 mg dose, but this did not cause increased discontinuation from therapy compared to placebo.

In patients with Paget's disease of bone

1. Once daily oral therapy with 40 mg alendronate is generally well tolerated
2. Musculoskeletal pain is increased with 40 mg alendronate compared to placebo
This adverse experience is generally mild-to-moderate and usually does not lead to patient discontinuation
3. Alendronate may be associated with mild upper gastrointestinal adverse experiences consistent with local irritation of the gastrointestinal mucosa. The most common of these, abdominal pain, is increased with 40 mg alendronate compared to placebo.
4. There is no adverse effect on skeletal integrity. Alendronate-treated bone is of normal quality. There is no association with osteomalacia at doses up to 80 mg/day for up to six months, with the exception of delays in mineralization that may occur rarely if decreases in serum calcium and phosphate levels are not corrected.
5. Laboratory adverse experiences are limited to those consistent with the pharmacologic action of alendronate as a specific inhibitor of bone resorption, such as asymptomatic, transient decreases in serum calcium and phosphate.
6. Formal drug interaction studies were not performed. However, based on studies in osteoporosis patients, no clinically significant drug-drug interactions are identified in alendronate-treated patients taking a wide variety of concomitant medications, with the possible exception of aspirin-containing medications.
7. The safety and tolerability profiles of alendronate do not differ in younger and older (> 65 years) patients, in patients with mild-to-moderate renal insufficiency compared to patients with normal renal function, and in men and women.

XIV. Postmarketing Experience

As of October 31, 1994, marketed experience is limited to Italy, where alendronate 5 mg is available for the treatment of postmenopausal osteoporosis. Approximately 11.2 million tablets of alendronate 5 mg have been manufactured and/or distributed through this date.

Only one spontaneous adverse experience report has been received by MRL. That WAFS report was of a non-serious adverse experience and does not alter the safety profile of alendronate.

As of November 30, 1994, published clinical literature for alendronate sodium included 36 articles, 22 abstracts, and 38 reviews in the three general areas of osteoporosis, Paget's disease, and oncology/clinical pharmacology/hyperparathyroidism. The efficacy and safety information reported in these 96 citations, some of which are referenced in the body of this application, is generally similar to data presented here, with several minor exceptions, as noted below.

In contrast to the pilot study with the oral formulation conducted by MRL where no apparent pain reduction was seen, three articles by Passeri et al. report efficacy of intravenous alendronate to decrease back pain; one article reports increased analgesic efficacy relative to calcitonin or ipriflavone. As these studies used intravenous doses of 5 mg/day over two to four days, the difference may be due to the much higher dose of alendronate.

A study by Rossini et al. of oral alendronate 20 mg/day for six months versus placebo in 30 women with postmenopausal osteoporosis reported smaller increases in hip BMD than were observed with this dose in the two Primary Phase III Osteoporosis Studies. Because this study used alendronate that was not synthesized by the Merck process, it is possible that the difference in efficacy reflects suboptimal bioavailability, an inference that is supported by the lesser response of biochemical markers of bone resorption reported in this study.

XV. Summary of Dosage Information in Labeling

A. Recommendations for Dosing

For the treatment of Paget's disease, the recommended alendronate regimen is 40 mg orally once daily for six months. Alendronate is to be taken at least one half hour before the first food, beverage, or medication of the day, with a full glass of plain water only, since other beverages (including mineral water), food, and some medications are likely to reduce its absorption. No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate impairment of renal function. This section will provide the rationale to support these recommendations.

B. Introduction

The main goal of antipagetic therapy is to halt the progression of the disease by suppressing disease activity as completely as possible. Serum alkaline phosphatase is a marker of osteoblastic bone formation activity. It is a reliable and readily available index of disease activity. Greater biochemical suppression, as assessed by a reduction in alkaline phosphatase (and other markers of bone turnover), is associated with more significant clinical benefits, including healing of osteolytic lesions and improvement of neurologic syndromes. Another important goal of treatment is to obtain a long-lasting remission so that further medical intervention may not be required for years. There is also evidence for a correlation between the degree of biochemical response and the duration of remission; therefore, where possible, serum alkaline phosphatase should be decreased into the normal range. However, dose adjustment on the basis of alkaline phosphatase response is impractical. A single treatment recommendation is likely to lead to better physician understanding and patient compliance, thus increasing the likelihood of achieving the desired therapeutic response.

C. Rationale and Justification for Dose Selection in the Clinical Studies

1. Dose Timing in Relation to Meals

Oral bisphosphonates, including alendronate, are relatively poorly absorbed, particularly if food or liquids other than water are taken with, or in proximity to, the time of dosing. Calcium and other divalent cations especially inhibit absorption of bisphosphonates. Indeed, even orange juice (without calcium supplement) and black coffee each reduced absorption of alendronate by approximately 60% compared with dosing with water.

For these reasons, studies were undertaken to assess the effect of timing of meals on bioavailability. Two studies demonstrated that, in comparison to dosing two hours before breakfast (the recommendation for other bisphosphonates, such as etidronate), administration of alendronate either one hour or one-half hour before a standardized breakfast reduced absorption similarly, by approximately 40%. In the same studies, dosing alendronate with, or two hours after, a standardized breakfast reduced its relative oral absorption by more than 90%. Based on these results, and recognizing that requiring a two-hour wait from the time of dosing to breakfast, as was done in the Phase II Studies, would result in poor patient compliance, dosing instructions for the Phase III Placebo-Controlled Study incorporated the one-half hour pre-breakfast timing. However, in the Phase III Etidronate Comparison Study, patients were instructed to

take study medication at least two hours before breakfast to be consistent with the dosing recommendations for etidronate. Bioavailability of the 40 mg dose in the Etidronate Comparison Study should have been significantly increased relative to that in the Placebo-Controlled Study so that patients in the former study effectively received a higher dose. That alendronate was similarly effective in decreasing serum alkaline and other markers of bone turnover in both studies supports the recommendation of dosing 30 minutes before breakfast and provides further evidence that 40 mg is at or near the top of the dose-response curve in terms of suppressing pagetic activity. Therefore, it is recommended that alendronate be taken on an empty stomach with a glass of plain water, at least 30 minutes before the first food, beverage, or medication of the day.

2. Dose Ranging and Duration of Treatment

The treatment regimen of alendronate 40 mg/day for six months for the Phase III Studies was selected for several reasons based on results of the Phase II Studies. In the Dose-Ranging Study, alendronate 20 mg/day for three months clearly had suboptimal effects on serum alkaline phosphatase, whereas 80 mg/day was highly effective. The effects of alendronate 40 mg/day for three months were intermediate between those of 20 and 80 mg. However, in the Phase IIb Osteoporosis Study, a higher incidence of upper gastrointestinal adverse experiences was noted in patients receiving alendronate 40 mg relative to patients on lower doses or placebo. Based upon this relationship between dose and tolerability, it was considered likely that the 80 mg dose would have greater potential for upper gastrointestinal side effects. This was one of the reasons it was decided to limit the dose for treatment of Paget's disease in the Phase III Studies to a maximum of 40 mg, but to extend therapy to six months to achieve a total dose equivalent to 80 mg daily for three months.

In the Treatment Duration Study, patients received alendronate 40 or 80 mg for three or six months. Patients treated with alendronate 40 mg/day for six months showed a 63% decrease in serum alkaline phosphatase at the end of the treatment period, versus a 55% decrease observed in the group receiving 40 mg alendronate for only three months. In addition, all patients in the six-month 40 mg group responded to treatment, as defined by a decline in serum alkaline phosphatase of at least 60% from baseline or to within the normal range, whereas 2 of 10 patients in the three-month treatment group failed to respond. This evidence that longer treatment produced greater efficacy was another reason for selecting 40 mg/day for six months as the most appropriate dosing regimen.

3. Additional Efficacy Considerations

The selection of alendronate 40 mg/day for six months for the treatment of Paget's disease is further supported by the results of the Phase III studies.

Serum Alkaline Phosphatase

Both in the Etidronate Comparison Study and in the Placebo-Controlled Study, alendronate 40 mg for six months markedly suppressed disease activity. The average decrease in serum alkaline phosphatase was approximately 75% in both studies. This degree of biochemical suppression far exceeds not only the 40 to 50% decrease in alkaline phosphatase commonly achieved by other forms of therapy, such as etidronate and calcitonin, but also the 40 to 55% suppression observed in patients who received alendronate 40 mg/day for only three months. In the Etidronate Comparison Study, the 79% reduction from baseline alkaline phosphatase with 40 mg alendronate was significantly greater than the 45% reduction induced by 400 mg etidronate.

In addition, approximately 85% of patients receiving 40 mg/day alendronate for six months achieved a therapeutic response, conservatively defined as either normalization of alkaline phosphatase or a decrease

of at least 60% from baseline. No placebo-treated patients and only about 30% of etidronate-treated patients responded.

Overall, the results indicate that a three-month duration of treatment with alendronate may be too short to achieve superior efficacy over currently available therapeutic options and that a six-month treatment duration is more appropriate.

Similar efficacy was seen in elderly patients (65 years and older) relative to younger patients. In addition, alendronate was equally effective in all patient subgroups, including males and females, those with mild-to-moderate impairment of renal function and those who had received previous treatment with oral bisphosphonates.

Other Biochemical Markers

Because of the lag between bone resorption and formation, the effects of alendronate on resorption markers over time are more appropriate than those on serum alkaline phosphatase in evaluating the relationship between duration of treatment and efficacy. Although most of the alendronate effects on resorption markers were seen in the first three months, further substantial decreases were evident at Month 6 in both studies. In the Etidronate Comparison Study, urinary deoxypyridinoline further decreased by 26.5% ($p < 0.001$) between Month 3 and Month 6. Similarly, the urinary cross-linked N-telopeptides of type I collagen further decreased by 38.7% ($p < 0.001$) between Month 3 and Month 6 in the Placebo-Controlled Study. Thus, these data indicate that the effects of six months of treatment with alendronate are significantly greater than those observed after only three months. As previously stated, it is very important to induce a biochemical suppression of disease activity as completely as possible, since greater biochemical response leads to greater clinical benefits and is likely to be associated with a longer-lasting remission. Therefore, treatment with alendronate 40 mg for six months is predicted to be superior to treatment for three months in terms of clinical benefits and duration of remission.

Duration of Effect

No relapses were observed in any of the patients treated with 40 mg alendronate for either three or six months during the nine- and six-month follow-up periods, respectively, in either of the Phase II Studies. This is consistent with previous studies showing that, unlike calcitonin, the biochemical (and clinical) response to bisphosphonates is maintained after cessation of treatment for many months or, in some cases, as long as several years. Ongoing extension studies will collect information to determine the full extent of maintenance of effect.

No specific data are yet available for patients who relapse following alendronate treatment, but studies are ongoing to acquire such data. Nevertheless, since similar responses to alendronate were observed in patients who had received prior therapy with other bisphosphonates and those who had not, retreatment may be considered following a six-month posttreatment evaluation period, both in patients who relapse (as assessed by an increase in serum alkaline phosphatase) and in those who fail to normalize their serum alkaline phosphatase.

4. Additional Safety Considerations

The selection of the 40 mg alendronate dose is supported by its favorable safety and tolerability profile. In the Phase III Studies, where duration of drug exposure was equal (six months), the difference in incidence of total clinical adverse experiences between the alendronate 40 mg and placebo groups was modest (78.3 versus 64.3%), and there was no difference in drug-related clinical adverse experiences (27.5 versus 28.6%). In the Paget's Disease Studies, where the duration of exposure was not equal, the incidence of total and drug-related clinical adverse experiences appeared greater in patients treated with

alendronate than with placebo (69.4 versus 45.1% and 28.1 versus 12.2%, respectively). This disparity probably reflects the fact that drug exposure (patient-months) for the placebo group was less than half that for the alendronate group in these studies overall. Patient withdrawals due to clinical adverse experiences occurred in 3.6, 8.7, and 14.9% of patients receiving placebo, alendronate (40 mg), or etidronate, respectively, in the Phase III Studies.

In the Phase II and III Paget's Disease Studies, the most common clinical adverse experiences whose incidences, regardless of causality, were increased in the 40 mg alendronate group compared with placebo were musculoskeletal pain, abdominal pain, and to a lesser extent, gastrointestinal disturbances (including diarrhea, dyspepsia, flatulence, and nausea). At 80 mg, musculoskeletal pain was not further increased and the incidence of abdominal pain was only slightly greater at 80 mg. Except for acid regurgitation, anorexia, and vomiting, other digestive disorders were not more frequent at 80 mg. As for placebo, the exposure (in patient-months) to the 80 mg dose was less than that for the 40 mg dose. This may explain the failure to observe, as anticipated from the Phase IIb Osteoporosis Study, a more consistent increased incidence of all upper gastrointestinal adverse experiences in the 80 mg treatment group compared to the 40 mg group.

As noted, musculoskeletal pain was one of the most common adverse experiences in the alendronate group compared with placebo. However, when pain was evaluated with the Brief Pain Inventory in the Phase III Studies, alendronate was found to actually decrease the overall pain score in pagetic patients. A transient increase in bone pain has been reported in patients receiving therapy with bisphosphonates, which probably reflects healing of pagetic lesions.

In the Phase III Paget's Disease Studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed more frequently in patients taking alendronate than placebo. In another study, the degree of decrease in calcium and phosphate was slightly greater at 80 mg than at 40 mg. Laboratory studies show no increased incidence of adverse effects of alendronate on serum liver-associated enzymes at oral doses up to 40 mg for six months relative to placebo. There was, however, an increased incidence of elevated liver-associated enzymes that were considered drug related in patients (6 of 30) treated with 80 mg alendronate versus those treated with alendronate 40 mg (2 of 30), although a causal relationship has not been established. Overall, the incidence of laboratory adverse experiences was slightly increased in the 80 mg (21.4%) versus 40 mg (17.6%) group.

Bone biopsies obtained in 33 patients receiving 40 mg alendronate for six months in the Phase III Paget's Disease Studies showed no impairment of bone mineralization relative to placebo. In addition, no woven bone, marrow fibrosis, or other qualitative abnormalities due to alendronate treatment were seen.

The safety profile of alendronate was similar in all patients subgroups, irrespective of age, impaired renal function, or gender. Thus, both clinical and laboratory adverse experience profiles favor a 40 mg dose.

D. Summary

In summary, multiple considerations of the data from the Phase II Studies supported the selection of the regimen, alendronate 40 mg/day for six months, investigated in Phase III. In turn, the Phase III data provide strong evidence for the superior efficacy of alendronate 40 mg/day for six months over etidronate at the recommended dose of 400 mg/day for six months. Most alendronate-treated patients experienced a decrease in alkaline phosphatase of at least 60% and, in more than half, the value fell into the normal range. Moreover, resorption markers, which respond rapidly to antiresorptive therapy, continued to decrease over the second three months of therapy, indicating that the magnitude of the response would

have been smaller had treatment been discontinued earlier. No relapses were observed in six months of follow-up of patients treated for six months in the Phase II Studies. Finally, the favorable safety profile of alendronate 40 mg/day for six months is evident from the Phase III Studies.

E. Conclusion

In conclusion, a six-month course of oral alendronate 40 mg daily has highly significant and clinically relevant effects on biochemical indices of Paget's disease activity. Efficacy is similar in all subgroups analyzed, including the elderly, patients with impaired renal function, and those who have received prior bisphosphonate therapy. Coupled with the efficacy data, the safety and tolerability profile fully justify this recommended regimen for the treatment of Paget's disease of bone.

XVI. Drug Abuse and Overdosage Information

There is no basis--preclinical, clinical, or theoretical--to suggest that alendronate will produce psychological and/or physical dependence. No behavioral changes have been noted in safety assessment studies or in clinical trials. This is similar to the experience with other bisphosphonates.

Studies using intravenous (IV) or high-dose oral alendronate can help predict the effects of drug overdose. In studies involving 32 patients with Paget's disease of bone, given IV infusions of 10 mg alendronate over one to four hours on five consecutive days, the most common adverse experience was the acute-phase response, consisting chiefly of transient pyrexia and transient decreases in leukocytes. Rigors were noted in one patient requiring discontinuation of therapy. No serious clinical or laboratory adverse experiences were observed. Thus, at IV doses equivalent to 1429 mg/day P.O. or thirty-five 40 mg tablets (assuming 0.7% oral bioavailability), alendronate produced no serious systemic toxicity.

As with other bisphosphonates upper gastrointestinal (GI) adverse events may result from oral overdose. Oral doses of up to 100 mg/day for five days were generally well tolerated in a Phase II study in patients with Paget's disease. Experience with chronic oral dosing in postmenopausal women with osteoporosis is available for up to 40 mg/day for one year and up to 20 mg/day for two years. A higher proportion of patients on oral alendronate 40 mg/day had an upper GI adverse experience than those on lower doses or placebo. No other adverse experiences were increased with the 40 mg/day alendronate dose.

Experience with oral dosing in Paget's disease is available for up to 40 mg/day or 80 mg/day for six months. A higher proportion of patients on these doses had an upper GI adverse experience than those on placebo.

The adverse effects of higher doses of alendronate on the upper GI mucosa appear to be local effects, since such changes were not evident in patients receiving IV alendronate. The available experience with chronic daily dosing suggests that a single large oral overdose may be associated with side effects related to upper GI mucosal irritation. However, in the clinical pharmacology study using increasing doses of oral alendronate acutely (≤ 3 weeks) up to 100 mg/day, no adverse experiences related to upper GI mucosal irritation were seen.

Treatment to prevent local GI effects of an oral overdose has not been specifically evaluated. However, studies have demonstrated that concomitant food ingestion dramatically inhibits absorption, probably by the formation of insoluble complexes with multivalent cations (e.g., Ca^{++} , Mg^{++} , Al^{+++}) or insoluble organic complexes. Therefore, in an overdose, administration of milk or antacids (containing calcium, aluminum, or magnesium) or of complex foods should be considered to reduce absorption. It is unknown whether this will decrease GI irritation.

In the oral alendronate clinical studies, small, transient, asymptomatic reductions of serum calcium and phosphate were observed infrequently in patients receiving chronic daily oral alendronate. This decrease in serum calcium and phosphate is an expected consequence of the action of alendronate to inhibit bone resorption. In clinical studies using doses of up to 10 mg alendronate IV daily for five days, small, transient decreases in serum calcium and phosphate were also seen, but again, without clinical sequelae. Therefore, it is unlikely that acute overdosage of oral alendronate would result in clinically significant hypocalcemia or hypophosphatemia, although calcium and phosphate should be monitored. In the Treatment Duration Study, there was an increased incidence of elevated liver-associated enzymes in patients treated with 80 mg oral alendronate for up to six months compared with 40 mg alendronate or placebo, however, a causal relationship has not been established. Such liver enzyme elevations have not been seen acutely with IV dosing of alendronate at doses up to 10 mg daily for five days.

To date, there have been no reports of overdosing by study participants. However, there have been two documented reported accidental ingestions by children related to study participants. A 23-month-old granddaughter of a patient in the U.S. Osteoporosis Study accidentally ingested two 5 mg alendronate tablets. Milk was given to inhibit drug absorption. No adverse experiences were noted following this event. In another incident, a 20-month-old grandson of a patient in a Phase III Osteoporosis Prevention Study (Protocol 055) may have accidentally ingested four or five tablets of study medication. Whether the study medication contained placebo or alendronate (maximum total dose = 25 mg) is unknown because the patient's treatment allocation was not unblinded. The child was treated with ipecac, but this failed to induce vomiting. Fluids were also given orally to minimize absorption. The child did not suffer any adverse experiences attributable to the ingestion.

In summary, the possible results of overdosage are acute GI irritation and (less likely) hypocalcemia and hypophosphatemia. Based on the food interaction studies, antacids, milk, or complex foods should be ingested to bind and thereby reduce the effect of alendronate. There is no evidence of abuse potential for alendronate.

XVII. Benefits Versus Risks Relationship

A. Introduction

Paget's disease of bone is a chronic, progressive focal disorder of bone remodeling. The primary abnormality appears to be markedly increased osteoclastic bone resorption, with subsequent compensatory increases in osteoblastic bone formation, resulting in disorderly bone turnover and the formation of abnormally structured and weakened bone. The treatment of Paget's disease is directed at suppressing the excessive osteoclastic activity typical of this condition.

Serum total alkaline phosphatase is typically increased in active Paget's disease, reflecting the compensatory increase in osteoblastic bone formation. Patients with the most extensive skeletal involvement (by x-rays or scans) usually have the largest increases in alkaline phosphatase. Moreover, this marker can be used as a means of monitoring response to antipagetic treatment. Although many patients with Paget's disease are asymptomatic, a significant number experience a variety of signs and symptoms, including bone pain (the most common complaint), bone deformity, pathological fractures, and neurological compression syndromes. There is a reasonable correlation between suppression of serum alkaline phosphatase and clinical response, as well as degree of stabilization and duration of response.

1. General

Biochemical markers of bone resorption, including urinary hydroxyproline, deoxypyridinoline, and cross-

linked N-telopeptides of type I collagen, can also be used to monitor response to antipagetie treatment, but the latter are not as widely available and their measurements have lower precision than that of alkaline phosphatase

2 Expected Benefits and Risks of Alendronate

Alendronate is a potent aminobisphosphonate that selectively inhibits osteoclastic bone resorption. As with all antiresorptive drugs, there is a secondary decrease in osteoblastic activity, due to the normal coupling of bone resorption and formation. As such, alendronate treatment specifically targets the underlying pathophysiologic mechanism of Paget's disease and results in marked suppression of serum alkaline phosphatase and other biochemical indices of bone turnover in pagetic patients.

The efficacy of daily oral alendronate 40 mg/day for six months to suppress disease activity in Paget's disease was clearly demonstrated in the two Phase III Studies, where this regimen decreased serum alkaline phosphatase by approximately 70 to 80% relative to baseline. These responses may be compared with the significantly smaller 44% decrease observed in patients treated with oral etidronate 400 mg daily in one of these studies and the lack of response to placebo in the other trial.

Alendronate was very effective in all patient subgroups studied, including those patients who had received previous treatment with other bisphosphonates (historically, a group resistant to retreatment) and those who had the highest elevations in serum alkaline phosphatase.

A large proportion of alendronate-treated patients at Month 6 (84% in the combined Phase III Studies) were classified as responders (response conservatively defined as either normalization or decrease from baseline of at least 60% in serum alkaline phosphatase), versus 30% of etidronate-treated patients and 0% of placebo-treated patients. Alkaline phosphatase normalized in 57% of all patients in the alendronate group, only 17% in the etidronate group, and 0% in the placebo group.

Similar, or even greater, percent reductions were also seen in the urinary markers of bone resorption, deoxypyridinoline and cross-linked N-telopeptides of type I collagen.

Radiologic improvement of osteolytic lesions was also observed in a significant proportion of alendronate-treated patients relative to placebo, and very few patients in the alendronate group showed worsening.

In the Phase II Treatment Duration Study, none of the nine patients treated with alendronate 40 mg/day for six months experienced a relapse during the ensuing six-month follow-up.

The results obtained in these studies confirm several previous studies and provide evidence that alendronate 40 mg/day for six months is effective in suppressing the abnormal bone turnover underlying Paget's disease. Furthermore, the magnitude of the alendronate effect exceeds that of etidronate, one of the most commonly used therapies.

The safety and tolerability profiles of 40 mg oral alendronate were also favorable, and the rate of discontinuation due to clinical or laboratory adverse experiences was not appreciably increased relative to placebo. Upper gastrointestinal adverse experiences, consistent with local irritation of the upper gastrointestinal mucosa, and musculoskeletal pain, as have been described with other bisphosphonates, were observed more frequently in alendronate-treated than in placebo-treated patients. The upper gastrointestinal adverse experiences were usually mild and, except for isolated cases of esophagitis and gastritis, did not generally lead to patient discontinuation. Likewise, musculoskeletal pain (combined

episodes at different skeletal sites, most commonly back pain and knee pain), which may be related to healing of lytic lesions, usually did not result in treatment withdrawal. Slight, transient and asymptomatic decreases in serum calcium and phosphate were observed in alendronate-treated patients, consistent with the drug effect to inhibit bone resorption and, thereby, induce a positive skeletal mineral balance. For this reason, adequate calcium and vitamin D supplementation should be ensured to patients receiving alendronate treatment.

In addition to the usual acquisition of clinical and laboratory adverse experience data, bone biopsies were obtained in both Phase III Paget's Disease Studies. Histomorphometry clearly showed the normal quality of bone formed during alendronate therapy, including restoration of lamellar bone in areas of previously disordered woven bone structure. The deleterious effects on bone mineralization previously reported in patients receiving etidronate were not observed in alendronate-treated patients. Only one patient, who developed significant but asymptomatic hypocalcemia and hypophosphatemia while on alendronate treatment, showed a small increase in osteoid volume (6.3%) in an area of pagetic bone. It is very likely that this increase resulted from the changes in calcium/phosphate homeostasis rather than from a direct alendronate effect to inhibit bone mineralization. Consistent with this report, etidronate 400 mg daily increased osteoid thickness and osteoid volume in patients in the Etidronate Comparison Study and caused frank osteomalacia in one patient, with no reduction in serum calcium or phosphate. The results for alendronate are also consistent with the extensive histomorphometry data collected in several preclinical studies and in alendronate-treated patients with postmenopausal osteoporosis.

In summary, alendronate is very efficacious and well tolerated with a good safety profile.

3 Expected Benefits and Risks of Other Therapies

Due to differences between patient populations included in different studies, direct comparability of efficacy among antipagetic therapies is not possible except in the setting of a randomized parallel group study. However, the general efficacy and safety profiles of alternative antipagetic therapies can be estimated from the literature. The published information regarding these therapies will each be reviewed briefly below, as will the direct etidronate comparison.

Only drugs approved for treatment of Paget's disease will be discussed: etidronate, pamidronate, and calcitonin.

a. Etidronate

Etidronate, the first bisphosphonate introduced into clinical use, is approved for treatment of Paget's disease in most countries. The most commonly employed regimen (5 mg/kg/day, not to exceed 400 mg/day, orally for six months) suppresses abnormal bone turnover as assessed from serum alkaline phosphatase by approximately 40 to 50%. This was confirmed in the Phase III Etidronate Comparison Study, where etidronate-treated patients showed a 44% decrease in alkaline phosphatase. Alkaline phosphatase often remains suppressed for as long as several years following cessation of etidronate treatment, particularly in patients with less extensive disease. Overall, etidronate appears to be more effective in patients with milder elevations in baseline serum alkaline phosphatase, i.e., patients with milder disease. Patients with very active disease tend to be less responsive and may become refractory to treatment.

The lowest dose that suppresses disease activity (5 mg/kg/day orally, usually given for six months) is also associated with focal osteomalacia, and higher doses (10 or 20 mg/kg/day) can inhibit the mineralization process completely, leading to florid osteomalacia and an increased risk of fracture. The mineralization defect is reversible on discontinuing etidronate.

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Patients receiving etidronate may experience increased or recurrent bone pain at pagetic sites. Such pain is usually mild and transient, when it may reflect healing of lytic lesions, but may not be because it is sometimes linked to worsening of lytic lesions due to the impairment of bone mineralization. Bone pain may also occur at previously asymptomatic sites. In addition, etidronate is associated with some gastrointestinal side effects, which include nausea, abdominal pain, and diarrhea.

Etidronate induces a rise in serum phosphate due to enhanced renal tubular reabsorption of phosphate. Although the exact significance of this increase is not fully established, it has been suggested that it may be related to the impairment of bone mineralization. In contrast, alendronate produces mild and transient decreases in serum phosphate, consistent with its inhibition of bone resorption without impairing mineralization.

b Pamidronate

Pamidronate, an orally and intravenously active aminobisphosphonate, has recently been approved in several countries, including the United States, for the treatment of Paget's disease. Pamidronate is substantially more potent than etidronate in decreasing osteoclast-mediated bone resorption. Pamidronate induces a rapid, dose-dependent suppression of biochemical markers of disease activity, particularly in patients with milder disease. In contrast, etidronate is similarly effective in patients regardless of disease severity.

As expected from its biochemical efficacy, pamidronate treatment induces clinical improvement and radiological evidence of healing, as well as restoration of the normal lamellar architecture of bone. The biochemical response to pamidronate may be long-lasting (up to two years in more than 50% of patients with mild-to-moderate disease) and is mainly related to the degree of suppression of bone turnover, as well as to the initial activity of the disease.

Mild mineralization defects have been reported in patients with Paget's disease receiving oral pamidronate. Oral pamidronate has been associated with a high incidence of upper gastrointestinal irritation and oral ulceration, making its oral administration extremely problematic.

Both parenteral and, far less commonly, oral pamidronate may induce a transient acute-phase reaction, characterized by low fever, mild flu-like symptoms or temporary bone pain, and lymphopenia, usually beginning the day after therapy. These transient, self-limited symptoms are observed in approximately 25% of patients treated intravenously. Similar acute-phase reactions have been observed following intravenous alendronate but in only one patient receiving an oral dose of 80 mg alendronate.

Like most other bisphosphonates, pamidronate can induce decreases in serum calcium and phosphate concentrations, due to the inhibition of bone resorption. These changes are seldom of clinical significance, although occasional patients with hypercalcemia of malignancy have had seizures that may be related to this effect. Asymptomatic hypokalemia and hypomagnesemia have also been reported. Soft-tissue symptoms (redness, swelling, tenderness) at the site of catheter insertion are also relatively common. Serious but rare side effects include cystitis and urethritis.

In summary, pamidronate is a potent agent in the treatment of Paget's disease, but repeated courses of intravenous therapy may be required in patients with more severe disease. The marked gastrointestinal toxicity of pamidronate makes oral administration problematic.

c Calcitonin

Calcitonin is a 32-amino acid polypeptide hormone secreted in humans by the parafollicular cells of the thyroid gland. The main biologic effect of calcitonin is to inhibit bone resorption by a direct receptor-mediated effect on the osteoclast. Salmon (the form most commonly used), human, and porcine calcitonins are available in different countries for the treatment of Paget's disease. Experience with eel calcitonin is still limited.

Injectable calcitonin is effective in suppressing pagetic activity as indicated by changes in serum alkaline phosphatase and urinary hydroxyproline. Calcitonin is also effective in improving pagetic bone pain and decreasing blood flow through pagetic bone. In addition, the radiodensity of osteolytic lesions increases with calcitonin treatment.

In general, however, the suppression of disease activity is incomplete. On average, the mean fall in alkaline phosphatase activity is approximately 30 to 50%, and only rarely does alkaline phosphatase normalize in patients with moderate to severe Paget's disease.

In addition, the response to calcitonin is only sustained for the duration of treatment, with biochemical relapse occurring almost invariably within a few months of cessation of therapy. Symptomatic responses and radiological healing are reported to be somewhat more sustained. Increasing the dose of calcitonin has little effect to produce greater suppression of bone turnover. Moreover, the duration of treatment does not affect the rate of relapse observed after discontinuation of treatment.

Tachyphylaxis often develops so that biochemical parameters may rebound to pretreatment values despite continued or reinstated therapy. This loss of response appears to be related to antibody formation in some patients, whereas in others resistance occurs without evidence of neutralizing antibodies, possibly due to down-regulation of calcitonin receptors.

Side effects of injectable calcitonin, which occur in about 30% of all patients, include nausea and/or vomiting, diarrhea, facial flushing, skin rash, diaphoresis, tingling in the extremities, urinary frequency, febrile reactions, and a metallic taste. These side effects rarely necessitate discontinuation and tend to decrease or even disappear with continued usage.

Similar to bisphosphonates, calcitonin may induce mild and transient decreases in serum calcium, usually of no clinical significance, due to its acute effect to inhibit bone resorption.

Most forms of calcitonin require repeated parenteral administration (usually daily or thrice weekly subcutaneous injections), which reduces tolerability substantially.

Alternative routes of calcitonin administration (intranasal, rectal) are associated with fewer side effects and better tolerability, but overall show less efficacy due to relatively low bioavailability. Most of the studies conducted were small and exhibited large interpatient variability, making it impossible to reliably assess dose-response relationships.

4 Discussion

Alendronate is a potent aminobisphosphonate, estimated to be at least 10 and 2000 times more potent than pamidronate and etidronate, respectively, in decreasing *in vitro* osteoclastic bone resorption. Several studies of both oral and intravenous alendronate indicate that it is very effective in decreasing indices of disease activity in Paget's disease. Furthermore, alendronate is generally well tolerated and has a favorable safety profile.

In contrast, currently available therapies are either only partially effective or are associated with poor patient acceptability because of their adverse experience profile or route of administration (or both)

Calcitonin is inconvenient due to the need for parenteral administration and may be poorly tolerated (especially because of nausea and flushing). For these reasons, calcitonin use is associated with significant compliance problems. Calcitonin produces an incomplete response and requires chronic administration. In contrast, no biochemical relapses were observed in patients treated with 40 mg alendronate for six months who were followed for up to six months after cessation of treatment. Longer duration studies in adequate numbers of patients are not available. Oral dosing of alendronate offers greater ease of administration.

The use of etidronate is compromised by impairment of bone mineralization at therapeutic doses, confirmed in the Phase III direct comparison study. Furthermore, its suppression of serum alkaline phosphatase is significantly less marked than that achieved with oral alendronate, and patients with more severe disease do not respond as well. In the Phase III Studies, the mean percent decrease in serum alkaline phosphatase with alendronate was approximately 75 to 80%, a greater effect than that observed in response to most other antipagetic therapies, including calcitonin and etidronate. In a direct comparison study, alendronate was significantly more effective than etidronate in decreasing serum alkaline phosphatase and other markers of bone turnover.

Pamidronate usually requires parenteral administration because of the significant gastrointestinal toxicity observed with oral administration. Like etidronate, pamidronate is less efficacious in patients with more severe disease. On the other hand, similar response rates to oral alendronate were seen in patients with greater or lesser elevations in serum alkaline phosphatase. Alendronate was similarly effective both in patients who had been previously treated with other bisphosphonates (who may be resistant to retreatment) and in those who had not.

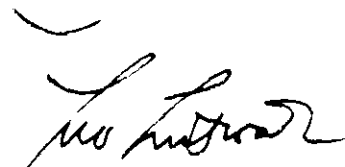
Although long-term data are not yet available on the duration of effect of alendronate, no relapses were observed in any patients treated with 40 mg/day for six months during a six-month follow-up period. Based on the clinical experience with other bisphosphonates, it is likely that alendronate, due to its marked suppression of bone turnover, will induce a sustained remission in most patients. However, the long-term effects of alendronate treatment remains to be determined. The Sponsor has submitted brief followup summary data on a small number of the patients studied in the 6 month pivotal studies. Although some patients continue to show significant reduction of serum alkaline phosphatase, it is apparent that return to elevated values occurs. The Sponsor wishes to recommend that, in parallel with the recommendation for the previously approved etidronate for Paget's disease, that retreatment with alendronate should be considered if alkaline phosphatase concentrations return to elevated levels.

The safety profile of alendronate also appears favorable, with no increased incidence of patient discontinuation from treatment in the alendronate group relative to placebo. The main side effects, abdominal pain and musculoskeletal pain, are tolerable and self-limiting. In addition, histomorphometry showed that alendronate decreased the elevated rate of pagetic bone turnover and that overall the quality of bone formed during treatment was normal.

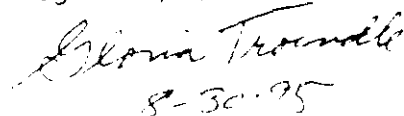
In summary, oral alendronate 40 mg/day for six months is an efficacious and generally well tolerated agent for the treatment of Paget's disease.

XVIII. MEDICAL OFFICER'S COMMENTS AND RECOMMENDATIONS

1. Although only small number of patients have been studied, alendronate is significantly more effective than placebo or etidronate in reducing elevated serum alkaline phosphatase in Paget's disease. After 6 months of treatment normalization of values was seen in 26/41 (63.4%) of patients receiving alendronate 40 mg daily as compared to 8/47 (17.0%) of those on etidronate 400 mg daily, the values were 13/27 (48.1%) of those on alendronate as compared to 0/27 on placebo in a parallel study.
2. No serious adverse reactions were seen with alendronate administered for this period of time at this dosage.
3. Mild to moderate gastrointestinal adverse events were reported, no more frequently than seen with etidronate.
4. Of some concern is the observation that in young growing animals, alendronate resulted in retention of primary spongiosa. While the significance of this to human clinical disease is unknown, it does suggest abnormalities in remodeling, raising some question concerning long-term safety of alendronate.
5. Additional studies of retreatment are needed, with significant numbers of subjects.
6. Alendronate is approvable for the indication of treatment of Paget's Disease of the Bone at a dosage of 40 mg per day daily for 6 months, using elevation of serum levels of alkaline phosphatase of at least twice upper limits of normal as index for therapy and normalization of these levels as the end-point.



Leo Lutwak, M.D., Ph.D.
August 24, 1995



8-30-95

cc: IND Arch.
HFD-510
HFD-510:GTroendle/SDutta/RHedin/LLutwak

1.1. Title and General Information**Medical Officer's Review**

- 1.1.1 NDA # 20-560
- 1.1.2 Submission date: 3/31/95
- 1.1.3 Review completed: 7/5/95

1.2 Drug Name:

- 1.2.1 Generic name: Alendronate sodium
- 1.2.2 Proposed trade name: Fosamax
- 1.2.3 Chemical name: (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate

- 1.3 Sponsor:** Merck Research Laboratories
Attention: Edwin L. Hemwall, Ph. D.
Director, Reg. Affairs
West Point, PA 19486

1.4 Pharmacologic category: Inhibits osteoclastic activity and, therefore, bone resorption.

1.5 Proposed Indications and Usage: Fosamax is indicated for the treatment of osteoporosis in postmenopausal women.

1.6 Dosage Form and Route of Administration: 10 and 40 mg tablets for p.o. use.

1.7 NDA Drug Classification: 1P

1.8 Important Related Drugs:

Approved bisphosphonates and their Indications and Usage

Table 1. Lists approved bisphosphonates with indications.

Drugs	Indications and Usage
Didronel (Etidronate disodium) Tablets	- For the treatment of Paget's disease of bone - For the treatment of heterotopic ossification
Didronel I.v. Infusion	- Hypercalcemia of malignancy (HCM)
Aredia (Pamidronate disodium) for Injection *	- Hypercalcemia of malignancy - For the treatment of Paget's disease of bone

* NDA supplement submitted for a new indication: For the treatment of metastatic bone disease.

The following investigational bisphosphonates (p.o. and i.v. formulations) are being investigated in the treatment metabolic bone diseases (e.g., Paget's disease of bone, hypercalcemia of malignancy, postmenopausal osteoporosis, and metastatic bone disease):

- Clodronate (Dichloromethylene-bisphosphonic acid)
- Tiludronate (Chloro-4-phenylthiomethylidene-bisphosphonic acid)
- Risedronate [2-(3-Pyridiny)-1-hydroxyethylidene bisphosphonic acid]
- BM21.0995 [1-Hydroxy-3 (methylpentylamino)-propylidene -bisphosphonic acid]
- 6-Amino-1-hydroxyhexylidene-bisphosphonic acid.

1.9 **Related Reviews:** Chemistry, Pharmacology, Biopharm, and Statistical reviews.

1.10 Material Reviewed:

Table 2. Description and volume numbers of this submission.

Description	Volumes
Synopsis of Application	2.2
Nonclinical Pharmacology/Toxicology	2.11-2.42
Human pK Data	2.43-2.58
Clinical Documents (Osteoporosis)	2.59-2.122
Case Report Forms (Osteoporosis studies)	2.175-2.240

Clinical documents were reviewed in-depth by this reviewer. Documents which are subjects of critical reviews by other disciplines are highlighted in the MCR.

1.11 **Chemistry and Manufacturing Controls:** See Chemistry review for details.

1.12 **Animal Pharmacology/Toxicology:**

A. Pharmacodynamics: These studies were directed to: 1) evaluate the efficacy of alendronate (ALN) in animal models of human bone diseases (particularly osteoporosis), 2) develop guidelines for human dosing schedule, and 3) examine the quality of bone formed during treatment.

Table 3. Preclinical studies and the species of the animal used.

Study Description	Species
Localization in bone and Mechanism of Action	Rats, Mouse
Effect on Estrogen-Deficient Osteopenia, Bone biomechanics	Rat
Effect on Estrogen-Def. Osteopenia, Histomorphometric and Biomechanics Eval.	Baboons
The treatment of HCM	Rat
Prevention of Bone Loss in Immobilization	Rat
In the Treatment of Hyperparathyroidism	Rat

Table 3 (continued).

On Bone Formation after Marrow Ablation	Rat
ALN vs Sod. Fluoride on Bone Formation	Minipig

ALN mode of action - At the cellular level, radioactive ALN has been shown to be localized at sites of bone resorption under osteoclasts. It inhibits osteoclast activity, but does not interfere with osteoclast recruitment and attachment. Uptake of ALN on osteoclasts is about 10-fold higher than that on osteoblast. Normal bone has been reported to form over ALN labeled osteoclasts. Buried ALN in the bone matrix become pharmacologically inactive. This provides the rationale for its continuous administration as opposed to the intermittent regimen in clinical trials.

Bone biopsy data revealed reduction in activation frequency (the number of sites at which resorption was initiated) and increase in wall thickness (the amount of bone formed in a remodeling cycle)

Studies in estrogen-deficient rats- Ovariectomized (OVX) rats were treated with ALN at doses of 0.224 mg/kg/mo s.c. (equiv. to 1 mg/kg/day p.o.) to 28 mg/kg/mo s.c. for 12 weeks. ALN treatment prevented bone loss and even at the lowest dose it increased bone volume above that of the non-OVX controls. Bone biopsy data showed about 30% decrease in "eroded surface" (resorption) and osteoid surface (formation). Thus, overall decrease in bone turnover.

When ALN treatment was initiated 4 months after ovariectomy and continued for 6 months at a dose of 0.28 to 28 μ Kg s.c. ex week, the bone strength (compression load) of L6 vertebra was reported to increase in a dose-dependent manner. The bone strength of L6 vertebra was 30% lower in OVX rats than in non-OVX animals. In addition, there was a good correlation between L6 ultimate load strength and L5 trabecular bone volume in OVX animals treated with ALN.

In a similar study, OVX animals (6-7 mo-old) were treated with ALN (initiated 6 months after removal of ovaries) at a dose of 1.8 to 18 μ g/Kg ex weekly (equiv. to human doses of 3.7 to 37 mg/50Kg/day with 0.7% absorption) for 12 months. The bone turnover was reported to increase by 2-fold in OVX animals at the end of vehicle treatment and decreased to non-OVX control levels or below control level in the ALN-treated animals. Both the total and cortical vertebral bone volume (BMD measured by DXA) significantly increased at the end of treatment with ALN. Increases in vertebral BMD and ash weight were associated with increase in bone strength.

In a comparative study, OVX rats (12 weeks old) were treated with 17beta-estradiol (0.83 μ g/day pellet) or ALN (1 mg/kg/day p.o.), or both together for 6 months. Estrogen deficiency resulted in increased bone turnover and decreased cancellous bone volume and strength of the vertebrae (by about 28% in L6) in OVX rats. Either treatment increased vertebral bone volume and strength compared to vehicle treated OVX animals.

Prevention of bone loss in estrogen-deficient baboons: Three groups of OVX baboons were treated with vehicle, ALN 0.05 and 0.25 mg/kg s.c. every 2 weeks. A fourth group of non-OVX baboons served as another group of controls. The treatment lasted for 24 months. Biochemical markers of bone turnover, vertebral BMD (by DXA), spinal x-rays, and iliac crest bone biopsies were performed periodically (3-6 months intervals) over 24 months. L5 (compression test) and femur (3-point bending test) bone strength was evaluated at sacrifice.

The results indicated increased levels of biochemical markers in blood and urine, characteristic of increased bone turnover in OVX vehicle treated baboons. ALN treatment maintained urinary excretion of lysylpyridinoline at control level at low dose. Suppression of urinary excretion of this marker did not increase with treatment time. Similar changes occurred with serum alk. phosphatase levels, indicating lack of harmful effect on bone formation. Bone histomorphometric data showed significant increase in "trabecular thickness" in ALN treated animals, relative to OVX-vehicle-treated animals.

With respect to the effect on cortical bone, turnover was suppressed significantly in the ALN-treated animals. Whereas, in OVX-vehicle-treated animals, bone turnover increased over the corresponding period. Osteoid spaces were also decreased in ALN-treated animals relative to OVX-vehicle-treated animals.

The BMD of the lumbar vertebrae (L2-L4) increased in the ALN-treated animals at a dose of 0.25 mg/kg compared to OVX-vehicle-treated animals. Increase in vertebral BMD was also associated with dose-dependent increase in cancellous bone strength in ALN-treated animals. In this animal model, ALN treatment at a dose equivalent of 12 times the projected human dose (10 mg/Kg/day), showed no evidence of histological or biomechanical abnormalities.

ALN effects on models of secondary hyperparathyroidism (including HCM): Evaluation of histomorphometric data from these studies showed increased thyroid hormone-induced bone turnover and decreased cancellous bone volume over time. ALN treatment prevented those changes.

Comparison of ALN and Etidronate (EHDP) effects on bone relative to margin of safety of these two bisphosphonates: ALN and EHDP were tested in models of Marrow ablation and Schenk assay. In marrow ablation model, ALN and EHDP were used at the following doses:

ALN- 0.005, 0.025, 0.125, or 0.625 mg P/Kg s.c. The doses are expressed in mg P/Kg, as phosphorus accounts for about 20% of molecular weight of ALN.

EHDP- 0.25, 1.25, or 6.25 mgP/Kg/day s.c.

Both drugs were administered to young growing rats for 10 days following marrow ablation. Inhibition of bone resorption and mineralization was estimated by the total bone volume retained and the fraction of osteoid per bone volume, respectively, at 10 days. ALN-treated animals showed increase in bone volume at all doses given. Significant increase in osteoid was reported only at a

dose of 0.625 mgP/Kg s.c., indicating a wide margin of safety of about 125 in this system. Whereas, EHDP showed increase in bone volume and inhibition of mineralization (increased osteoid volume) at a dose of 1.25 mgP/kg s.c. (margin of safety of 1).

In Schenk assay model, ALN and EHDP were administered at the following doses:

ALN-0.001, 0.01, 0.1, 1, 3, or 3 mg P/Kg /day s.c.

EHDP- 0.01, 0.1, 1.03, 6, 10 or 30 mg P/Kg/day s.c.

Both drugs were given daily for 10 days to growing rats. Total bone volume and osteoid volume were measured histomorphometrically at Day 11. The results indicated increase in bone volume in the ALN-treated samples at a dose of 0.001 mg P/Kg/day. Osteoid volume increased at a dose of 6 mg P/Kg/day (6000 times the antiresorptive dose). EHDP increased bone volume and osteoid volume at a dose of 6 mgP/Kg/day s.c. (margin of safety of 1).

Experiments performed for localization of radio-labeled ALN and EHDP in bone. ALN (regardless of its dose) showed 2.5-fold higher selectivity for osteoclast surfaces than EHDP. EHDP showed higher uptake on osteoblast bone formation surfaces.

Effect of ALN and fluoride on pig bone- Groups of growing minipigs were treated with ALN (1mg/kg/day p.o.), sod. fluoride (2 mg/kg/day), or matched vehicle for one year. Histomorphometric analysis of iliac crest bone biopsy at the end of one year showed increased bone turnover in NaF-treated animals and decreased bone turnover in ALN-treated animals, compared to vehicle-treated controls. Mineralization lag time was not significantly different among three groups. In the ALN-treated animals, biomechanical strength of femur and core of L4 vertebra increased significantly. NaF-treated animals showed decrease in vertebral (L4) strength compared to controls and ALN-treated animals. Moreover, ALN-treated animals showed a good correlation between bone volume and bone strength. Such a correlation was not seen in NaF-treated animals.

B. Preclinical pharmacokinetics- Pharmacokinetics properties of ALN was studied in several species of animals (see Table 4.)

Table 4. pK studies with species of animals used.

Study Description	Animal Species
Lack of biotransformation	Rat, dog
Estimates of absorption	Mouse, rat, dog, monkey
Excretion	Rat, dog, monkey
Uptake by bone tissue	Rat, dog

Table 4 (continued).

Renal excretion	Rat
Invitro plasma protein binding	Rat, dog, monkey

Metabolism in rats and dogs-

³H and ¹⁴C-labeled alendronate was used to determine the extent of metabolism in rats and dogs. The results of these studies demonstrated that "Alendronate was not significantly metabolized."

Absorption- Alendronate was found to be poorly absorbed in mice, rats, dogs, and monkeys. After an oral dose of alendronate, its blood level was too low to be determined by HPLC. By using double radio-labeled technic, the absorption in fasted animals was estimated to be 0.7% in rats, 1.8% in dogs, and 1.7% in monkeys. Presence of food in the stomach interfered with the absorption of alendronate. The order of absorption appeared to be jejunum > duoderum > ileum > gavage. The results of absorption studies indicated an increased degree of absorption with increasing dose. Breakdown of intestinal mucosa tends to increase absorption of alendronate from the gut.

Excretion- In a multiphasic fashion the drug was rapidly removed from plasma of rats, dogs, and monkeys. About 30%-40% of an i.v. dose of the drug was excreted in urine within 24 hours. Most of it was excreted in first 3-4 hours. A trace of drug was excreted in the bile. Urinary excretion appeared to be the only route of its elimination. Renal excretion of alendronate appeared to be dose-dependent and its renal clearance was inhibited by etidronate in a dose-dependent fashion. Probably due to involvement of an unidentified transport mechanism in a competitive manner.

Tissue distribution- After i.v. administration of 1 mg/kg dose, the drug has been reported to be widely distributed in calcified and non-calcified tissues of rats. From the decalcified tissues, most of the drug disappeared rapidly within 5 minutes to 1 hour. The highest concentration of alendronate has been reported in the kidneys lasting for about 48 hours. Phagocytosis of alendronate complexes with metal ions leads to its accumulation in soft tissues.

At a low dose, the drug has been reported to be accumulated in bone tissue to the extent of 60% to 70% of it. Peak levels of alendronate occurs in tibia and femur in rats in about 1 hour, and remains there virtually unchanged over a 72-hour period. In rats, the level of alendronate in bone appeared to decline in a multiphasic manner. For the earlier phase, the half-life of alendronate was about 30 days and showed a half-life > 200 days for the terminal phase. In dogs, based on multiphasic urinary excretion profile of the drug, its terminal half-life was reported to exceed 1000 days. Chronic dosing was reported to provide no evidence of saturation in bone. The uptake of alendronate by bones of young rats was greater than that of older rats.

Plasma-protein binding- Plasma-protein binding of alendronate was species-specific. It was found to be highly plasma-protein bound in rats, but not in dogs and monkeys.

C. Preclinical toxicology: The safety of alendronate has been tested in several species of animals. See Pharmacology review for the results of these studies, comments, and recommendation. From safety point of view, long-term (2-3 years) treatment with alendronate in rats and dogs provided no evidence of deleterious effect on bone "quality."

Medical reviewer's overall comments on preclinical studies with alendronate:

The results of both invitro and vivo studies demonstrated that alendronate is a potent inhibitor of bone resorption like other bisphosphonates. It localizes under the osteoclasts and thereby inhibits their resorptive action on bone. When it is incorporated in newly formed bone, it becomes pharmacologically inactive and does not interfere with new bone formation. The mechanism of action of alendronate has been determined in several species of animals.

The margin of safety of alendronate treatment in growing rat model is much higher than that of etidronate.

Alendronate has been shown to prevent bone loss and increase in cancellous bone volume in OVX rats at a dose of about 1 mg/kg/day p.o. (equivalent to 7 μ g/kg/day s.c.). In OVX rat model, alendronate treatment (initiated 6 months after ovariectomy) increased vertebral bone volume and strength (by compression test) in a dose-dependent fashion.

Similar experiment was performed in OVX baboons. These animals were treated with alendronate at doses equivalent to 25 and 125 mg/kg/day p.o. in humans (with 0.7% absorption) for 24 months. Alendronate treatment resulted in suppression of biochemical markers and histomorphometric parameters of bone turnover, an increase in vertebral BMD (cancellous bone volume), and an increase in vertebral bone strength (by compression test).

In rat osteopenia model, alendronate treatment at a dose equivalent to 28 x the human dose (10 mg/50 kg/day) showed no evidence of interference with bone formation and mineralization. Dogs, pigs, and baboons treated for 1 to 3 years with alendronate at multiples (5 to 12.5 times) of dose (10 mg/50 kg/day) recommended for humans, showed no evidence of fracture, woven bone or marrow fibrosis.

In rats, baboons, and pigs, a good correlation between increase in bone density and bone strength was noticed at dose equivalent to up to 12 times human osteoporosis dose.

The drug is poorly absorbed from the intestine (0.2% to 1.8%) in mouse, rats, monkeys, and dogs. It is widely distributed in the body (non-calcified and calcified tissues). In bones, alendronate is concentrated to the extent of 60% to 70% of a single dose and slowly released. Terminal half-life of alendronate in bone is > 200 days in rat, and > 1000 days in dogs. The drug is not metabolized

and renal excretion is the only route of its elimination from the body.

The overall preclinical pharmacodynamics, pharmacokinetics, and toxicology data submitted to this application provided a reasonable safety profile of the product for its use in clinical trials.

Clinical Background

5.1 **Relevant human experiences:** The proposed use of alendronate is for the treatment of osteoporosis in postmenopausal women (PMOP).

Highlights of pathophysiology of PMOP- PMOP is a major public health problem in the U.S. It is a disease characterized by low bone mass and increased risk of traumatic fractures resulting from low bone mass. The common sites for osteoporotic fractures are distal forearm, thoracic and lumbar vertebrae, and hip. It has been estimated that after menopause one in three women is at risk of developing fractures in one's lifetime. It is generally classified into Type I and Type II, based on the patterns of fractures that occur due to low bone mass. In Type I osteoporosis, distal forearm and vertebral fractures are common. The Type II osteoporosis is characterized by loss of both cortical and trabecular bone, and hip fractures are common. Various other factors are associated with osteoporotic syndrome(s). PMOP without a fracture is entirely asymptomatic. When osteoporotic fractures occur, the symptoms and signs are related to the fracture itself. Osteoporotic vertebral fractures may occur in the absence of acute pain. The discussion of orthopedic management of osteoporotic fractures is outside the scope of this review.

Many prospective studies have demonstrated that the risk of osteoporotic fractures increase progressively as the bone mineral density (BMD) declines. Fracture risk has been reported to increase by 1.5- to 3-fold or more for each standard deviation (SD) decrease in BMD (irrespective of sites). In recent years, the methods of determining BMD have been greatly improved to reflect high accuracy and precision. An individual with a value of vertebral BMD that "lies between 1 and 2.5 SD below the young adult mean value is considered osteopenic" and a candidate for prevention of further bone loss. If the value of BMD is more than 2.5 SD below the adult mean value and the individual has experienced one or more vertebral fractures, then it is a case of established osteoporosis.

Recently, the study of biochemical markers of bone turnover has found its place in the assessment of PMOP. The markers of bone resorption include fasting urinary calcium and hydroxyproline, pyridinoline crosslinks and related peptides, and plasma tartrate resistant acid phosphatase (TRAP). Markers of bone formation include serum total and bone specific alkaline phosphatase, serum osteocalcin, and procollagen extension peptides. After menopause bone turnover is generally increased by several folds. Such increases are reflected in changes in bone markers.

Estrogens and salmon calcitonin are the agents currently approved for the prevention and treatment of PMOP. Estrogens are antiresorptive agents in that they inhibit increased bone resorption. The mechanism(s) of antiresorptive action of estrogens is not clear. At menopause, women at risk of

developing osteoporosis may be given estrogen replacement therapy (ERT). The decision to use ERT must weigh the risk/benefit ratio for each individual patient. Patients as well as physicians are often reluctant to use ERT because of fear of breast or uterine cancer. Synthetic salmon calcitonin (sCT) is also approved for the treatment of established PMOP. sCT (s.c. or i.m. injection or intranasal formulation) is also an antiresorptive agent. In clinical trials, it has been reported to increase total body calcium over a period of 18-24 months. Antifracture efficacy of sCT has not been demonstrated. The major drawbacks of sCT therapy in the treatment of PMOP include: a) the high cost, b) parenteral or intranasal administration, c) plateau effect on bone mass, and d) frequent side effects such as nausea and flushing.

5.2 Important information from related INDs and NDAs:

for the treatment of postmenopausal osteoporosis. The drug has not been approved for use in the proposed indication.

Known toxicities associated with other bisphosphonates: Didronel (tablets) is an approved drug for the treatment of Paget's disease of bone and heterotopic ossification. The adverse reactions listed in the package insert include diarrhea, nausea, and increased or recurrent bone pain at pagetic sites. Worldwide post marketing experience with Didronel also reports the following adverse reactions possibly related to Didronel: alopecia, arthropathies, bone fractures, esophagitis, glossitis, hypersensitivity reactions (including angioedema, follicular eruptions, macular rash, pruritis, a single case of Stevens-Johnson syndrome), osteomalacia, neuropsychiatric events, and paresthesia. In clinical trials with pamidronate about 50% of patients developed pyrexia (usually 1-2° C) lasting for about 3 days. Changes reported with other aminobisphosphonates included decrease in peripheral lymphocytes, an increase in C-reactive protein, and a decrease in serum zinc. Side effects of bisphosphonates differ from one compound to other. Intravenous administration of bisphosphonates (e.g., etidronate disodium, pamidronate) has been reported to cause asymptomatic hypocalcemia, and hyperphosphatemia. Rapid i.v. administration of pamidronate can cause renal failure, due to formation of insoluble calcium bisphosphonate complexes in the blood.

5.3 **Foreign Experiences:** Table 5. Countries where alendronate sodium has received approval for the treatment of PMOP.

Country	Date of Authorization
Italy	July 1993
Mexico	November 1994
Honduras	March 1995
Guatemala	March 1995

The sponsor states that
of treatment of PMOP.

5.4 Human Pharmacokinetics : Bisphosphonates in general are known to have limited oral bioavailability. The results of preclinical studies indicate that alendronate is very poorly absorbed from the G-I tract and thus, the blood level following oral administration of ALN is likely to be below the limit of meaningful quantitation. Most of these pK studies have been performed with intravenous formulation of the drug and measuring drug concentrations in the urine. The pK data have been presented in order of distribution, metabolism, elimination, and absorption

Table 6. Biopharmaceutics Studies.

Protocol #	Description	Dosage Form/Dose	Subjects (Number)
39	ALN disposition	i.v./10 mg	Female Breast CA (12)
60	pK profile after single and multiple doses	i.v./125 μ g/dose x 7 doses	Healthy postmenop.(10)
23	Long-term elimination /4-day dosing	i.v./7.5 mg/day x 4d	Healthy postmenop.(23)
13	Pilot oral bioavailability	i.v., 50 mg cap.,p.o./250 μ g (i.v.) and 50 mg (p.o.)	Healthy postmenop.(7)
17	Oral bioavailability	i.v. and p.o./125 μ g (i.v.),5,10, & 40 mg (p.o.)	Healthy postmenop.(15)
065	Oral bioavailability	i.v. and p.o./125 μ g (i.v.) ,5,10,& 40 mg (p.o.)	Healthy postmenop.(20)
69	Oral bioavailability	i.v.and p.o./250 μ g (i.v.) 10 mg (p.o.)	Healthy male (16)
32	Relative bioavailability with food & calcium	p.o./20 mg	Healthy postmenop.(15)
53	Oral bioavail. effect of timing of meals	p.o./10 mg	Healthy postmenop.(49)

Table 6 (continued).

66	Relative oral bioavail. with juices and coffee	p.o./10 mg	Healthy postmenop. (40)
48	Gastric absorp. effect of pH	i.v. and p.o./20 μ g (i.v.), 40 mg (p.o.)	Healthy postmenop.(10)

Drug formulation- For the pK studies ALN was formulated as tablets and i.v. solution.

Tablets: 1, 2.5, 5, 10, 20, 40, and 80 mg tablets.
intravenous - Solutions of 0.25 and 2.5 mg/mL.

Disposition of ALN- Following i.v. administration of a single dose of ^{14} C-labeled ALN (10 mg), plasma, feces, and urine samples were collected sequentially in a group of breast cancer patients. Within 6 hours of administration, plasma level of ALN (including radio-labeled) decreased by >95%. Systemic and renal clearances were reported to be <199 ml/min and 71 ml/min, respectively. The estimated volume of distribution was >28 L. Radioactivity in the feces was negligible. Approx. 45% of the dose was recovered in urine. From the plasma and urine data it was concluded that metabolism of ALN in humans was negligible or "non-existent." The results of this study supported the use of urinary excretion of ALN in other pK studies.

Drug elimination- Following a single i.v. administration of ALN (at doses of 20 μ g to 10 mg) to a group of healthy postmenopausal women, about 40% of an administered dose was reported to be rapidly excreted in the urine. However, by 72 hours 40% to 60% of an administered dose was retained in the body and its urinary excretion markedly decreased. The fraction of a dose retained in the body after initial rapid excretion was reported to be independent of dose and duration of infusion (range of 0.25 to 12 hours).

Half-life of ALN- Patients with postmenopausal osteoporosis were treated with ALN (i.v.) at a dose of 7.5 mg/day over 12 hours for 4 consecutive days. Urine samples were collected at designated time intervals for up to 24 months after dosing. Based on its measured excretion rate, it was estimated that in humans the elimination half-life of ALN "is at least 10 years."

Bioavailability of oral doses of ALN- The study was conducted in healthy postmenopausal women at doses of 5 to 80 mg (with i.v. reference doses of 125 or 250 μ g). The results indicated that bioavailability of ALN was about 0.7% of the oral dose. Studies in men also showed similar bioavailability. ALN was recovered from urine in linear fashion over the doses tried (5 to 80 mg).

Influence of food, beverages, and calcium on absorption- Studies were carried out in postmenopausal

women. With regard to the effects of timing of the meal and calcium supplementation, the presence of food in the stomach was reported to decrease the absorption of ALN to varying degrees. Eating of meals one-half or one hour after dosing resulted in decreased absorption by about 40%. Similarly, alendronate dosing immediately after or 2 hours after breakfast resulted in marked decrease (85% to 90%) in bioavailability. Drinking of coffee or orange juice has also been reported to decrease bioavailability of ALN. Thus, the recommended dosing of ALN should be taken at least one-half hour before breakfast with water after an overnight fast.

Effect of elevated gastric pH on absorption of ALN- No measurable effect of raising gastric pH (by giving ranitidine) on systemic disposition of ALN was noted in postmenopausal subjects. Although, absorption of ALN was reported to increase by 2-fold compared to normal endogenous pH in the stomach.

Drug interaction- Drug interaction studies were not conducted. The sponsor has suggested that because of very low plasma level of alendronate after its absorption, it is unlikely there will be a significant displacement interaction due to plasma protein binding. Since the drug is neither metabolized nor eliminated in the bile, but excreted intact exclusively by the kidney (involving a suggested active secretory pathway and not engaging acidic or basic tubular transport processes).

Reviewer's Comments: The overall results of human pK studies are in agreement with those of preclinical studies. The detailed comments and recommendation on human pK studies are in the biopharm review.

The overall results seem to indicate the following:

1. About 50% of an i.v. dose of ALN is excreted in urine within the first few days postdose.
2. Excreted almost exclusively through kidney unchanged.
3. No metabolites of ALN have been identified.
4. The terminal half-life is > 10 years in humans.
5. The oral bioavailability of ALN is about 0.7% (over a dose range of 5 to 80 mg) in postmenopausal women.
6. Elevated gastric pH (as in hypo- or achlorhydria) causes 2-fold increase in the absorption of ALN with no significant effect on its disposition.
7. Presence of food in the stomach decreases oral absorption of ALN. Calcium supplementation with breakfast at one or 2 hours postdose does not interfere with oral absorption beyond that caused by food itself. Beverages such as orange juice and coffee interfere with oral absorption of ALN. Water has not been shown to affect absorption of ALN.

8. The pk profile of ALN may not contribute toward significant interactions with other drugs. However, no formal interaction studies have been conducted. Drug interaction information is likely to be generated from further clinical experience with ALN.

5.5 Relevant Background Information (meeting, commitments):

- ◆ On August 30, 1988, the IND () was submitted by Merck Research Laboratory (MRL).
- ◆ On August 22, representatives of MRL met with the FDA to discuss the clinical development program.
- ◆ On December 24, 1991, the sponsor discussed ongoing clinical program. Extension of pivotal Phase III studies from 2 to 3 years was discussed. Also, protocol for the fracture efficacy study was discussed. There was some discussion on the results of preclinical studies.
- ◆ On July 23, 1992, representatives of MRL and FDA met to discuss the filing strategy and contents of alendronate NDA submission. The sponsor discussed the marketing policy of ALN in other countries where 2-year BMD data might be adequate for filing an NDA. MRL also introduced the concept of Spinal Deformity Index (SDI) in the fracture efficacy studies, and indicated that complete preclinical data will be submitted to the agency prior to formal submission of an NDA.
- ◆ On November 2, 1992, representatives of MRL discussed the methods of validation of BMD and SDI.
- ◆ On February 4, 1993, the sponsor submitted the data analysis plan for Phase III osteoporosis trial.
- ◆ On March 3, 1993, representatives of MRL discussed the second preclinical model for osteoporosis.
- ◆ On April 22, 1993, members of MRL discussed with us the clinical study endpoints and overall statistical plans for analyses of data from Phase III osteoporosis trials.
- ◆ In April and May of 1994, MRL submitted complete reports on preclinical safety and bone biology to IND (). Two-year clinical data summary from osteoporosis treatment studies were submitted.
- ◆ On June 7, 1994, the sponsor discussed the year-2 data from osteoporosis treatment studies, and provided the rationale for use of 10 mg/day dose of ALN in the treatment studies. In this meeting, the agency suggested that if the results of two year were carried over to 3rd year without "deterioration," then ALN could be considered approvable according to our current Osteo-Guidelines. The agency also suggested additional approaches to the analysis of SDI and digitized vertebral fracture x-rays.

- ◆ On August 9, 1994, a pre-NDA meeting was held to discuss the submission of 3-year data from osteoporosis treatment trials. The statistical data analysis plans and format for presentation of serious adverse experiences were discussed.
- ◆ On October 10, 1994, the sponsor submitted the Chemistry, Manufacturing, and Controls data to the agency.
- ◆ On March 9, 1995, representatives of MRL met with the agency to review the 3-year results of Phase III osteoporosis treatment studies with particular reference to fracture efficacy. The agency expressed some opinion on the approval of ALN for the treatment of osteoporosis, "pending verification during the NDA review process." The agency also commented on the approval of ALN for the prevention of osteoporosis based on the review of fracture data.
- ◆ On August 19, 1994, the sponsor gave preliminary demonstration of Computer Assisted New Drug Application before some members of our division.

5.6 Direction For Use (proposed by the sponsor): Alendronate (Fosamax) must be taken at least one-half hour before first food, beverage, or medication of the day with a full glass of plain water only, since other beverages (including mineral water), food, and some medications are likely to reduce the absorption of Fosamax.

6 Description of Clinical Data Sources (IND and non-IND):

6.1 Study Type and Design/Patient Enumeration, Demographics, Extent of Exposure:

Table 7. Summary of clinical data sources for efficacy.

Study Type	Study Design	No. of Pt.	Demographics	Duration of Tx (Exposure)
Phase IIb	D-B,P-C,R*	188	Postmenopausal	2 years
Phase III (US)	D-B,P-C,R	478	Postmenopausal	3 years
Phase III (International)	D-B,P-C,R	516	Postmenopausal	3 years
sCT Comparison**	D-B,P-C,C	286	Postmenopausal	2 years
Elderly Pt.***	D-B,P-C, R	359	Postmenopausal	2 years

* Double-blind, placebo-controlled, randomized study.

** Included a blinded control group, but sCT group received intranasal sCT without blinding.

*** Aged more than 59 years.

In addition to these 5 efficacy studies, three other studies have been carried out to define the safety of ALN: Table 8. Summary of additional safety studies.

Study Type	Design	No. of Pt.	Demographics	Duration of Tx (Exposure) /ALN Dose
Ref.#D-13 Bone loss prevention	Placebo-Controlled	Total=447 ALN=357 PBO*=90	Early menop. Women	36 Mo/1-20 mg
Ref.#D-17 Bone loss prevention	Placebo-Controlled	Total=290 ALN=234 PBO= 56	Early menop. Women	6-24Mo/5-10 mg
Ref.# D-27 Pain	Placebo-Controlled	Total=97 ALN=49 PBO=48	Postmenop. Women	12 Weeks /5 mg

*= Placebo

6.2 Postmarketing experience: Postmarketed experience with Fosamax was limited to Italy, where it was made available for use in the treatment of PMO since October 31, 1994. In Italy, the drug was available as 5 mg tablets for this indication. About 11.2 million 5 mg tablets were manufactured and/or distributed through the date of submission of this NDA. Only one adverse experience reported to the sponsor was the following:

A female patient with hypothyroidism and a history of non-specific allergy to drugs was treated with ALN at a dose of 5 mg/day. Concomitantly, she was receiving levothyroxine and lorazepam. The patient received ALN for just one day (in the morning), and in the evening she developed purpura over her limbs and diffuse petechial suffusion (eventually mostly around ankle joints). She also started to develop swelling and tenderness of both knees, one wrist, and one elbow joints. On the following day she did not take any medication, the swelling and petechiae started to regress. On the next day (Day 3), she took levothyroxine; petechia and swelling got worse in the evening. Patient was treated with steroid for the reactions and started to experience regression of swelling and petechia, but developed another bout of papular rash (some papules were inflamed). The reporting physician felt that adverse drug reaction (skin rash) was allergic nature. The patient took only one tablet of Fosamax and had no previous history of taking bisphosphonate. The physician also felt that adverse drug reaction could be due to drug interactions between ALN and lorazepam and/or levothyroxine. Subsequently, when the patient started taking levothyroxine again, purpura and joint swellings got worse.

Reviewer's comments: In this particular case, it is difficult to evaluate a causal relationship between reported ADR and ALN treatment (for one day). A drug interaction between ALN and concomitant medications (levothyroxine and/or lorazepam) is possible. The sponsor has indicated (by phone to this reviewer) that they would soon submit an updated report on postmarketing clinical experiences.

6.3 Literature Reports:

a. Literature reports relevant to human pharmacokinetics and bioavailability: The references provided by the sponsor dealt with pK studies (in animal models and in human) of bisphosphonates. The results of MRL studies have been discussed earlier. Just a few of published reports dealt with ALN, but again these are animal studies (probably reviewed by the pharmacology reviewer). The information on human studies have already been covered in earlier section of human pharmacokinetics.

b. Clinical effects: The sponsor has not provided a formal list of published reports to support the data from controlled clinical trials. However, references cited in the body of this submission are listed separately. Relevant references will be commented as the medical review progresses. The published literature reports on ALN included 36 articles, 22 abstracts, and 38 reviews in areas covering osteoporosis, Paget's disease of bone, and oncology/clinical pharmacology/hyperparathyroidism. The sponsor cited three references (not based on MRL-

sponsored trials), in which i.v. ALN 5 mg/day over 2-4 days in contrast to oral formulation, decreased back pain/increased analgesic efficacy relative to sCT or ipriflavone (Passeri et al. Bone Miner 1993;22 Suppl.: S23-S52). In another independent study (Rossini et al. J. Bone Miner. Res. 1994, 9: 1833-1837), ALN was reported to cause smaller increase in hip BMD at a dose of 20 mg/day p.o. for six months, compared to observed changes in hip BMD of primary MRL trials. ALN used in this study was not synthesized by the Merck process. It was suggested that difference in response was possibly due to less suboptimal bioavailability of non-Merck product. The biochemical response to non-Merck product was also reported to be less than that of Merck product in this study.

7 Clinical Studies

7.1 Trial #1 (Sponsor's Ref. #D-12/JO-37,JO-49)/ Protocol #026:

Title: A double-blind, randomized, placebo-controlled, parallel group, multicenter study to evaluate safety, tolerability, and effect on bone density of daily oral alendronate sodium for 1 or 2 years in osteogenic postmenopausal women.

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7.1.1 Objective/rationale:

Primary objectives:

- a. To collect data on safety and tolerability of ALN 5 to 40 mg/day p.o. for up to 2 years, 40 mg /day for three months followed by 2.5 mg/day for 21 months in postmenopausal osteopenic women.
- b. To determine the effects of ALN at the above-mentioned dosage schedule on BMD of lumbar spine (primary efficacy endpoint), proximal femur (secondary efficacy endpoint), and forearm (secondary efficacy endpoint) in postmenopausal osteopenic women compared with placebo-treated subjects.
- c. To determine the persistence of BMD effects of ALN at the above-mentioned dosage regimens over 12 months after discontinuation of 2-year treatment

Other secondary objectives:

- a. To study the effects of ALN treatment (5 to 40 mg/day p.o. for 24 months) on biochemical markers of bone turnover. Study of resolution (over 12 months) of ALN effect on biochemical markers after completion of 24 months of treatment.
- b. To compare the effects of ALN treatment (40 mg/day for 3 months followed by 2.5 mg/day for

21 months) and a dose of 40 mg/kg for one year on BMD of spine, proximal hip, and forearm. Also to compare the rate of BMD change over a period between 9 and 24 months at a dose of 40/2.5 mg/day with the placebo.

c. To collect preliminary data on the utility of total body calcium measurement as an index of bone mass effects to ALN treatment (compared to placebo treatment) over 2 years of active treatment and over 12 month after discontinuation of therapy.

d. To collect data on the correlation between BMD indices obtained by using Hologic QDR-1000/W and Lunar DPX-L densitometers.

Reviewer's comments: The study objectives are clear and likely to generate data to provide an efficacy profile of ALN (mainly in terms of BMD changes in lumbar spine, proximal hip, and forearm) in postmenopausal osteopenic women. In addition, the study will generate information regarding resolution of effects (on BMD) after discontinuation of 2-year treatment with ALN.

7.1.2 Design: Double-blind, randomized, placebo-controlled, parallel group study.

7.1.3 **Protocol summary--**

Title-A double-blind, randomized, placebo-controlled, parallel group study to evaluate safety, tolerability, and effect on bone density of daily oral ALN sodium for 1 or 2 years in osteopenic postmenopausal women.

Purpose/Objectives- See earlier discussion.

Design - See earlier discussion.

ects and groups- A total of 188 patients were enrolled in this study. See Table 9 (Vol. D-3307) for groups.

reatment by groups.

Table 2 ††.

Treatment by Group--As Outlined in Amended Protocol No. 026-03

Group	Treatment Months 1 Through 3	Treatment Months 4 Through 12	Treatment Months 13 Through 24	Posttreatment Months 25 Through 36
A	Placebo A ⁽¹⁾	Placebo A and Placebo B ⁽¹⁾	Placebo	Continued evaluation without treatment
B	5 mg/day ALN	5 mg/day ALN and Placebo B	5 mg/day ALN	Continued evaluation without treatment
C	10 mg/day ALN	10 mg/day ALN and Placebo B	10 mg/day ALN	Continued evaluation without treatment
D	20 mg/day ALN	20 mg/day ALN and Placebo B	Placebo	Continued evaluation without treatment
E	40 mg/day ALN	40 mg/day ALN and Placebo B ⁽²⁾	Placebo	Continued evaluation without treatment
F	40 mg/day ALN	2.5 mg/day ALN and Placebo A	2.5 mg/day ALN	Continued evaluation without treatment

(1) Placebo A matches the 5 to 40 mg ALN tablet image and Placebo B matches the 2.5 mg tablet image. Beginning Month 13, all tablets were manufactured in the same image (5 to 40 mg).

(2) All but six patients completed 12 months of treatment before switching to placebo. Six patients received nine months of 40 mg ALN followed by placebo Months 10 through 12.

†† Table Number in NDA Submission.

Type of subjects- Healthy postmenopausal (for at least 5 years) women, aged 42 to 75 years.

Key inclusion criteria-

- a. Subjects who had low lumbar spinal BMD ($\leq 0.86 \text{ g/cm}^2$ by Lunar DPX or $\leq 0.86 \text{ g/cm}^2$ by Hologic QDR). The osteopenia corresponds to a BMD about 2SD below the mean BMD of mature premenopausal Caucasian women in the US.
- b. Subjects in good health based on medical history, PE, and laboratory screening evaluation.
- c. Body weight of the subjects no more than 15% below or 30% above the ideal body weight (defined in Metropolitan Life Ins. height and weight table).

Key exclusion criteria- The exclusion criteria were comprehensive, adequate, and appropriate for the study.

Controls- Placebo-controlled.

Dosage and duration- See Table 9 for doses of ALN and duration of treatment. Alendronate should be taken while fasting and at least 2 hours before breakfast, with an eight ounce glass of water.

Calcium supplementation- During the study all patients will receive daily dietary calcium supplement of 500 mg of elemental calcium as the carbonate salt (OS-Cal 500).

Screening and baseline investigations: See Table 10. All participants to the study will receive general instructions on lifestyle changes to decrease the risk of osteoporotic fractures. Dietary calcium intake will be assessed in each patient.

- ^a C = Complete medical history; I = Interval history to identify new or changed symptoms and medication usage.
- ^b C = Complete physical examination; L = Limited physical examination and includes cardiac, pulmonary, abdominal, musculoskeletal, and neurological examinations, with a more extensive examination performed when indicated to evaluate symptoms or if abnormal at previous clinical visit. Both C and L examinations include vital signs.
- ^c Not needed if normal chest X ray (PA and lateral) obtained within six months and lateral thoracic and lumbar X ray obtained within three months and a report is available. Only spine X ray at 24 months.
- ^d Performed using Hologic QDR 1000 or 1000/W bone densitometry equipment.
- ^e Height measured using a Harpenden stadiometer.
- ^f Iliac crest bone biopsy after double tetracycline labeling was performed in ten consenting patients.
- ^g Lumbar spine bone density only at screening. Not needed if patient is known to have low bone mineral density meeting the entry criteria.
- ^h T lymphocyte studies performed at all centers.
- ⁱ Performed every six months at sites with Hologic 1000/W or Lunar DPX whole body calcium bone densitometry equipment.
- ^j Tablet counts of study drug recorded.
- ^k Urine chemistry performed on fasting second morning voided urine samples (about one to two hours). Pyridinolines were not determined on the screening specimen.
- ^l One card collected at screening. Patients with gastrointestinal symptoms that indicated ulcer activity were given a fecal hemoglobin (Hematest) test on each visit when symptoms were noted.
- ^m Clinic Visit 1 was carried out on Study Day -2 or -3 when more than three weeks elapsed since screening laboratory studies were performed. Patients were not administered the first MK-217 dose until the investigator reviewed all Clinic Visit 1 laboratory safety studies.
- ⁿ Not needed if normal mammogram was obtained within 12 months and a report was available. Patients may decline this examination and enter the study.

†† Table Number in NDA Submission.

Efficacy parameters- The effect of ALN on BMD of lumbar spine, femoral neck, trochanter, total hip, total body, 1/3 rd forearm (radius and ulna), 1 lateral spine, Ward's triangle, total forearm, and ultradistal forearm. Prevalent vertebral fractures at baseline and incident fractures at month 24 were tabulated.

The effects of ALN treatment on parameters of mineral homeostasis (i.e., serum calcium, phosphorus, PTH, and 1,25 dihydroxyvitamin D), biochemical markers of bone turnover, and stature were also evaluated.

Safety parameters- Included recording of all clinical adverse experiences graded as: mild, moderate, and severe. Routine laboratory parameters (hematology, serum and urine chemistries, and U/A) were also recorded.

Data analysis- A sample size of $n=24$ per treatment group was to provide 80% power (at $\alpha = 0.05$, two-tailed test) to detect a difference from baseline of 2.7% (within the group) and a between-treatment group difference of 3.7% in the mean lumbar spine BMD.

Data were analyzed by a) per-protocol (P-P) approach, in which patients with important protocol deviations were excluded from the analysis, and b) intent-to-treat (ITT) approach.

• comments: The primary objectives of the study were: a) to collect data on safety and tolerability of ALN (5-40 mg/day for 24 months) in osteopenic postmenopausal women, b) to compare the effect of ALN treatment on BMD of spine, hip, and forearm with those of the placebo group, and c) to collect data on the resolution of ALN effects over a period of 12 months after discontinuation of treatment.

The dosage-range of ALN and duration of treatment were adequate to generate data on safety and tolerability of the product (within a relatively narrow dose-range) for use in long-term Phase III studies. The data to be collected on changes in biochemical markers of bone turnover in ALN-treated patients will provide important guidance for selection of optimum dose for the drug in future studies. The evaluation criteria for efficacy and safety were adequate. The power and sample size of the study were based on objective criteria and data obtained from this study are likely to support the results of Phase III studies with similar study endpoints.

This study has another important objective to determine the persistence of ALN effect on BMD of spine, hip, and forearm and the time course of resolution of such effect.

The study is well designed to achieve the stated primary and secondary objectives.

7.1.4 RESULTS:

7.1.4.1 Patient comparability/disposition: Ninety-seven percent of enrolled patients were reported to have at least one secondary diagnosis prestudy. The sponsor has provided lists of secondary diagnoses by body system and treatment group. The 5 mg ALN group was reported to have a greater proportion of patients with "body as a whole site unspecified" secondary diagnoses compared to placebo group. Also, greater proportion of patients in the placebo group had cardiovascular disease (mainly hypertension). Review of the data showed no clinically significant differences between two treatment groups with regard to secondary diagnosis either by body system or by specific disorder.

Demographic baseline characteristics of patients with respect to age, height, weight, body mass index (BMI), years since menopause, lumbar spine BMD, estimated daily calcium intake, and biochemical markers of bone turnover (serum osteocalcin, deoxypyridinoline/creatinine) are

all listed in Table 8 of this submission (vol 84, pp.3336-3340). Except for serum osteocalcin, baseline characteristics were not significantly different between the treatment groups. The differences in observed baseline mean serum osteocalcin values were not large enough to be of any clinical significance.

Patient disposition- Table 11 presents accounting of patients in the study (Table 9 of vol. 84, p. D-3342 of this submission).

Table 9.

	Total	Placebo	5 mg	10 mg	20 mg /Placebo	40 mg /Placebo	40/2.5 mg
ENTERED:	188	31	32	30	32	32	31
COMPLETED THERAPY AT:							
Month 12*	14	2	2	2	2	2	4
Month 24	140	24	24	25	24	24	19
TOTAL	154	26	26	27	26	26	23
DISCONTINUED THERAPY:	34	5	6	3	6	6	8
Clinical Adverse Experience							
Through Month 12	13	1	2	0	2	4	4
Months 13 to 24	5	0	1	1	0	1	2
TOTAL	18	1	3	1	2	5	6
Laboratory Adverse Experience							
Through Month 12	1	0	0	0	1	0	0
Months 13 to 24	0	0	0	0	0	0	0
TOTAL	1	0	0	0	1	0	0
Patient Withdrew Consent							
Through Month 12	8	2	2	1	2	0	1
Months 13 to 24	2	0	1	1	0	0	0
TOTAL	10	2	3	2	2	0	1
Protocol Deviation							
Through Month 12	2	2	0	0	0	0	0
Months 13 to 24	3	0	0	0	1	2	1
TOTAL	5	2	0	0	1	2	1
DISCONTINUED STUDY:							
DURING OFF-DRUG							
EVALUATION PERIOD†:							
Lost to Follow-up	5	1	1	2	0	0	1
Patient Withdrew Consent	1	0	0	0	0	1	0
TOTAL	6	1	1	2	0	1	1

Table 9 (continued).

COMPLETED STUDY:**	152	25	26	25	26	27	23
* Fifteen patients did not consent to a second year of treatment†							
** Includes 13 patients who completed the study at the end of Month 24							
† Months 12 through 24 for patients not consenting to a second year of treatment and Months 24 through 36 for patients consenting to two years of treatment							

Of total 188 patients who entered the study, 154 patients (14 completed at 12 months and 140 at 24 months) completed either 1 or 2 years of study. Fifteen patients were reported to deny second year of treatment and remained off drug during the second year. Six patients withdrew from the study during off-drug evaluation period. Two patients (who initially consented for second year of therapy) withdrew from the study during the second year. A total of 34 patients were reported to discontinue therapy. Table 11 presents the reasons for discontinuation. It appears that more patients (compared to placebo and 5-20 mg ALN-treated groups) in the 40 mg/placebo and 40/2.5 mg ALN groups discontinued therapy due to clinical adverse experience.

Not all patients completed clinical visits on specified dates. For designated "Time point" visits "Relative Day Ranges" were established (see Table 10, vol. 84, p. D-3343).

The sponsor has provided accounting summaries of patients for clinical efficacy (in terms of changes in spinal BMD) based on intent-to-treat and per-protocol analyses in Appendix 4, Tables 1-4, vol. 84, pp. D-3587-3594).

Patients were not included in the clinical efficacy analyses for one or more of the following reasons:

- a. Protocol violation
- b. No data available in the relative day range
- c. Violation of off-drug rule (off-drug for a total of more than 25% of time spent in the study/missed more than 25% of expected total number of doses)
- d. Violation of biochemical off-drug rule (off-drug for more than 15 days during the 45 days prior to a visit/exclusion of biochemical observation).

Table 12. Number of patients included in the clinical efficacy resolution analysis.

Per-protocol analysis	Treatment	No. of Pt.
	Placebo	21
	ALN 5-40/2.5 mg	110
		Total= 131
Intention-to-Treat analysis	Treatment	No. of Pt.
	Placebo	24
	ALN 5-40/2.5 mg	123
		Total= 147

The total number of patients evaluated in the biochemical resolution efficacy analysis was 122; including 21 patients in the placebo group.

7.1.4.2 Efficacy:

The efficacy of ALN therapy was assessed by examining the PA lumbar spine, proximal femur, total body, 1-3rd forearm, lateral spine, Ward's triangle, total forearm, and ultra-distal forearm BMD.

Table 13 Time points at which % change in BMD from baseline was calculated.

BMD Sites	Months
Total Body	6,12,18,24,30, and 36
L3 Lat. Spine	3,6,9,12,15,24, and 36
All other sites	3,6,9,12,15,18,21,24,27,30,33, and 36

The baseline BMD was defined as the last value obtained in the range of Days -100 to 14. Percent change in BMD from Months 12 to 36 and from Months 12 to 24 was calculated for the placebo, 20 and 40 mg/placebo groups. Also, % change from Months 24 to 36 was calculated for the placebo, and 5, 10, and 40/2.5 mg ALN groups.

BMD parameters were corrected by using the following method:

$$\text{Corrected BMD} = \text{PT. BMD in the day range} + \text{Phantom correction factor} \times \frac{\text{Patient's BMD}}{\text{Baseline phantom BMD}}$$

Biochemical efficacy parameters: See table 14.

Table 14. Biochemical parameters of bone turnover.

Biochemical Parameters for	Parameters
Bone resorption	Urinary fasting calcium, deoxypyridinoline (DPyr), pyridinoline (Pyr)*
Bone formation	Serum alk. phosphatase, and osteocalcin

* All values were expressed as ratios to urine creatinine levels.

Fraction of baseline (Ln) was calculated by dividing the observed value by the baseline value and then applying the natural log. Baseline was defined as the last obtained in the range of Days -100

through 1. Measurements of these parameters, and of serum PTH and metabolites of vitamin D were made at designated time points over 36 months.

Stature-Height measurements were taken by using Harpenden Stadiometer. Changes from baseline was calculated at Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, and 36. The mean height was determined from 3 to 5 measurements at each visit. Baseline was defined as the last value obtained in the range of Days-100 through 14.

Effect on BMD:

a. Lumbar spine (L-spine) BMD:

Per-protocol data-

Table 15. Summarized data (Table 17 Vol. 84, p. D-3354).

Table 17 ††
Lumbar Spine BMD (g/cm³)
Analysis of Percent Change From Baseline at Month 24
Per-Protocol Approach

Treatment	Means (Observed)			Percent Change From Baseline			
	N	Baseline	Year 2	Mean	S.D.	Adjusted Mean	LSD Interval
Placebo	22	0.76	0.75	-1.35 *	2.84	-1.31	(-2.33, -0.29)
5 mg	23	0.76	0.81	7.27**	4.26	7.31	(6.30, 8.31)
10 mg	24	0.75	0.81	7.21**	2.39	7.17	(6.19, 8.15)
20 mg/placebo	24	0.75	0.80	6.24**	3.02	6.26	(5.28, 7.24)
40 mg/placebo	21	0.74	0.79	6.16**	3.03	6.21	(5.17, 7.26)
40/2.5 mg	19	0.74	0.77	4.48**	4.37	4.45	(3.35, 5.55)

Within-Treatment Test of Mean = 0, **: p 0.01 *: p 0.05

Adjusted Trend-Test			Comparison Between Doses		
Dose included	p-Value		Placebo	5 mg	10 mg
Placebo through 10 mg	<0.001				
Placebo through 5 mg	<0.001	5 mg	<0.001	.	.
		10 mg	<0.001	0.892	.
		20 mg/placebo	.	.	.
		40 mg/placebo	.	.	.
		40/2.5 mg	<0.001	0.008	0.011

In the placebo group, lumbar spine BMD was reported to decrease significantly (1.35%) from baseline over 24 months. Whereas, spinal BMD of patients treated with ALN 5, 10, 20 mg/placebo, 40 mg/placebo, and 40 mg/2.5 mg daily showed mean increases of 7.27, 7.21, 6.24, 6.16, and 4.48%, respectively over the corresponding period.

The overall results indicated that all ALN-treated groups had significantly larger ($p < 0.001$) mean percent change (from baseline) in spinal BMD compared to placebo group.

Lumbar spine BMD changes from month 12 to 24 were reported to be -0.39, 1.82, 1.96, and 0.43 for placebo, 5, 10, and 40/2.5 mg ALN groups, respectively. The increases in the 5 and 10 mg ALN groups were significantly ($p < 0.01$) different from zero and larger than placebo ($p < 0.006$).

Resolution of the treatment effect on lumbar spine BMD:

Over 12 months, after ALN treatment for 2 years- The results are presented in Table 16 (Table 18, vol. 84, p. 3357) and Figure 1 (Fig 2, vol. 84, p. D-3359).

Table 16. Resolution of Treatment Effect on Spine BMD.

Table 18 ††

Lumbar Spine BMD (g/cm²)
 Analysis of Treatment Effect Resolution One Year After the End of Active Treatment
 Per-Protocol Approach

Treatment	N	Means (Observed)		Percent Change From Months 24 to 36			
		Month 24	Month 36	Mean	S.D.	Adjusted Mean	LSD Interval
Placebo	21	0.74	0.73	-1.16	3.16	-1.21	(-2.01, -0.40)
5 mg	22	0.81	0.80	-1.44*	3.12	-1.55	(-2.34, -0.77)
10 mg	21	0.81	0.81	-0.41	2.12	-0.27	(-1.08, 0.54)
40 mg/2.5 mg	15	0.77	0.77	0.58	1.81	0.63	(-0.32, 1.58)

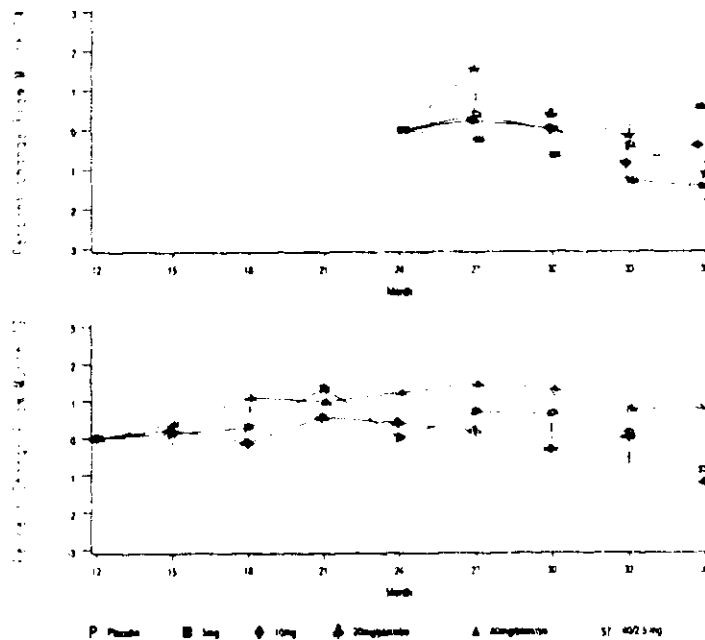
Within-Treatment Test of Mean = 0, **: p 0.01 *, p 0.05
 Treatment-by-Center Interaction p-Value: 0.683

Dose Included	Adjusted Trend-Test		Overall p-Value	Comparison Between Doses	Pooled S.D.
	p-Value				
Placebo through 10 mg	0.275	0.066	5 mg	0.665	2.60
Placebo through 5 mg			10 mg	0.250	
			40/2.5 mg	0.042	

Figure 1. Spinal BMD changes (24-36 months).

Figure 2 †††

Lumbar Spine BMD (g/cm^3)
 Plot of Mean Percent Change From the End of Active
 Treatment S.E. vs Month



††† Figure Numbers in NDA Submission

The results showed no significant difference in resolution of mean spinal BMD changes between placebo and ALN 5 or 10 mg. However, the differences between placebo and ALN 40/2.5 mg, and ALN 5 mg and 40/2.5 mg were reported to be significant. The results from intent-to-treat analysis were similar to those of the per-protocol analysis. The sponsor claims that there was no significant treatment-by-center interaction regarding one-year resolution of the treatment effect on spinal BMD.

Two-year (after one year of treatment with ALN 20 or 40 mg) - The results were similar in all groups (two ALN-treated and placebo groups).

The sponsor has concluded that after discontinuation of ALN treatment, "patients, on average" lost bone mass at a rate similar the placebo-treated did.

Longitudinal analysis of spinal BMD data: The slopes for each treatment group within each period have been compared. Comparisons were made among groups with similar treatment schedules over time, i.e., groups with one-year ALN treatment and two-year drug off were compared to each other, groups with two-year ALN treatment and one-year drug off were compared to each other. The results are presented in Table 17 (Table 20, vol. 84, p. D-3361).

All ALN-treated groups were reported to show significant ($p < 0.001$) positive slopes compared to a significant negative slope for the placebo group during the treatment period.

During the period after active treatment (refers to ALN), slopes for placebo and ALN 5 mg groups were negative ($p \leq 0.05$). No significant differences between placebo and all ALN dose (except for 40/2.5 mg) were reported.

Threshold analysis of spinal BMD data- Proportion of patient who attained a particular threshold of response. The results are presented in Figure 2. (Fig. 4, vol. 84, p. D-3363). There were no patients in ALN 5 and 10 mg groups that had a measurable decrease from baseline in lumbar spine BMD at Month 24.

Table 17. Longitudinal analysis of lumbar spine BMD.

Table 20 ††

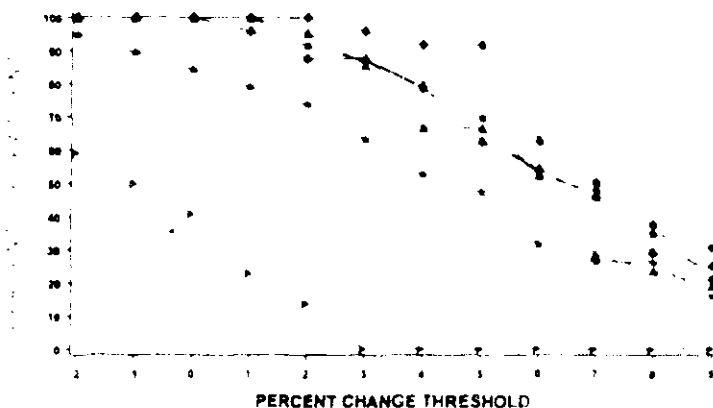
Longitudinal Analysis of Lumbar Spine BMD

Treatment	N	Slope ^e	S.E.	Slope Analysis			Model Fitting Information			
				Comparisons Between Treatments			Mean % Change From			
				Placebo	5 mg	10 mg	20/Placebo	Baseline to the End of Active Treatment	Predicted	Period (Month)
Active-Treatment Period										
Placebo ¹	31	-0.0026*	0.0010					-1.055	-1.205	0 to 24
5 mg ²	30	0.0158***	0.0011	<0.001				7.498	6.882	0 to 36
10 mg ³	28	0.0167***	0.0012	<0.001	0.571			7.223	7.190	0 to 24
40 mg/2.5 mg ⁴	25	0.0116***	0.0013	<0.001	0.015	0.003		4.784	5.042	0 to 24
20 mg/placebo ⁵	31	0.0176***	0.0015	<0.001				6.282	6.088	0 to 12
40 mg/placebo ⁶	31	0.0147***	0.0015	<0.001			0.175	4.853	5.041	0 to 12
End of Active Treatment to End of Study										
Placebo ¹	31	-0.0026*	0.0010					-1.021	-0.151	24 to 36
5 mg ²	30	0.0052**	0.0016	0.172				-1.585	-1.592	24 to 36
10 mg ³	28	0.0015	0.0016	0.575	0.108			-0.401	-0.493	24 to 36
40 mg/2.5 mg ⁴	25	0.0006	0.0018	0.116	0.015	0.371		0.307	0.196	24 to 36
20 mg/placebo ⁵	31	-0.0009	0.0012	0.290				-1.351	-0.434	12 to 36
40 mg/placebo ⁶	31	0.0028*	0.0011	<0.001			0.024	0.853	1.136	12 to 36
Within-Treatment Test of Slope = 0, *** p 0.001 ** p 0.01 * p 0.05 @ Slope is the coefficient of ln (Month + 1) in the model fitted † A single line was fitted for the placebo group throughout entire study period †† From Baseline through Month 24 † From Baseline through Month 12 † From Months 24 through 36 † From Months 12 through 36										

Figure 2. Threshold analysis of spinal BMD.

Figure 4 †††

Percent of Patients With 24-Month Change in Lumbar Spine BMD Exceeding Thresholds Ranging From -2% to 9%



- P = Placebo
- = 5 mg
- ◆ = 10 mg
- ♣ = 20 mg/placebo
- ▲ = 40 mg/placebo
- ★ = 40/2.5 mg

b. Femoral neck BMD: Mean % changes from baseline in femoral neck BMD at Month 24 are presented in Table 18 (Table 21, vol. 84, p. D-3366). The placebo group was reported to show a non-significant decrease (from baseline) in femoral neck BMD at Month 24. The mean % changes in ALN 5, 10, 40/2.5, and 40/placebo groups were significantly greater than the placebo group.

Table 21††

Femoral Neck BMD (g/cm^3)
Analysis of Percent Change From Baseline at Month 24
Per-Protocol Approach

Treatment	Means (Observed)			Percent Change From Baseline			
	N	Baseline	Year 2	Mean	S.D.	Adjusted Mean	LSD Interval
Placebo	22	0.60	0.60	-0.97	4.22	-1.16	(-2.29,-0.02)
5 mg	23	0.64	0.66	3.02**	2.50	2.75	(1.64, 3.87)
10 mg	24	0.60	0.63	5.03**	3.40	4.79	(3.70, 5.89)
20 mg/placebo	24	0.67	0.68	1.02	4.20	0.70	(-0.41, 1.80)
40 mg/placebo	21	0.62	0.64	3.34**	3.92	2.99	(1.81, 4.17)
40/2 5 mg	17	0.61	0.62	1.91	4.61	2.01	(0.73, 3.30)

Within-Treatment Test of Mean = 0. ** p < 0.01 * p < 0.05

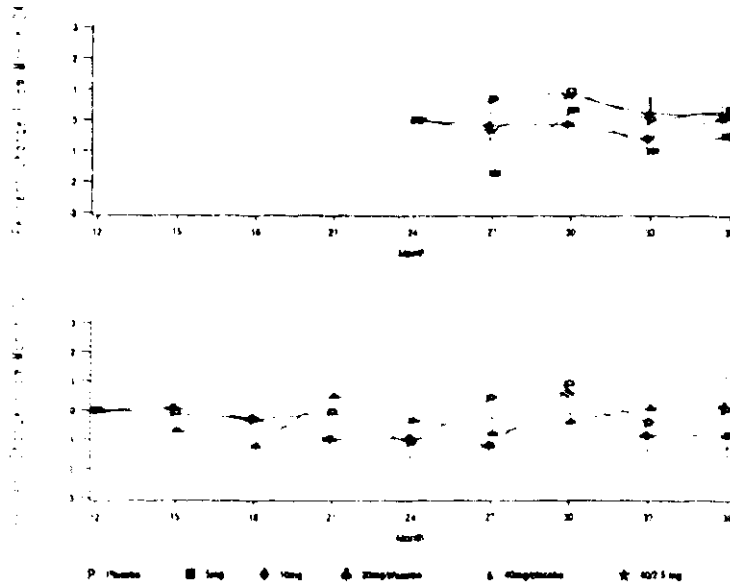
Adjusted Trend-Test			Comparison Between Doses		
Dose included	p-Value		Placebo	5 mg	10 mg
Placebo through 10 mg	<0.001	5 mg	0.001	.	.
Placebo through 5 mg	<0.001	10 mg	<0.001	0.068	.
		20 mg/placebo	.	.	.
		40 mg/placebo	.	.	.
		40/2 5 mg	0.011	0.545	0.023

Resolution of the treatment effect on femoral neck BMD- Both one- and two-year resolution data showed no significant changes from zero. Figure 3 (Fig 6, vol. 84, p. D-3371) presents plot of mean % change from the end of active treatment ($\pm$ S.E.) vs month. After cessation of active treatment, femoral neck lost bone mass at the same rate similar to that of the placebo group.

Figure 3. Resolution of treatment effect on femoral BMD.

Figure 6 †††

Femoral Neck BMD (g/cm^3)
 Plot of Mean Percent Change From the End of Active
 Treatment S.E. vs Month



Positive longitudinal slopes for all ALN groups and a negative slope for the placebo group were seen during the treatment period. The ALN 10 mg group was reported to have a significantly larger slope than that of 5 mg group. During the posttreatment period, none of the slopes were significantly different from each other or from zero.

c. Trochanter BMD: The placebo-treated group showed a nonsignificant mean decrease of 0.86% in trochanter BMD from baseline over 24 months. Whereas, all ALN-treated groups showed significant mean increases ranging from 3.58% to 7.58%. The results are summarized in Table 19 (Table 25, vol 84, p. D-3378).

Table 19. Trochanter BMD changes.

Table 25 ††

Hip Trochanter BMD (g/cm^3)
Analysis of Percent Change From Baseline at Month 24
Per-Protocol Approach

Treatment	N	Means (Observed)		Percent Change From Baseline			
		Baseline	Year 2	Mean	S.D.	Adjusted Mean	LSD Interval
Placebo	22	0.52	0.52	-0.86	4.06	-0.94	(-2.04, 0.15)
5 mg	23	0.55	0.58	5.30**	2.80	5.16	(4.08, 6.23)
10 mg	24	0.52	0.56	7.58**	4.09	7.33	(6.28, 8.39)
20 mg/Placebo	24	0.57	0.60	5.01**	3.78	4.91	(3.85, 5.98)
40 mg/Placebo	21	0.54	0.57	5.44**	4.26	5.37	(4.23, 6.51)
40/2.5 mg	17	0.54	0.56	3.58**	2.98	3.68	(2.44, 4.92)

Within-Treatment Test of Mean = 0. **: p 0.01 *: p 0.05

Adjusted Trend-Test			Comparison Between Doses		
Dose Included	p-Value		Placebo	5 mg	10 mg
Placebo through 10 mg	0.001	5 mg	0.001		
Placebo through 5 mg	0.001	10 mg	0.001	0.044	
		20 mg/Placebo			
		40 mg/Placebo			
		40/2.5 mg	0.001	0.213	0.002

Resolution of treatment effect on trochanter BMD- One year after the end of active treatment, mean % changes in ALN 5, 10, and 40/2.5 mg groups were -0.09, -0.46, and 1.68, respectively. Over the same period, the placebo group showed a mean % decrease of -1.31. The ALN 40/2.5 mg group showed a significant difference from the placebo group. However, ALN 5, and 10 mg groups behaved similar to the placebo group. Two-year resolution data for the ALN 20 and 40 mg were similar to those of placebo group.

d. Total hip BMD: At Month 24, all, ALN-treated groups showed significant % increases (2.45% to 5.27%) from baseline. The placebo group showed a decrease of 1.20% over the same period. The changes in the 10 mg group was significantly greater than that observed with the 5 mg group ($p=0.46$).

Resolution of treatment effect on total hip BMD- The ALN 5, and 10 mg, and placebo groups showed decreases in mean % change ranging from 0.27% to 0.71% during one year after the end of treatment. The analysis of two-year resolution data showed no significant difference between ALN 20 and 40 mg groups, and placebo. The ALN 40 mg group seems to take a longer time for resolution of treatment effect.

e. Total body BMD: Placebo group was reported to show a mean % decrease of 0.31% from baseline at Months 24. The ALN treated groups showed significant mean % increases of 1.58%, 2.53%, 2.37%, and 2.34% at 5, 10, 20, 40 mg/placebo groups, respectively.

Resolution of treatment effect on total body BMD: The resolution of treatment effect on total body BMD was very similar in pattern with BMD changes at other sites during one and two years after active treatment. Patients in the ALN groups lost BMD at the same rate as placebo patients after discontinuation of active treatment.

Longitudinal analysis of total body BMD data: Table 20 presents summary of results (Table 34, vol. 84, p. D-3402). All ALN treated groups showed positive slopes ($p \leq 0.01$), while the placebo group manifested a slope not significantly different from zero. During the drug off period, there was no difference between slopes of different treatment groups, as well as slopes were not significantly different from zero.

Table 20. Longitudinal analysis of total body BMD.

Table 34

Longitudinal Analysis of Total Body BMD
Treatment Period

Treatment	Slope Analysis					Model Fitting Information			
	N	Slope ^a	S.E.	Comparisons Between Treatments			Mean % Change From Baseline to the End of Active Treatment		Period (Month)
				Placebo	5 mg	10 mg	20/Placebo	Observed	
Treatment Period									
Placebo ¹	19	-0.0008	0.0009				0.58	-0.284	0 to 24
5 mg ¹	19	0.0049***	0.001	<0.001			1.742	1.646	0 to 24
10 mg ¹	16	0.0058***	0.0011	<0.001	0.544		2.554	2.035	0 to 24
40 mg/2.5 mg ¹	16	0.0032**	0.0012	0.007	0.245	0.094	1.107	1.035	0 to 24
20 mg/placebo ¹	19	0.0068***	0.0013	<0.001			1.981	1.808	0 to 12
40 mg/placebo ¹	21	0.0074***	0.0012	<0.001			1.937	1.974	0 to 12
Off-Drug Period									
Placebo ¹	19	-0.0008	0.0009				0.213	0.035	24 to 36
5 mg ¹	19	0.0016	0.0013	0.129			0.449	0.427	24 to 36
10 mg ¹	16	-0.0008	0.0014	0.981	0.206		-0.275	-0.224	24 to 36
40 mg/2.5 mg ¹	16	0.0016	0.0015	0.166	0.997	0.236	0.332	0.412	24 to 36
20 mg/placebo ¹	19	0.0008	0.0009	0.199			0.633	0.275	12 to 36
40 mg/placebo ¹	21	-0.0002	0.0009	0.613			0.119	-0.052	12 to 36

Within-treatment test of slope = 0, *** p 0.001 **, p 0.01 *, p 0.05

^a Slope is the coefficient of ln (Month+1) in the model fitted

¹ A single line was fitted for the placebo group throughout entire study period

² From Baseline through Month 24

³ From Baseline through Month 12

⁴ From Months 24 through 36

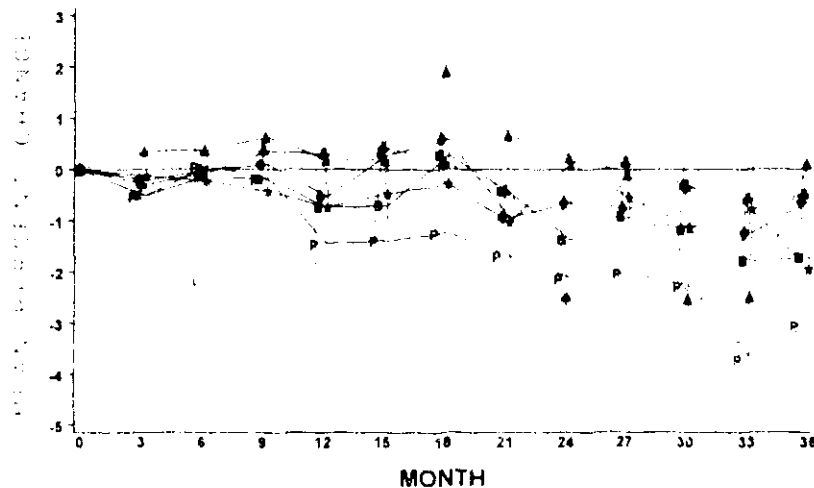
⁵ From Months 12 through 36

One-third distal forearm BMD:

At this site more than 95% of bone is cortical in nature. Figure 4 (Fig. 15, Vol. 84, p. D-3405) presents the average treatment effect on forearm BMD and its resolution. The placebo group showed a significant ($p \leq 0.05$) mean decrease of 1.99% in BMD. The ALN groups showed nonsignificant changes (-1.46% and -0.66%) in 5 and 10 mg groups, respectively. Based on two-year study results, there were no statistically significant differences in % change of forearm BMD in any of the groups.

Figure 4. Treatment effect on forearm BMD.

Figure 15 †††
One-Third Distal Forearm (Radius + Ulna) BMD
Mean Percent Change + S.E. of the Mean
Per-Protocol Approach



P = Placebo

■ = 5 mg

◆ = 10 mg

♣ = 20 mg/placebo

▲ = 40 mg/placebo

★ = 40/2.5 mg

Solid line = Active-treatment period

Dotted line = Period after active treatment

Note: For placebo, the solid line indicates on placebo and the dotted line indicates the off-drug period

One-year resolution of effect data showed that all ALN treatment groups behaved similar to placebo group. With regard to two-year resolution of treatment effect, % changes in both placebo and ALN 20 mg groups were significantly less than zero.

Sponsor's summary of BMD results:

a. Alendronate treatment in doses from 5 to 40 mg daily resulted in increases in BMD at skeletal sites with a high proportion of trabecular bone (i.e., lumbar spine, trochanter, and total proximal femur) during the first year. There was little evidence of dose-response over the first year of treatment.

b. During the second year of treatment with ALN at doses of 5 and 10 mg, BMD of lumbar spine, trochanter, and total hip region continued to show increase. The effects of 5 and 10 mg of ALN were similar in magnitude at most sites, except at the total hip region, where BMD at 10 mg dose level was significantly greater over 24 months. The effects on predominant cortical sites (i.e., femoral neck and total body BMD) were not significant during the second year of treatment. ALN treatment at doses of 5 and 10 mg/daily prevented further loss of BMD at one-third distal forearm site (95% cortical bone).

c. Changes in BMD after the end of two years of ALN treatment at doses of 5 or 10 mg, or at the end of one year treatment at doses of 20 or 40 mg, were similar to those observed in placebo-treated group. There was no evidence of "catch up" bone loss during posttreatment period. The results suggest continued dosing of patients with AL 10 mg/daily in order to achieve progressive increase in BMD of spine and hip.

Effect on stature:

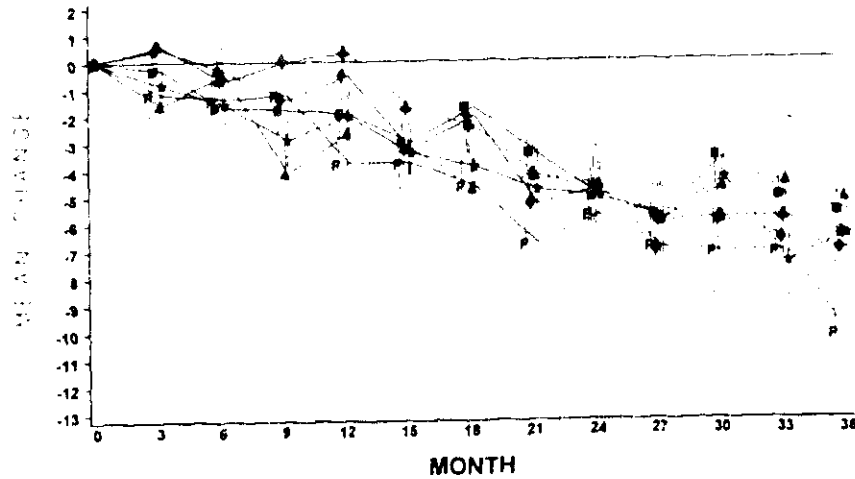
The sponsor has indicated an error in the data file for a patient (#AN 233) in the ALN 40 mg/placebo group. Height recorded at Months 27 and 30 was about 100 mm higher than all prior and subsequent measurements. The values did not match data in the source document at the site. Graphs were prepared with and without incorrect values

Mean change ($\pm$ S.E.) in stature (mm) over 36 months was presented in Figure 5 (Fig.16 without incorrect values, vol. 84, p. D-3412). The results showed no significant differences between various treatment groups with respect to changes (in median values) in stature from baseline at Month 36. The placebo group seemed to experience a maximum decrease in stature of about 10.2 mm.

Figure 5. Effect of alendronate treatment on stature.

Figure 16†††

Stature (mm)[†]
 Mean Change $\pm$ S.E. of the Mean
 Per-Protocol Approach



P = Placebo

■ = 5 mg

◆ = 10 mg

♣ = 20 mg/placebo

▲ = 40 mg/placebo

★ = 40/2.5 mg

Solid line = Active-treatment period

Dotted line = Period after active treatment

Note: For placebo, the solid line indicates on placebo and the dotted line indicates the off-drug period

† Incorrect values for AN 233 have been deleted from this figure

Effect on biochemical markers of bone turnover:

Biochemical markers were evaluated to provide information on the effect (and resolution) of ALN therapy on bone formation, bone resorption, and to investigate further the mechanism of effect on bone mass. The endpoints such as serum calcium, phosphorus, PTH, 1,25-dihydroxyvitamin D, and urine calcium to creatinine ratio were evaluated in order to study the effect of ALN therapy on calcium and mineral homeostasis. The biochemical indices are expressed as % of baseline levels.

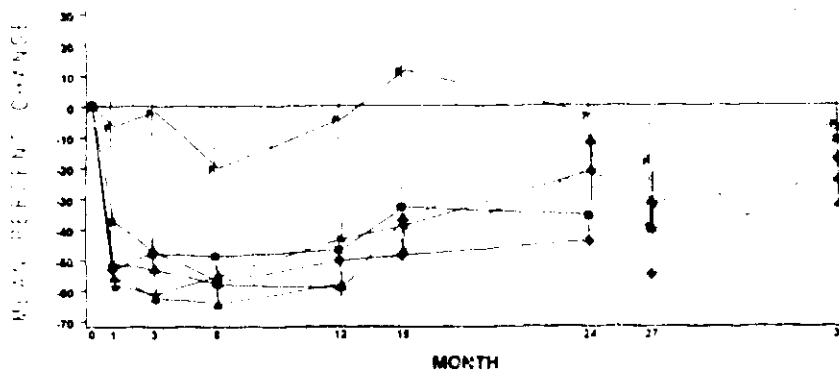
a. Bone resorption markers-

Urine DPyr corrected for creatinine- Figure 6 presents mean % change in urinary DPyr (U/DPyr) over 36 months (Figure 17, vol. 84, p. D-3417). The results showed significant decrease in U/DPyr during the first three months of treatment with ALN. In the placebo-treated patients U/DPyr did not show any consistent change over the same period. After first three months, changes in U/DPyr seem to stabilize and showed no further decrease. At Month 12, the mean % decreases from baseline ranged from 43.5% to 59.4%. At Month 24, decreases of 35.80% and 44.12% ($p \leq 0.01$) were reported in ALN 5 and 10 mg groups, respectively. The placebo and ALN 40/2.5 mg groups also showed nonsignificant decreases at the same time point.

Figure 6. Effect of alendronate treatment on u/DPyr /Cr excretion

Figure 17 ††

Urine Deoxypyridinoline/Cr
 Mean Percent Change $\pm$ S.E. of Mean Transformed
 From In (Fraction of Baseline)
 Per-Protocol Approach



P = Placebo

■ = 5 mg

◆ = 10 mg

♣ = 20 mg/placebo

▲ = 40 mg/placebo

★ = 40/2.5 mg

Solid line = Active-treatment period

Dotted line = Period after active treatment

Note: For placebo, the solid line indicates on placebo and the dotted line indicates the off-drug period

After two-year active treatment, U/DPyr started to return to baseline levels; -11.24%, -17.54%, and -7.42%, respectively, for ALN 5, 10, and 40/2.5 mg groups at Month 36. The treatment effect of ALN on U/DPyr appeared to resolve within a year after termination of active treatment. The one-year resolution data showed that the treatment effect of ALN at dose 20 and 40 mg on U/DPyr somewhat longer.

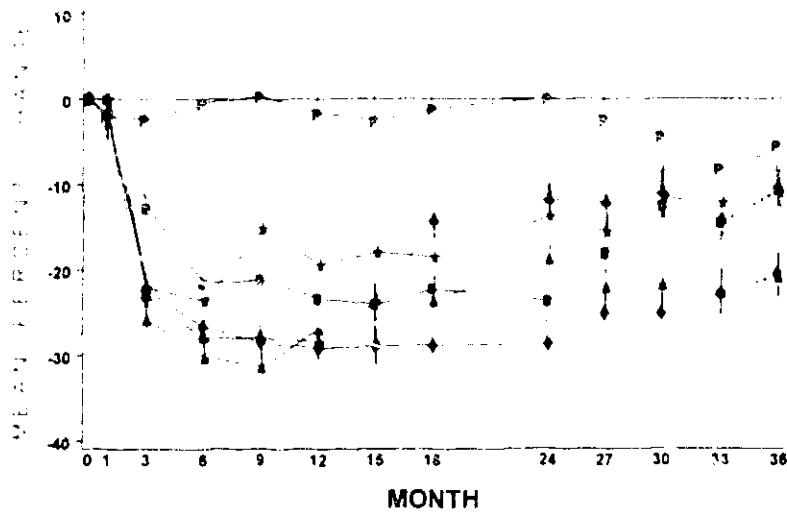
U/Pyr corrected for creatinine- Since this marker is considered to be less specific for bone resorption, the results were presented in Appendix 26. The results were variable. One year after treatment, placebo, ALN 5, and 10 mg showed decreases from base line (3% to 13%). The ALN 40/2.5 mg group showed about 11% increase after one year of treatment.

b. Bone formation markers -

Serum alkaline phosphatase (SAP)- The results are summarized in Figure 7 (Fig. 18, vol. 84, p. D-3423). SAP levels in ALN treated groups decreased during the first 3-6 months of treatment and then stabilized during the rest of treatment period. The placebo-treated group showed no significant decrease in SAP over the corresponding period. At Month 12, the mean % decreases in SAP ranged from: 19.2% to 29.2%. At Month 24, % decreases in SAP were 24%, 28.7% and 12.9% in ALN 5, 10, and 40/2.5 mg doses, respectively. In the placebo group there was a nonsignificant change of 0.14%.

Figure 7. Changes in serum alkaline phosphatase

Figure 18 †††
 Serum Alkaline Phosphatase (U/L)
 Mean Percent Change $\pm$ S.E. of Mean
 Transformed From ln (Fraction of Baseline)
 Per-Protocol Approach



P = Placebo

■ = 5 mg

◆ = 10 mg

♣ = 20 mg/placebo

▲ = 40 mg/placebo

★ = 40/2.5 mg

Solid line = Treatment period

Dotted line = Off-drug Period

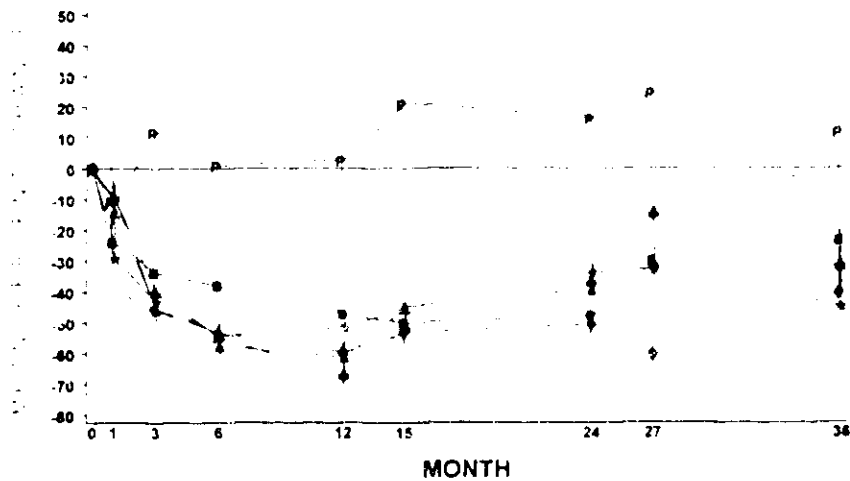
One-year resolution of treatment effect data showed return of SAP toward baseline mean level at Month 36; -10.7%, -20.45%, and -11.09% at 5, 10, and 40/2.5 mg doses, respectively. One year after the end of treatment, the % changes from baseline in ALN treated patients remained significantly smaller than zero. The treatment effect appeared to be persistent at dose of 10 mg.

The two-year resolution data showed return of SAP toward baseline over two years, from -28.5% to -10.44% and from -26.85% to -20.83% in 20 and 40 mg/placebo groups, respectively. At Month 36, there was no difference between 20 mg dose and placebo in mean % change from baseline. However, for the 40 mg/placebo group, the mean % change from baseline remained significantly different from zero and placebo response.

Serum osteocalcin- The results are summarized in Figure 8 (Fig. 19, vol.84, p. D-3431). Serum OC levels decreased in all ALN-treated groups within the first few months of treatment and then tended to stabilize. In the placebo-treated group there was no significant change in serum OC levels throughout the treatment period. At Month 12, the mean % changes from baseline in ALN groups ranged from -47% to -67.32%. At Month 24, the % decreases in all ALN-treated groups were maintained almost at same level as seen at Month 12.

Figure 8 †††

Serum Osteocalcin (ng/mL)
 Mean Percent Change $\pm$ S.E. of Mean
 Transformed From ln (Fraction of Baseline)
 Per-Protocol Approach



P = Placebo

■ = 5 mg

◆ = 10 mg

♣ = 20 mg/placebo

▲ = 40 mg/placebo

★ = 40/2.5 mg

Solid line = Active-treatment period

Dotted line = Period after active treatment

Note: For placebo, the solid line indicates on placebo and the dotted line indicates the off-drug period

The overall resolution data showed persistent suppression of serum OC after cessation of active treatment with ALN. Although the extent of suppression was somewhat less than that observed

during active treatment.

c. Calcium and mineral homeostasis:

Serum PTH levels in all treatment groups showed sharp increases within one month after initiation of treatment. Thereafter, PTH levels returned toward baseline means by 15 to 24 months. In the placebo group, there were some fluctuations at different time points; these changes were not significantly different from zero. One- and two-year resolution data showed no clinically significant changes.

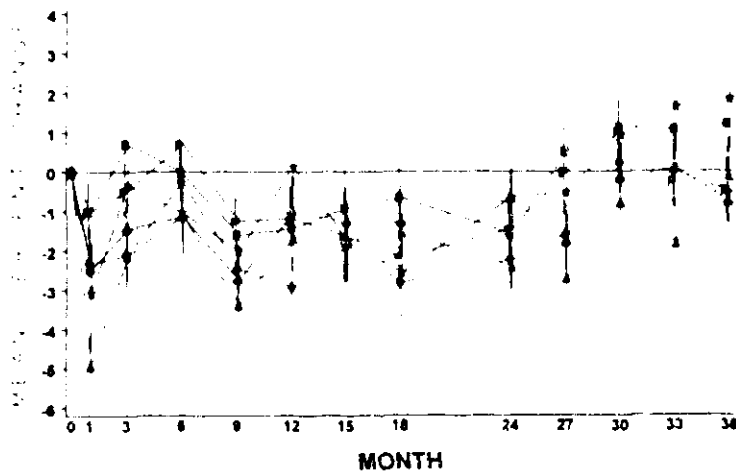
1,25-dihydroxyvitamin D showed basically similar pattern of change during and after treatment in all ALN-treated and placebo groups. By the end of treatment period with 5 and 10 mg of ALN, vitamin D metabolite levels returned to baseline.

Changes in serum calcium during and after active treatment periods are summarized in Figure 9 (Fig. 22, vol. 84, p. D-3445). During the first few months after initiation of ALN/placebo treatment, serum calcium was reported to decrease in all groups. Changes were not significant in ALN 5 mg and placebo groups. One year after active treatment, serum calcium levels tended to return to baseline. The two-year resolution data showed similar response as one-year.

Figure 9. Changes in serum calcium.

Figure 22 †††

Serum Calcium (mg/dL)
 Mean Percent Change $\pm$ S.E. of Mean
 Transformed From ln (Fraction of Baseline)
 Per-Protocol Approach



P = Placebo

■ = 5 mg

◆ = 10 mg

♣ = 20 mg/placebo

▲ = 40 mg/placebo

★ = 40/2.5 mg

Solid line = Active-treatment period

Dotted line = Period after active treatment

Note: For placebo, the solid line indicates on placebo and the dotted line indicates the off-drug period

Changes in serum phosphate levels were similar to those seen with serum calcium during treatment with ALN or placebo. Except for 10 mg ALN group, serum phosphate levels returned to baseline at Months 36. Phosphate level in ALN 10 mg group remained decreased at Month 24 (not significantly different from placebo). The sponsor states that due to lack of a dose-response trend interpretation of these data is difficult.

Urinary excretion of calcium (corrected for creatinine) showed marked decrease during the first month after initiation of treatment. Thereafter, urine calcium returned to baseline at Months 24. In the placebo group, urine calcium levels increased progressively over the first 6 months and then stabilized close to baseline for the rest of treatment period and at Month 24.

7.1.4.3 Safety

ALN treatment groups were compared with placebo group for the proportion of patients with:

- a. at least one adverse experience
- b. adverse experiences within each body system
- c. specific adverse experiences

In addition, changes in body weights, blood pressure, pulse, and temperature were also evaluated.

During the first year of the study, almost all assigned patients remained on active or placebo treatment except for 6 patients in ALN 40 mg. These patients were switched to placebo beginning at 10 months. During the second year of treatment, patients in 20 and 40 mg of ALN were switched to placebo. Fifteen patients declined to participate in the second double-blind treatment year of the study and received neither ALN nor placebo. Summaries for the Years 1 and 2 combined were presented for the placebo, ALN 5 and 10 mg groups. Adverse experiences for the Year 1 were evaluated for ALN 20 and 40 mg groups. Adverse experiences for the ALN 40/2.5 mg were evaluated for Years 1 and 2 combined and compared to Year 1 alone. Adverse experiences for patients who were switched to placebo or did not receive any treatment during the second year were included in the analysis for the treatment groups in which they belonged originally.

Clinical adverse experiences (AEs)- About 94.1% (177 of 188) of patients were reported to experience AEs during the two years of treatment. Patient information is provided in Table 21.

Table 21. Overall patient information regarding AEs (Table 50, vol.84, p. D-3451).

No. of Pt With Serious AEs	No. of Pt With Possib., Prob., or Definite Drug-Rel. AEs	No. of Pt. Withdrawn From Study**
18*	50	18

* Including one death; 3 additional patients withdrawn from the study due to serious AEs.

** Eighteen patients withdrawn from the study due to AEs (14 nonserious and 4 serious); 9 were drug-related.

The overall AEs profile appeared to be similar to that of the placebo group. Ten of 32 patients in the ALN 40 mg group were reported to experience drug-related AEs during the first year of the study compared to 2 of 31 patients in placebo group. There was no difference between ALN 20 mg and placebo group with regard to number of patients who experienced AEs during Year 1.

AEs by body system- There were no clinically significant differences between placebo and ALN groups with regard to proportion of patients with AEs in any particular body system, except for the ALN 10 mg group. Slightly larger proportion of patients in the latter group experienced "musculoskeletal disorders" during Years 1 and 2, compared to placebo group.

Most common AEs- The following AEs were reported to have incidence rate of 10% or more : upper respiratory tract infection, abdominal pain, back pain, headache, nausea, cough, and influenza. There were no clinically significant differences between ALN (5, 10, and 40/2.5 mg) groups and placebo with respect to the incidence rate of common AEs. The common AE profile for ALN 20 and 40 mg was reported to be similar to that for the placebo.

Drug-related AEs- During the first two years of the study, possibly, probably, or definitely drug-related AEs for the ALN 5, 10, and 40/2.5 mg groups were not significantly different from those of the placebo group. However, more patients (10/32) in the ALN 40/2.5 mg group experienced AEs during the first year compared to 2/31 in the placebo group. Of 10 drug-related AEs in the ALN 40 mg group, 7 were upper G-I side effects. There was no difference in drug-related AE profile between these two groups during Year 2 of the study. In the 20 mg group the proportion of patients with drug-related AEs was similar to that experienced in placebo group during Year 1 of treatment.

Serious AEs- A total of 23 patients were reported to experience AEs during 5 years of study. The number of patients who were reported to experience serious AEs during the first two years of study are shown below (Table 22):

Table 22. The number patients with serious AEs during the first two years of the study.

Treatment	No. of Patients
Placebo	3
ALN 5 mg	4
ALN 10 mg	0
ALN 20 mg	2
ALN 40 mg/placebo	4
ALN 40/2.5 mg	5

None of the serious AEs were considered to be drug-related by the investigators. There was one death reported. The patient was on ALN 5 mg/day. She suffered a hip fracture while on medication and had undergone surgical repair. Study drug was discontinued during hospitalization and rehabilitation. The patient died subsequently; necropsy report indicated the cause of death as chronic obstructive pulmonary disease. The investigator did not think that fracture or death was drug-related. Serious AEs are listed in Table 54 (vol. 84, pp. D-3462-3464).

Patients discontinued from treatment due to AEs- A total of 18 patients were reported to discontinue treatment during the first two years of treatment due to AEs (13 pt. during Year 1 and 5 during Year 2).

Upper G-I AEs- Additional analyses were performed since upper G-I AEs are known to occur with oral administration of bisphosphonates. A total 18 patients were withdrawn from the study due to AEs, 9 of them experienced drug-related upper G-I AEs. However, no upper G-I AEs were considered serious. The proportion of patient with these AEs in ALN 5, 10, 40/2.5 mg groups were reported to be greater than placebo group during the first two years of study. The difference between ALN 10 mg and placebo groups was significant. During Year 1, significantly greater proportion of patients in ALN 40 mg were reported to experience these AEs compared to placebo group. No patient withdrew from the study during first year due to upper G-I AEs. The most frequent upper G-I AEs were abdominal pain and nausea.

Fractures- During the 3-year study period, 21 of 188 patients were reported to experience vertebral and nonvertebral fractures. No fractures were considered drug-related by the investigators. All treatment groups (including placebo) had similar % of patients (3.1% to 3.3%) who experienced these fractures (Table 59, vol. 84, p. D-3478).

Skin rash- Skin rash and/or erythema were reported to occur in patients treated with ALN or placebo. There was no difference in the incidence of these AEs between ALN and placebo groups.

AEs during the off-drug period- Three patients in one study center withdrew from the treatment

for the following reasons: leg and foot cramps (1 pt.), "fingernails seem to break more." (1 pt.) and back pain (1 pt.).

Laboratory AEs: During the treatment period, 41 of 186 patients with "planned laboratory tests" were reported to experience at least one AE. Nine were considered drug-related AEs. One patient was reported to withdraw from the study due to non-drug-related AEs. Review of the results indicated similar laboratory AE profiles for the ALN and placebo groups. The most common laboratory AEs were increased urine WBC and increased serum ALT levels during the first two years of the study.

There were four cases of decreased leukocyte counts during Year 1 of the study; one each in placebo, ALN 10, 20, and 40/2.5 mg groups. In some patients these changes were transient. According to the investigators, decrease in leukocyte counts was considered "probably drug-related," or probably worsening of a preexisting condition. Three additional patients were reported to experience transient decrease in leukocyte count possibly related to study drug. In these patients treatment with study drug was continued and repeat leukocyte counts returned to baseline values. During the second year of the study, one patient was reported to experience transient decrease in leukocyte count, which returned to normal subsequently. The patient completed treatment without any interruption.

In this study, no serious laboratory experience was reported. One patient was discontinued from the study due to an increase in B-lymphocytes on ALN 20 mg group. She was reported to have elevated B-lymphocyte count at baseline. The investigator did not think rise in B-lymphocyte count clinically significant.

Adverse experiences detected by means of other safety tests (e.g., PE, x-ray, ECG):

One patient in the placebo group experienced a new vertebral fracture during the first two years of the study. None in ALN groups experienced any incident vertebral fracture. Three to five patients in each treatment groups had one or more prevalent (baseline) vertebral fractures.

Changes in blood pressure, pulse rate, and temperature were clinically insignificant in either group of treatment.

Laboratory safety measurements (pre-defined limits of change from baseline)- Changes exceeding predefined limits may occur in normal individuals based on variability of laboratory analysis, diurnal and other causes for intra-individual variations, or inter-individual variations. Only changes in serum AST were considered important for discussion. Of the 19 elevated values of serum AST during the Year 1, only one value was higher than 3 x the upper limit of normal. All elevated values were reported to be transient and returned to normal in subsequent measurements.

The corrected serum calcium concentrations (CSCC) were decreased in slightly greater proportion in ALN treated groups (34% to 53%) compared to 31% in the placebo group. There

was no clinical adverse experiences of "hypocalcemia."

7.1.5 Sponsor's discussion and summary of efficacy (BMD and stature): Alendronate therapy at a dose 5 and 10 mg/day for two years resulted in increased lumbar spine BMD (primary efficacy endpoint) over the first year and further increase continued in the second year of treatment. At a dose of 10 mg, the increases were 6.66% and 7.21% at the end of one and two years of treatment, respectively. In the placebo treated group, there was a decrease of about 1.35% over two years.

Although marked increase in spine BMD was observed during the first 3 months of treatment, the increase progressively continued over the second year in both 5 and 10 mg doses. Increases in the second year were similar in both groups (1.82% in 5 mg and 1.96% in 10 mg groups). The two-year lumbar spine BMD data showed no evidence of plateauing of spinal BMD effect.

The results indicated that ALN-induced change in lumbar spine BMD was more closely related to the daily dose of the drug rather than to the cumulative dose. The group-treated with 40/2.5 mg of ALN received about 40% more of ALN compared to ALN group treated with 5 mg at the end of 2 years. The BMD increase at the end of two years at 5 mg dose was 7.27% compared to 4.48% at 40/2.5 mg dose. Measurement of lumbar spine BMD at lateral position also showed significant increase.

Alendronate treatment at doses of 5 and 10 mg daily for 2 years increased mean total hip BMD by 3.57% and 5.27%, respectively. The placebo group experienced a 1.20% decrease over corresponding period. In the second year of treatment, there was progressive increase in hip BMD, 0.85% and 1.05% in 5 and 10 mg groups, respectively. Only 10 mg group achieved a statistically significant change. An average change of 1% per year would be clinically significant in preventing osteoporotic hip fracture. A longer study is needed to establish the efficacy of alendronate on the hip.

Changes in total body BMD also showed significant increase as a result of alendronate treatment. There was no increase in forearm BMD at any of the sites examined following treatment with alendronate. However, bone loss was prevented by alendronate at three sites tested.

The resolution of treatment effect on BMD of spine (during 12 months after end of 2-year active treatment) was similar among the 5 mg, 10 mg, and placebo groups. The loss of BMD was reported to resume after the end of treatment. In the literature, the spinal BMD effect of ALN treatment for 6 months at a dose of 20 mg/day was reported to be maintained for additional one year (Rosin et al. J. Bone Min. Res. 9:1833, 1994). The oral ALN used by these investigators was not prepared by MRL. Clinical study with another bisphosphonate, tiludronate, has been reported to show "small additional increase in spine BMD" over 6 months after the end of initial treatment.

In summary, the predominantly trabecular bone in lumbar spine was most responsive to ALN

therapy. ALN 10 mg/day caused greater increase in BMD than 5 mg dose at several nonvertebral sites including the hip. There was preservation of BMD at the forearm as opposed to increase noticed at other sites. During two years of active therapy, increase in BMD or preservation of BMD was continuous. Pronounced changes occurred at the spine and proximal femur. The increase in BMD at the hip noticed with ALN treatment at a dose of 10 mg/day for 2 years is likely to decrease the risk of osteoporosis-related hip fractures.

At the lumbar spine, almost 100% of patients treated with ALN (5 or 10 mg/day for 2 years) showed increase in BMD by 1% or greater compared to about 23 patients with similar response in the placebo group. None of the patients in the placebo group manifested increase in lumbar spine BMD $\geq$ 3% compared to 95% of patients at the 10 mg dose.

The results for ALN-induced change in stature (height) were inconclusive, because all groups showed significant decrease from baseline at Month 36. The study did not have adequate power to detect a meaningful effect on height.

With regard to the effect of ALN on biochemical indices of bone resorption, urinary excretion of DPyr decreased rapidly after 1 month of treatment to the extent of about 55% from baseline at a dose of 40 mg/day. In the ALN 5 mg dose group, changes in DPyr excretion were gradual, 36% at 1 month and 51% after 6 months. Changes in biochemical indices of bone formation (serum alk. phosphatase and osteocalcin) were not observed until after three months of treatment with ALN at a dose of 40 mg/day. The maximum decreases in SAP and OC were 29% and 57%, respectively, until after 6 months of treatment and no further decrease was noticed thereafter in spite of continued therapy. Changes in bone formation markers (SAP and OC) induced by ALN treatment were similar in time course and magnitude to those reported following estrogen replacement (ERT) therapy (Lufkin et al. *Ann. Intern. Med.* 117: 1, 1992) or hormone replacement (HRT) therapy (Christiansen and Riis, *JCFM* 71:836, 1990).

With the 5 and 10 mg doses, resolution of effect of ALN on DPyr was nearly complete within a year. At higher doses (20 and 40 mg), a small residual effect of suppression was evident two years after end of treatment. Biochemical resolution of formation indices took longer time.

7.1.6 Discussion on safety :

Of 19 patients discontinued treatment, 18 were due to clinical adverse experience and 1 for laboratory abnormality. Thirteen of 18 clinical discontinuations occurred during the first year of treatment and were in the 20 or 40 mg group. These patients were discontinued for the following AEs : nausea in 3 patients, gastritis in 2, esophagitis in 1, and abdominal pain in 1; six in 40 and 1 in 20 mg groups. G-I adverse experiences occurred with higher doses of ALN and within the first month of treatment.

Four serious adverse experiences that caused discontinuation of treatment were not considered drug-related by the investigator. These were death attributed to COPD, recurrence of breast cancer, uterine cancer, and glomerulonephritis. Laboratory AEs did not show any increased

frequency in patients treated with ALN relative to placebo.

7.1.7 Sponsor's conclusion:

The results of this study indicate safety and tolerability of ALN at daily doses of 5 to 20 mg for two years. Upper G-I adverse experiences were mostly observed at a dose of 40 mg/daily, resulting in discontinuation of therapy.

ALN at all doses for up to 2 years caused increased BMD of lumbar spine, proximal femur, and total body. At 5 and 10 mg daily, there was progressive increase in BMD of spine, proximal femur, and total body when the treatment was continued for a second year.

At the forearm site, no increase in BMD was noted, but further loss of bone mass was prevented.

ALN treatment (20 and 40 mg/daily for one year or 5 and 10 mg/daily for 2 years) caused significant decrease in biochemical indices of bone turnover that reached new steady state levels after 6 months of treatment. These changes are consistent with the known specific antiresorptive action of bisphosphonates.

Following the termination of treatment with ALN (after 2 years with 5 and 10 mg doses, and one year after with 20 mg dose), the rate of change in BMD for the spine, proximal femur, and total body was similar to that of the placebo group.

Resolution of ALN effect on biochemical markers of bone turnover was spread over 6 to 12 months following termination of treatment with 5 or 10 mg/daily for 2 years.

7.1.7 Reviewer's overall comments and conclusion:

One of the primary objectives of this study was to determine the safety and tolerability of ALN, 5 to 40 mg/day for up to 2 years and 40 mg/day for 3 months and then 2.5 mg/day for 21 months. The study was appropriately designed and the results indicated that ALN was relatively safe for up to two years and its safety profile similar to that of placebo. Only at higher doses, the drug caused increased incidence of upper GI side effects including abdominal pain, nausea, gastritis, and esophagitis in a small percentage of patients. The incidence of laboratory AEs (hematology and blood chemistries) was similar to that of the placebo.

With regard to the effect of ALN treatment (compared to placebo) on BMD of spine, proximal femur (including total hip), and total body, the results showed significant increases at these sites over two years of treatment. The placebo group showed decrease in BMD at these sites over corresponding period. Spinal BMD data indicated that response was more closely related to daily dosing of ALN, rather than to the cumulative dose of the drug.

At the spinal site, the magnitude of response in BMD was similar for both 5 and 10 mg dose and the increase continued to occur over the two years of treatment (lack of plateau of effect seen

with estrogens and salmon calcitonin). At several appendicular sites (including hip), the response with 10 mg was greater than that of 5 mg dose. Contrary to ALN-induced increases in BMD in spine, hip, and total body, bone loss at forearm site was prevented.

Increases in BMD of total body (with ~ 80% cortical bone) as a result of treatment with ALN at 5 and 10 mg doses, demonstrate that increases in individual sites did not occur at the expense of bone loss elsewhere.

The rate of change in BMD of spine, hip, and total body following the end of ALN treatment (5 and 10 mg for up to two years and 20 mg for 1 year) was similar to that observed with placebo treatment.

Invitro studies have shown a close correlation between mineral density and bone strength; 40% to 80% of variance in bone strength may be explained by measurements of density. It is generally accepted that bone mass is inversely related to risk fractures in postmenopausal women. The bone mineral density of proximal femur seems to have greater relationship to risk of hip fracture than BMD of spine to vertebral fractures. Progressive increases in hip and spinal BMD are likely to reduce the risk of fractures at those sites.

Treatment with ALN for up to two years caused decreases in biochemical indices of bone turnover to new steady state levels after 6 months. These changes are consistent with the mechanism of action of bisphosphonate in general. There was no evidence of progressive inhibition of bone turnover process with continued ALN treatment. Suppression of biochemical indices of bone turnover resolved over 6 to 12 months after cessation of treatment at doses of 5 and 10 mg/day for up to two years.

The overall results of this double-blind, randomized, placebo-controlled, parallel group study seem to demonstrate the safety and tolerability of alendronate sodium at a daily dose of 5 and 10 mg for up to two years in women postmenopausal for at least 5 years. Additionally, this study has provided three-year (two years on active treatment and 1 year off drug) data to show progressive increases in BMD of spine, hip, and total body during treatment and resolution of effect during off-drug period. Changes in biochemical indices of bone turnover are consistent with the known mechanism of action of bisphosphonates, i.e., inhibition of bone resorption.

7.2 Trial #2 (Sponsor's Ref. # D-15/JO-44)/Protocol # 035

7.2.1 Title: A double-blind, randomized, placebo-controlled, parallel-group, multicenter-study to evaluate the safety and effect on bone density of daily oral MK 217 for 3 years in osteopenic postmenopausal women.

7.2.2 Objective/rationale:

Primary objectives are : a) To determine the safety and tolerability of daily oral administration

of ALN (5, 10, and 20 mg for up to 3 years) in postmenopausal osteopenic women; b) To determine the effect of ALN treatment (5 and 10 mg daily for 3 years and 20 mg daily for 2 years followed by 5 mg daily for additional 1 year) on BMD of PA lumbar spine in same study population, compared to placebo treatment; c) To determine the effect of ALN treatment on the biochemical indices of bone turnover, and mineral metabolism. The rationale for use of ALN in the proposed study population is the same as stated for the study under protocol # 26.

7.2.3 Design: As stated earlier. The proposed study design is adequate and in conformity with our Osteo-Guidelines.

7.2.4 Protocol:

7.2.4.1 Investigators Centers: A multicenter study involving 18 centers:

Table 23. Lists the investigators and their locations.

Investigators	Location*
Mary Z. Baker, M.D.	Oklahoma City, OK
Norman H. Bell, M.D.	Charleston, SC
Michael Bliziotis, M.D.	Portland, OR
Henry G. Bone, M.D.	Detroit MI
Robert W. Downs, M.D.	Richmond, VA
Ronald D. Emkey, M.D.	W Reading, PA
Murray Favus, M.D.	Chicago, IL
C. Conrad Johnston, M.D.	Indianapolis, IN
Robert Marcus, M.D.	Falo Alto, CA
Harris Mellwain, M.D.	Tampa, FL
Jeffrey L. Miller, M.D.	Tampa, FL
Robert R. Recker, M.D.	Omaha, NE
Richard D. Tonino, M.D.	Burlington, VT
Joseph Tucci, M.D.	Providence, RI

Richard D. Wasnich, M.D.

Honolulu, HI

Nelson B. Watts, M.D.

Atlanta, GA

Robert B. Weinstein, M.D.

Augusta , GA

Stuart R. Weiss, M.D.

San Diego, CA

* These are the locations for investigators. Investigational sites are listed in vol. 90, p.3 of this submission.

All investigators are qualified.

Protocol summary:

Design- Randomized, double-blind, placebo-controlled, parallel-group study. Randomization procedure followed a block allocation schedule.

The original protocol was to include 4 groups of patients to be treated with placebo, 5, 10, and 20 mg/day ALN for up to two years, followed by an additional 1 year of treatment in an open-label manner. In order to meet our current Osteo-Guidelines requirement, the protocol was amended to provide a continued blinded treatment during the third year to consenting patients. Patients who received ALN 20 mg/day for 2 years, were switched to 5 mg/day blindly during the third year.

Number of patients and groups- The original protocol called for enrollment of 300 subjects (20-25 subjects per center), but enrollment was increased to a total of 500 subjects. Table 24 shows the treatment groups at years 1, 2, and 3.

Table 24. Groups and treatment by year.

Group	Treatment-Years 1 and 2	Treatment-Year 3
A	Placebo	Placebo
B	ALN 5 mg/day	ALN 5 mg/day
C	ALN 10 mg/day	ALN 10 mg/day
D	ALN 20 mg/day	ALN 5 mg/day*

* This group is referred to as 20/5 mg treatment group.

Patients (N=14) who declined to continue third-year double-blind treatment, received open-label ALN therapy at a dose of 5 mg/day.

Type of subjects- Postmenopausal (for at least 5 years) women in good health, aged 45 to 80 years.

Key inclusion criteria-

a. The patient with BMD of lumbar spine $\leq 92 \text{ g/cm}^2$ (by Lunar DPX measurement), or $\leq 80 \text{ g/cm}^2$ (by Hologic QDR measurement).

Comments: There is a minor difference in the definition of osteoporosis between protocol # 26 and this study (protocol # 35). In this study, the definition of osteoporosis corresponds to a BMD of lumbar spine (L1 to L4) approx. 2.5 SD below the mean BMD of mature White women in the US. This is about 30th to 40th percentile for BMD of 65-year-old women. In subjects of protocol

#26, the BMD of lumbar spine was approx. 2 SD below the mean BMD of mature White women in the US.

The inclusion criteria are similar to those of the protocol # 26 and they are appropriate and acceptable.

Key exclusion criteria- The exclusion criteria are very comprehensive and similar to those of protocol # 26.

Controls- Placebo controlled

Screening and baseline investigations- See Table 25 (Appendix 1, Table 1, vol. 90, p. 5870). In this study, bone biopsy originally planned at the end of second year, were performed at the end of Year 3 (in consenting patients). Comments: The sponsor states that histomorphometric data from these biopsies will be reported separately (D-31, vol. 109 and 110).

Table 25. Screening and baseline investigations.

Table 11
Observation and Evaluation--Schedule for Study Procedures

	Screening Days	Treatment											
		Double-Blind, Controlled Phase											
		Day	Months										
			-29 to -8	-1	1	3	6	9	12	18	24	27	30
Clinic Visit ID	Screen	1 ^a	2	3	4	5	6	7	8	9	10	11	
Medical history ^a	C	I	I	I	I	I	I	I	I	I	I	I	I
Physical examination ^b	C	L	L	L	L	L	L	L	L	C	L	L	C
Hemocult ^b		X											
12-lead electrocardiogram	X									X			X
Chest X-ray ^c	X												
Mammogram ^d	X												
Lateral spine (thoracic and lumbar) X-rays	X						X		X				X
Height ^e	X	X		X	X	X	X	X	X	X	X	X	X
Bone densitometry ^f	X	X		X	X		X	X	X		X	X	X
Serum chemistry	X	X	X	X	X ^g	X	X ^g	X ^g	X ^g	X	X ^g	X ^g	X ^g
Bone biochemistry		X	X	X	X		X	X	X		X	X	X
Urine chemistry ^h	X	X	X	X	X		X	X	X ⁱ		X	X	X
24-hour urine chemistry ^j		X							X				X
Thyroid chemistry	X												
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X
Tablet counts				X	X	X	X	X	X	X	X	X	X
Bone biopsy ^h													X

^a C = Complete medical history; I = Interim history to identify new or changed symptoms and medication usage

^b C = Complete physical examination; L = Limited physical examination includes cardiac, pulmonary, abdominal, musculoskeletal, and neurological examinations, with a more extensive examination performed when indicated to evaluate symptoms or if abnormal at previous clinical visit. Both C and L examinations include temperature, pulse rate, blood pressure, and weight. The complete physical examination performed at baseline will include a fecal hemoglobin determination, which may be performed on a specimen returned by the patient at the Study Day -1 visit and analyzed prior to dispensing study medication. Fecal hemoglobin will also be determined on each visit when gastrointestinal symptoms are noted.

^c Not needed if documentation of a normal chest X-ray (PA and lateral) performed within the preceding six months is obtained.

^d Not needed if documentation of a normal mammogram performed within the preceding year (women >50) or two years (women 45 to 49) is obtained.

^e Height measured using a Harpenden stadiometer.

^f Performed using Hologic QDR-1000 or 1000/W, Lunar DPX-L, or Norland XR-26 dual-energy X-ray densitometers. At screening, only a PA scan is required. At all other visits, sites studied include the lumbar spine (PA and lateral), forearm, proximal femur and, at sites with this test available, total body. Note: After Clinic Visit 6, the lateral spine scan will be performed at year end visits only. Lunar forearm scans have been eliminated.

^g Tests performed on a second morning fasting sample (about two hours duration) at each visit indicated include creatinine, calcium, phosphorus, and pyridinolines.

^h Iliac crest bone biopsy after double tetracycline labeling will be performed in 50 to 60 consenting patients. A urine sample will be sent to a central laboratory to confirm patient compliance.

ⁱ Clinic Visit 1 should normally be carried out on Study Day -1. When more than four weeks have elapsed since screening laboratory studies were performed, Clinic Visit 1 should be carried out on Study Day -2 or -3 to allow for reporting of the safety chemistry and hematology studies before the start of treatment on Study Day 1.

^j A 24-hour sample will be collected before the Study Day -1 visit and after the second and third years for creatinine clearance.

^k Thyroid test will be performed every six months only if the patient is receiving thyroid hormone replacement or there is a history of any problem.

^l NAG (N-acetyl-glucosaminidase) Excretion Studies should be performed at Visit 8 for all patients.

All patients received instructions on "lifestyle change" in order to minimize the risk of osteoporotic fractures. Screening investigations included assessment of daily dietary intake of calcium, AP lumbar spine DXA, history, PE, laboratory tests, 12-lead ECG, and radiologic tests. Body height was measured by Harpenden Stadiometer

Vertebral fractures were evaluated by two different methods: a) review by local physician at the study site, b) central digitized computer-assisted review by an expert radiologist. Digitized computer-assisted evaluation was performed in a blinded (to both sequences and treatment allocation) manner.

Dosage and duration- According to the randomization block schedule, patients received ALN or placebo tablets daily in the morning (at least one hour before or 3 hours after breakfast) in fasting state. The duration of treatment has been discussed earlier in connection with numbers and groups.

Efficacy parameter- The effect of ALN on bone density was evaluated by examining the PA lumbar spine, femoral neck, total body, lateral spine, Ward's triangle, trochanter, and total hip (Hologic only), ultra distal (radius + ulna) wrist (Hologic only), and 1rad distal (radius + ulna) wrist BMD. Percent changes from baseline were calculated at designated intervals over 36 months as in protocol # 26. Percent changes in BMD from Month 12 to Months 24, and then from Month 24 to Month 36 were also calculated. From Quality Assurance point of view, BMD values were corrected as in protocol # 26.

Biochemical efficacy variables included parameters for mineral homeostasis (serum calcium, phosphate, vitamin D metabolites, PTH, and urinary calcium), and biochemical markers of bone turnover.

Body height was measured at designated interval by using Harpenden Stadiometer. At least 3 measurements were taken at each visit and the mean height determined calculated at each visit was used for evaluation. Due to some instrumental problems, stature measurements were excluded at 3 study sites (Drs. Favus, Bell, and Tucci).

Safety parameters- Clinical and laboratory parameters (blood and urine chemistries and hematology) were the same as in study #26.

At baseline and at Months 12, 24, and 36 lateral/thoracic spine x-rays were evaluated by the study site physician in order to detect the presence of prevalent fractures. Vertebral bodies affected by fracture were excluded from lumbar spine BMD analysis.

The procedure for digitization of lateral spinal x-ray films involved first marking of 6 landmarks on each vertebra; 3 along the upper edge and 3 along the lower edge of each of 14 vertebrae (T4 to L5). See Figure 10 (Figure 1, vol 111, p. D-13929). There were 3 heights for each of 14 vertebrae and a total of 42 heights per patient film.

Figure 10. Digitization landmarks on vertebral body.

Figure 1 †††

Vertebral Body--Lateral Aspect
Landmark Placement on the Bony Process of the Vertebra

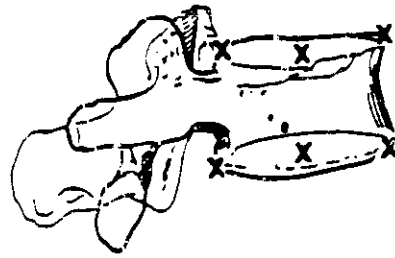
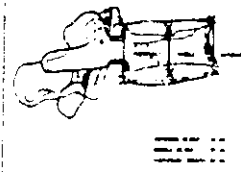


Figure 2 †††

Vertebral Body--Lateral Aspect
Demarcation of Anterior, Middle, and Posterior Heights of the Vertebra



Prevalent fracture was determined by comparing each patient's baseline vertebral heights with those of a reference population. In determining the incident fracture, patient's baseline vertebral heights were compared with her follow-up heights. Any vertebral height ratio more than 3 SD below its corresponding population value was considered as prevalent vertebral fracture. Patients with a prevalent fracture were included in the Prevalent Fracture Group. Patients in the nonvertebral Fracture Group had at least 11 vertebral bodies digitized and without any vertebral body fractures.

An incident vertebral fracture was defined as $\geq 20\%$ decrease (or an absolute reduction of 4 mm) in any heights between baseline and follow-up. If an incident fracture was detected, this patient was included in the Incident Fracture Group, even if some vertebral levels from baseline or follow-up were not digitized. Where some vertebrae could not be digitized at baseline (Year 0) or Year 3, a combination of baseline data with Year 1 (as baseline) and a combination of data for the Year 2 and Year 3 (as follow-up) was used.

Statistical Plans and analysis of data- The original power calculations were based on an estimated sample size of $n=50$ at Year 2 for ALN treatment groups and $n=100$ for the placebo. The study had a 95% power to detect a difference of 3% in mean % changes from baseline spinal BMD between placebo and ALN treated groups. For comparing the effect between ALN groups, the estimated sample sizes were to provide a power of 95% to detect a 4% between-group difference. The actual sample sizes after completion of the study at Month 36 were larger than the anticipated sample sizes with a between-patient standard deviation of $3.9\% \approx 4.0\%$.

The sponsor performed a Year 2 interim analysis of data for the purpose of submitting applications to "some regulatory agencies." However, the study investigators remained blinded during the entire three-year course of the study as the original protocol called for.

Intent-to-treat and per-protocol approaches were used for the analysis of the results. The per-protocol analysis was primary for the biochemical efficacy-related parameters, and intent-to-treat was the primary approach for analysis of BMD and stature data. For the patients who opted to receive ALN 5 mg/day (open-label) during the 3rd year, were also subjected to intent-to-treat analysis. In these patients the 2-year data were carried forward and 3rd year data were deleted. For the open-label period no data were carried for the analysis of % change from Month 24 to Month 36. This was referred to as modified intent-to-treat analysis.

Analysis of BMD- The primary analysis was the % change from baseline to Month 36 time point using the intent-to-treat analysis. Baseline was defined as the average of data collected within 100 days preceding and 14 days after initiation of treatment. Step-wise trend test was applied to examine the dose-response relationship for the different doses of ALN and comparison of response at each dose of ALN with placebo. The statistical tests were applied in a stepwise fashion in order to determine the "minimal acceptable dose that was statistically significantly different from placebo."

For each dose of ALN which was statistically significantly different from the placebo by the trend

test. an 84% confidence interval (CI) was computed for the adjusted mean response. Other routine statistical tests were applied to evaluate the treatment-by-center interaction.

Percent change in BMD (at all sites) from baseline to Month 12, and Months 12 to 24, and from Months 24 to Months 36 was also analyzed in order to elucidate how "treatment effects varied over time." However, the study was not adequately powered to detect significant differences between treatment groups in each year.

Stature- Statistical approaches similar to those applied for the BMD were used to analyze stature data.

Biochemical parameters of bone turnover and mineral metabolism-The fraction of baseline (In) value was analyzed for the biochemical parameters which included SAP, OC, DPyr, Pyr, serum calcium, serum phosphate, urine calcium/creatinine ratio, 1,25 (OH)₂D, serum PTH. The time response profiles for these parameters were evaluated. One of three patterns of response for each of the parameters was identified: (i) a peak followed by a return to baseline, (ii) a nadir which was maintained during the course of study, and (iii) a nadir followed by return to baseline. Correlation analyses were performed in order to examine the relationship between biochemical indices of bone turnover and changes in BMD.

To assess the treatment effect in all of the prespecified subgroups (in terms of age, race, prevalent vertebral fracture, cigarette smoking, oophorectomy status, renal function, baseline calcium intake, number of years since menopause, height, weight, body mass index (BMI) and baseline lumbar spine BMD), routine statistical methods (ANOVA and ANCOVA) were applied.

Safety analysis- The significance of clinical and laboratory adverse experiences were evaluated by using routine statistical approaches.

Baseline comparability of various treatment groups was evaluated by using routine statistical approaches.

Clinical supplies-This submission provides adequate patient instructions and information on drug supplies and daily calcium supplementation. There were some variations in the final processing of "supplies." Sponsor states that change in final manufacturing processes (direct compression vs wet-granulation) caused no change in composition and dissolution profiles. Comments: Chemistry review of this submission may have additional comments on this issue.

7.2.4.2 Results:

Table 26. Number of patients entered into study and treatment groups.

Protocol #	No. of Investigators	Placebo	ALN 5 mg	ALN 10 mg	ALN 20/5 mg	Total No. of Pt.
035 (U.S.)	18	192	98	94	94	478

Baseline patient characteristics are summarized in sponsor's table 8 (vol. 90, pp. D-5672-5675). The following baseline characteristics were summarized: age, lumbar spine BMD, body mass index, estimated calcium intake, height, number of years since menopause, and weight. Except for significant difference in age and baseline lumbar spine BMD (measured by Hologic machine) between treatment groups (Table 27), there was no significant difference between treatment groups with respect to other variables.

Table 27. Baseline difference between treatment groups with respect to age, and lumbar spine BMD (measured by Hologic machine).

Variables	Treatment	Mean	S.D.	Range	p-Value
Age (years)	All	64.6	7.0	45.0-82.0	.017
	Placebo	64.2	7.4	45.0-78.0	
	5 mg	66.5	6.9	49.0-82.0	
	10 mg	63.9	6.4	50.0-79.0	
	20/5 mg	63.8	6.8	45.0-75.0	
L.spine BMD (g/cm ²)	All	0.71	0.08	0.46-0.89	0.25
	Placebo	0.72	0.08	0.46-0.84	
	5 mg	0.70	0.09	0.48-0.82	
	10 mg	0.70	0.09	0.50-0.89	
	20/5 mg	0.73	0.07	0.47-0.85	

There was a difference of 1.9 years in mean age between ALN 5 mg dose and other treatment groups. The ALN 20/5 mg treatment group had the highest mean baseline lumbar spine BMD and 5 and 10 mg groups had the lowest mean baseline BMD. (Comments: The recommended dose of ALN proposed for the treatment of osteoporosis is 10 mg/day. The baseline mean value for this group is in fact lower than that of the placebo group. These small differences in baseline age and lumbar spine BMD are unlikely to significantly influence the final clinical outcome of the study).

There was no significant difference between treatment groups with respect to baseline demographic characteristics which included cigarette smoking, alcohol intake, family history of osteoporosis, oophorectomy status, renal insufficiency, and prevalent vertebral fractures. Almost 43% of patients enrolled into this study had family history of osteoporosis, 20.5% were oophorectomized, 91% were Caucasians, and 28.6% (of number of patients evaluated) were with ≥ 1 prevalent vertebral fractures.

Baseline BMD values for lumbar spine, femoral neck, trochanter, total body, lateral spine, Ward's triangle, total hip ultra distal wrist and one-third distal wrist are presented in Table 10 of this submission (vol. 90, pp. D-5677-5680). Hologic and Norland densitometers were reported to provide similar calibrated measurements and they were grouped together. BMD measurements determined by Lunar machine were calibrated differently and listed separately. Review of the baseline BMD values at all of these sites showed no meaningful differences between treatment groups.

Baseline biochemical parameters of bone turnover and mineral metabolism are presented in Table 11 of this submission vol. 90, pp.5681-5682). These parameters included serum alk. phosphatase, serum calcium, serum OC, serum PTH, serum phosphate, U/Ca, U/DPyr/Cr ratio, U/Pyr/Cr ratio, and serum $1,25(\text{OH})_2\text{D}$. Review of these data showed no clinically meaningful differences between treatment groups.

Secondary diagnoses by body system and by treatment groups are presented in Table 12 (vol 90, p. D-5683). Of the 478 patients entered into the study, 475 patients (99%) were reported to have at least one secondary diagnosis. Among various secondary diagnoses, digestive system disorders, musculoskeletal disorders, and urogenital disorders were reported to be more common (in $\approx 55\%$ to 71% of patients). There were no significant differences between treatment groups with respect to secondary diagnosis.

With respect to prior therapies, there were no significant differences between treatment groups. Prior use of central nervous system drugs, G-I drugs, and vitamins/minerals were common in this study population. Similarly, there were no significant differences between treatment groups with regard to the types of concomitant drugs used.

Patient accounting in the study is presented in Table 28 (Table 15 vol. 90, p. D-5688).

Table 28. Patient accounting in the study.

Table 15 ††

Patient Accounting

	Total	Placebo	ALN 5 mg Oral	ALN 10 mg Oral	ALN 20/5 mg Oral
ENTERED: Total (age range, years)	478 (45 to 82)	192* (45 to 78)	98 (49 to 82)	94 (50 to 79)	94 (45 to 77)
DISCONTINUED: Total	72	31	13	12	16
Clinical Adverse experience	28	13	3	5	7
Laboratory Adverse experience	0	0	0	0	0
Patient withdrew consent (prior to 36 months)	34	14	6	5	4
Protocol deviation	8	3	4	1	0
Lost to follow-up	0	0	0	0	0
COMPLETED: 36 months**	406	161	85	82	78
* One patient (AN 503) inadvertently received 10 mg alendronate for two days. At all other times during the study, patient received placebo. All data for this patient is presented under the placebo treatment group. ** Includes 14 patients who elected open-label treatment during Year 3.					

Overall 85% (406 of 478) of enrolled patients completed 36-month study. Both in ALN 5 and 10 mg doses groups, about 87% of patients completed the study. Almost twice the number of patients in the placebo group discontinued the study compared to number of patients in each of the ALN-treated groups. Thirteen patients in the placebo group discontinued the study because of clinical AEs, compared to 3, 5, and 7 patients in ALN 5, 10, and 20/5 mg groups, respectively. None of the patients in ALN groups were reported to discontinue the study due to laboratory AEs.

Accounting for patients in the analysis- Relative day ranges were established for the patients who could not come for their clinical visits on the exact day (Table 29).

Table 29. Relative day ranges for efficacy and safety analyses (Table 16, vol. 90, p. D-5689).

Table 16 ††

Relative Day Ranges for Efficacy and Safety Analyses

Timepoint	Relative Day Ranges			
	Efficacy			Safety
	BMD	Stature	Biochemical	Clinical and Laboratory
Baseline	-100 to 14	-100 to 14	-100 to 1	-100 to 1
Month 1	--	--	2 to 59	2 to 59
Month 3	15 to 134	15 to 134	60 to 134	60 to 134
Month 6	135 to 272	135 to 224	135 to 224	135 to 224
Month 9	--	225 to 317	225 to 317	225 to 317
Month 12	273 to 454	318 to 454	318 to 454	318 to 454
Month 18	455 to 637	455 to 637	455 to 637	455 to 637
Month 24	638 to 819	638 to 775	638 to 775	638 to 775
Month 27	--	776 to 865	776 to 865	776 to 865
Month 30	820 to 1002	866 to 1002	866 to 1001	866 to 1001
Month 36	1003 to 1184	1003 to 1185	1002 to 1199	1002 to 1199

If a patient had data for multiple visits "within a day range" at any given time point, then the valid data from the last visit were used in the final analysis. The baseline values for the clinical efficacy parameters were average of the values observed in the day range of -100 to 14 and for the safety parameters in the day range of -100 through 1. For the biochemical parameters, the last pretreatment value (in the day range of -100 to 1) was considered as the baseline. Change in the stature was also analyzed using same relative day range procedure.

Patients who were excluded from the ITT and P-P analyses of lumbar spine BMD at Month 36 are listed in Tables 1 and 2 (Appendix 4, vol. 90, pp. D-5898-5905).

Patients or particular data points from individual patients were excluded from P-P analysis for one or more of the following reasons:

- a. Protocol violations.
- b. Clinical or laboratory AEs.
- c. No baseline data.
- d. Patient withdrew consent.
- e. Protocol deviations.
- f. Patient lost to follow-up.
- g. Violation of the off-drug requirements.
- h. Patient declined consent to 3rd-year double-blind treatment.
- i. Multiple violations (more than one of the above).

The reasons for not including patients in the P-P analysis of biochemical efficacy were almost the same as listed above. In addition, an observation was excluded in the analyses (at a specific time point), if the patient was off-drug for more than 15 days during the 45 days prior to a visit. Patients on concomitant thiazide diuretics were excluded from ITT and P-P analyses for changes in U/Ca (corrected for creatinine) excretion.

Table 30. Number of patients in the L-spine BMD analysis at Month 36 (modified Table 17, vol. 90, pp. D-5691-5692).

Table 30 summarizes the number of patients in the L-spine BMD analysis at Month 36.

	Placebo	ALN 5 mg	ALN 10 mg	ALN 20 mg
Total	192	98	94	94
P-P*	130	67	66	60
ITT**	186	89	88	86

* Per-protocol analysis. ** Intent-to-treat analysis.

EFFICACY

1. Bone Mineral Density (BMD)

In this study the lumbar spine BMD is the primary efficacy endpoint. Femoral neck, trochanter and total body BMD are important secondary efficacy endpoint. Total body BMD measured the effect of treatment on the entire skeletal system. The BMD at forearm sites were studied only at investigational sites with Hologic machine (early version of Lunar machine software had problems). BMD measurement of distal 1rad-forearm provided an assessment of treatment effect on cortical bone (trabecular bone $\leq 5\%$ at this site). Ward's triangle and L1 lateral spine BMD had poor precision and in agreement with the available information in the published literature.

Modified ITT analysis included patients who received placebo for 24 months and then switched to 5 mg/daily from Month 24 to Month 36.

a. Lumbar spine (L-spine) BMD

The results (based on ITT analysis) are shown in Table 31 (Table 18, vol.90, p. 5696) and Figure 11 (Fig. 1, vol. 90, p. D-5695). Patients in the placebo group experienced a significant ($p < 0.05$) decrease in BMD by about 0.6% over 36 months. Patients in the ALN groups, 5, 10, and 20/5 mg/day all showed significant increases relative to baseline mean values by 5.6%, 9.6%, 7.9%, respectively, and placebo ($p < 0.001$). The mean increase in BMD at ALN 10 mg dose was significantly greater than 5 mg ($p < 0.001$) and 20/5 mg ($p < 0.004$) groups. No significant treatment-by-center interaction was observed.

The percent change in L-spine BMD from Month 12 to Month 24 was evaluated and the results indicated a non-significant increase in the placebo group, and significant increases by 1.3%, 1.9%, and 1.8% , respectively at 5, 10, and 20/5 mg doses. During the 3rd year of the study, BMD continued to increase by 0.8% and 1.7%, respectively at doses of 5 and 10 mg ($p < 0.05$). During the same period, the placebo and ALN 20/5 mg groups both showed nonsignificant increases by 0.1% and 0.6%, respectively. ALN (10 mg/day)-induced increase in spinal BMD during the 3rd year of treatment was statistically significant compared to changes in placebo ($p < 0.001$), 5 mg ($p < 0.034$), and 20/5 mg ($p < 0.012$) groups.

Table 31. Effect on spine BMD.

Table 18 ††

Lumbar Spine BMD (g/cm^3)
 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	S.D.	Adjusted Mean	LSD Interval
Placebo	186	0.75	0.74	-0.64*	3.58	-0.74	(-1.15, -0.33)
5 mg	89	0.73	0.77	5.60***	4.50	5.57	(4.98, 6.16)
10 mg	88	0.73	0.80	9.58***	4.00	9.54	(8.94, 10.13)
20/5 mg	86	0.75	0.80	7.88***	4.52	7.79	(7.19, 8.39)

Within-treatment test of mean = 0 ***: p 0.001 *: p 0.05
 Treatment-by-center interaction p-value: 0.628

Adjusted Trend-Test		Overall p-Value		Comparison Between Doses			Pooled S.D.
Dose Included	p-Value			Placebo	5 mg	10 mg	
Placebo through 20/5 mg	<0.001	<0.001	5 mg	<0.001	.	.	3.98
Placebo through 10 mg	<0.001		10 mg	<0.001	<0.001	.	
Placebo through 5 mg	<0.001		20/5 mg	<0.001	<0.001	0.004	

Analyses of data using the P-P and modified ITT approaches showed similar results in term of efficacy of ALN at all three doses compared to placebo treatment (Table 32 and 33).

Figure 1 †††

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

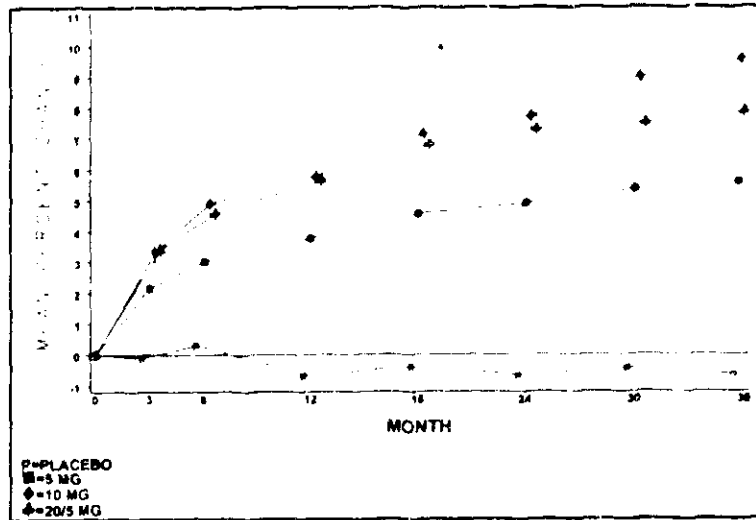


Table 32 (Append. 6, Table 17, vol. 90). Percent change in L-spine BMD from baseline to Month 36 (by per-protocol analysis).

Appendix 6

Table 17: Lumbar Spine BMD ††
Analysis of Percent Change From Baseline at Month 36
(Per-Protocol Approach)

Treatment Interval	Means (Observed)				Percent Change From Baseline		
	N	Baseline	Month 36	Mean	S.D.	Adjusted Mean	LSB
Placebo	133	0.75	0.75	-0.70*	3.37	-0.60	(-1.23)
0.31 mg	67	0.73	0.77	5.98***	4.33	5.94	(5.25)
6 mg	66	0.74	0.81	9.37***	3.72	9.35	
8.7 mg	60	0.75	0.81	8.32***	4.90	8.09	(7.68)

Within Treatment Test of Mean: 0 ***; P<=0.001 **; P<=0.01 *; P<=0.05
Treatment by Center Interaction P-value: 0.657

Table 32 (continued). Percent change in L-spine BMD from baseline to Month 36 (by per-protocol analysis).

Adjusted Trend-Test		Overall		Comparison Between Doses	
Pooled	P-Value	P-value	placebo	5 mg	10 mg
Dose Included					
S.D					
Placebo Through 20/5 mg	<0.001	<0.001	5 mg	<0.001	
3/92					
Placebo Through 10 mg	<0.001		10 mg	<0.001	
Placebo Through 5 mg	<0.001		20/5 mg	<0.001	0.135

Table 33 (Appendix 7, Table 9, vol. 90, p. D-6003). Percent change in L-spine BMD from baseline to Month 36.

Appendix 7

Table 9: Lumbar Spine BMD ††
 Analysis of Percent Change From Baseline at Month 36
 (Modified Intention-to-Treat Approach)

Treatment	N	Means (Observed)			Percent Change From Baseline			
		Baseline	Month 36		Mean	S.D.	Adjusted Mean	LSD Interval
Placebo	186	0.75	0.74		-0.76**	3.53	-0.85	(-1.26, -0.44)
5 mg	89	0.73	0.77		5.55***	4.49	5.53	(4.94, 6.12)
10 mg	88	0.73	0.80		9.59***	4.01	9.55	(8.96, 10.15)
20/5 mg	86	0.75	0.80		7.84***	4.56	7.75	(7.15, 8.35)

Within Treatment Test Of Mean: 0 ***: P<=.001 **: P<=.01 *: P<=0.05
 Treatment-by-Center Interaction P-value: 0.542

Dose Included	Adjusted Trend-Test P-Value	Overall p-value	Comparison Between Doses			
			placebo	5 mg	10 mg	Pooled S.D.
Placebo Through 20/5 mg	<0.001	<0.001	<0.001			3.97
Placebo Through 10 mg	<0.001		<0.001	<0.001		
Placebo Through 5 mg	<0.001		<0.001	<0.001	<0.001	

Slope analysis or annual rates of changes in L-spine BMD over 3 years of study are presented in Figure 12 (Fig. 2, vol. 90, p. D-5699).

Figure 12. Annual rates of changes in L-spine BMD in year 1, 2, and 3 of the study (ITT analysis).

Figure 2 †††

Lumbar Spine BMD (g/cm^3)
Annual Change S.E. of the Mean
(Intention-to-Treat Approach)

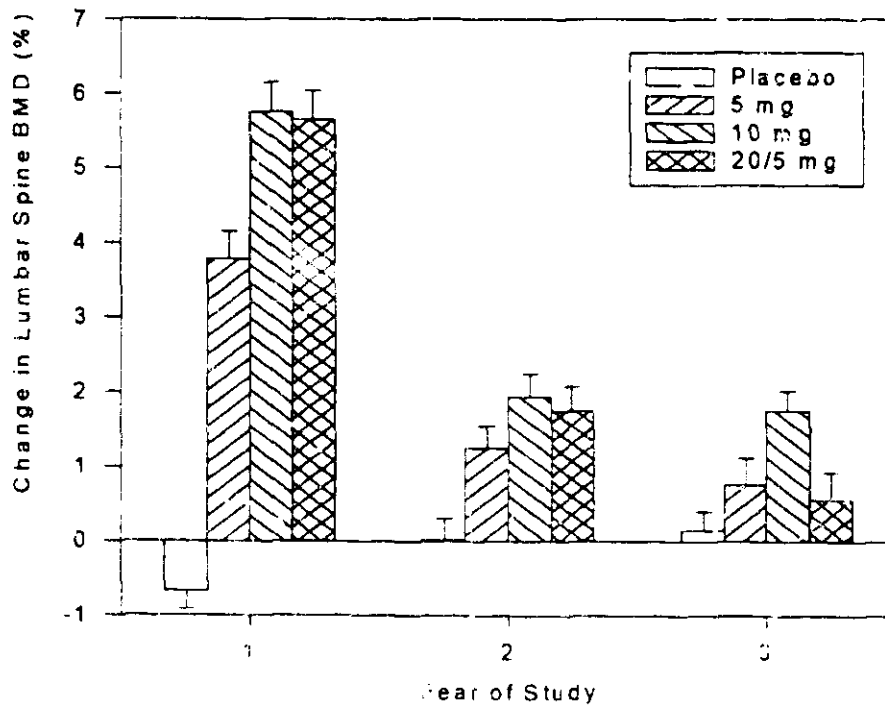
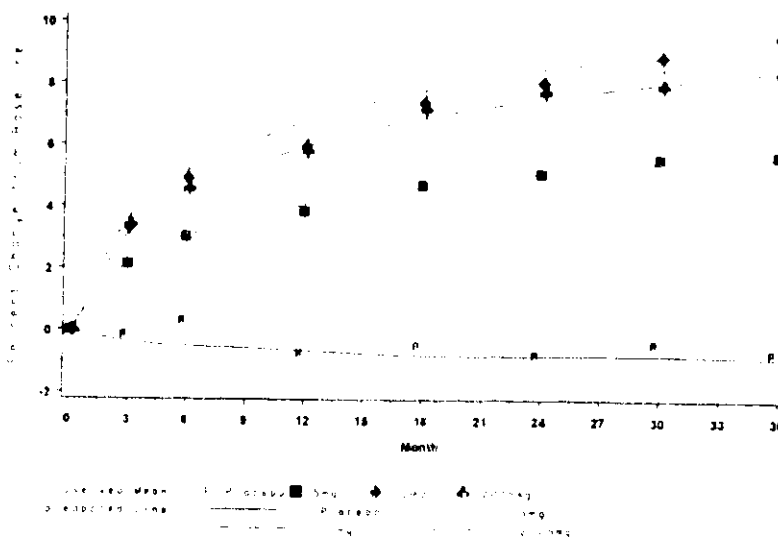


Figure 13 (Append. 5, Fig. 5, vol. 90, p.D-5937) presents the observed and predicted mean % changes in L-spine BMD ($\pm$ S.E.) from baseline over months. To note that observed and predicted values fit very well on the graph.

Figure 13. Observed and predicted mean percent changes in spine BMD.

Figure 5 †††
Plot of Observed ($\pm$ S.E.) and Predicted Mean Percent Changes
From Baseline Over Time
Lumbar Spine BMD

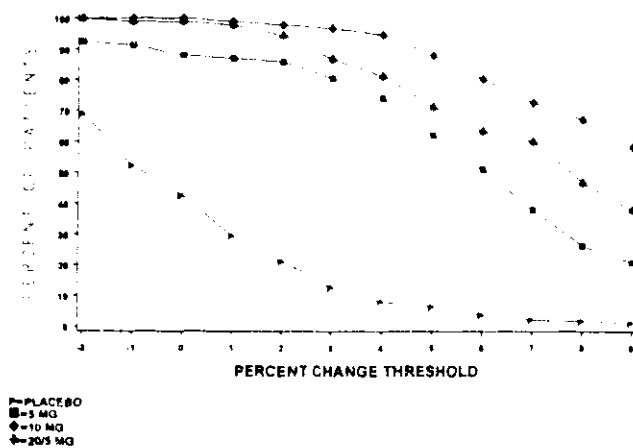


The relative efficacy among three ALN groups in terms of proportion of patients with a particular threshold of response from baseline is shown in Figure 14 (Fig. 3, vol. 90, p. D-5700).

Figure 14. Percent of patients with changes in L-spine BMD (from baseline) at Month 36 exceeding thresholds.

Figure 3 †††

Percent of Patients With Change in Lumbar Spine BMD From Baseline
at Month 36 Exceeding Thresholds Ranging From -2 to 9%
(Intention-to-Treat Approach)



Eighty-seven percent of patients at ALN 10 mg/day dose had $\geq 5\%$ increase in L-spine BMD and about 58% of patients had an increase of $\geq 9\%$. The results indicated that majority of patients treated with ALN at this dose responded.

b. Femoral neck BMD

The results are presented in Table 34, and Figure 15.

Table 34. Percent change in femoral neck BMD from baseline at Month 36 by ITT analysis (Table 22, vol. 90, p. D-5704).

Table 22 ††							
Femoral Neck BMD (g/cm ³)							
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	S.D.	Adjusted Mean	LSD Interval
Placebo	178	0.63	0.62	-1.50***	5.41	-1.51	(-2.08, -0.95)
5 mg	89	0.62	0.64	2.76***	5.05	2.83	(2.03, 3.63)
10 mg	87	0.60	0.63	4.69***	6.63	4.66	(3.85, 5.47)
20/5 mg	86	0.64	0.65	3.26***	5.12	3.22	(2.40, 4.04)

Within-treatment test of mean = 0 ***: p < 0.001
 Treatment-by-center interaction p-value: 0.050

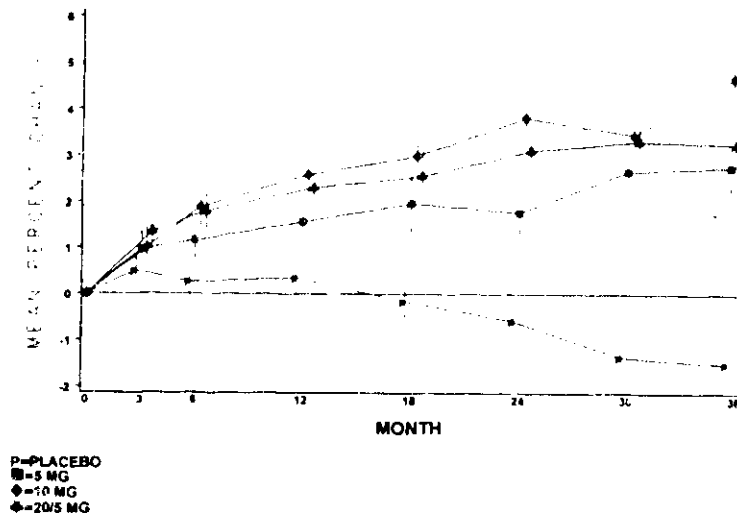
Adjusted Trend-Test		Overall p-Value		Comparison Between Doses			Pooled S.D.
Dose Included	p-Value			Placebo	5 mg	10 mg	
Placebo through 20/5 mg	<0.001	<0.001	5 mg	<0.001			5.41
Placebo through 10 mg	<0.001		10 mg	<0.001	0.026		
Placebo through 5 mg	<0.001		20/5 mg	<0.001	0.635	0.083	

The mean increases from baseline in femoral neck BMD were 2.8%, 4.7%, and 3.3% ($p \leq 0.001$) at ALN doses of 5, 10, and 20/5 mg doses, respectively at Month 36. In contrast, the placebo group showed a significant ($p \leq 0.001$) decrease by 1.5% from baseline at Month 36. The mean increase at Month 36 with 10 mg dose was significantly greater than that observed with 5 mg dose of ALN. While at 5 and 10 mg doses femoral neck BMD continued to rise through Month 36, the increase at 20/5 mg dose appeared to level off during the 3rd-year of treatment (on 5 mg daily dose).

Figure 15. Femoral neck BMD.

Figure 4 †††

Femoral Neck BMD (g/cm^2)
 Mean Percent Change S.E. of the Mean
 (Intention-to-Treat Approach)



There was significant treatment-by-center interaction, but variations in the magnitude of effects among investigators were not marked. The rates of change in BMD over three years were reported to be significantly "different" from zero. When observed and predicted mean % changes from baseline were plotted, the values were comparable only at Months 24 and 36.

The proportion of patients who achieved a particular threshold of femoral neck BMD increase was much less compared to proportion of patients with a particular threshold of L-spinal BMD response. About 48.3% of patients with $\geq 4\%$ increase of femoral neck BMD vs 94.3% of patients with an increase of $\geq 4\%$ at ALN 10 mg dose (Table 35).

Table 35 (Append. 5, Table 21, vol. 90, p. D-5943) Proportion of patients with percent change in femoral neck BMD.

Femoral neck BMD analyzed by the per-protocol approach showed a non-significant mean percent increase (0.76%) during the third year of treatment.

Table 35. Proportion of patients with percent change in femoral neck BMD.

Table 21. ††

Femoral Neck BMD (g/cm³)
 Analysis of Percent Change From Baseline at Month 24
 Per-Protocol Approach

Treatment	Means (Observed)		Percent Change From Baseline				
	N	Baseline	Year 2	Mean	S.D.	Adjusted Mean	LSD Interval
Placebo	22	0.60	0.60	-0.97	4.22	-1.16	(-2.29, -0.02)
5 mg	23	0.64	0.66	3.02**	2.50	2.75	(1.64, 3.87)
10 mg	24	0.60	0.63	5.03**	3.40	4.79	(3.70, 5.89)
20 mg/placebo	24	0.67	0.68	1.02	4.20	0.70	(-0.41, 1.80)
40 mg/placebo	21	0.62	0.64	3.34**	3.92	2.99	(1.81, 4.17)
40/2.5 mg	17	0.61	0.62	1.91	4.61	2.01	(0.73, 3.30)

Within-Treatment Test of Mean = 0. **: p 0.01 *: p 0.05

Adjusted Trend-Test	Dose included	p-Value	Comparison Between Doses					Pooled S.D.
			Placebo	5 mg	10 mg	20 mg /Placebo	40 mg /Placebo	
Placebo through 10 mg	Placebo through 5 mg	<0.001	0.001	.	.	.	.	3.79
		<0.001	<0.001	0.068	.	.	.	
Placebo through 5 mg	Placebo through 5 mg	<0.001	0.011	0.545	0.023	.	.	3.79
		<0.001	<0.001	0.068	.	.	.	

c. Trochanter BMD

The results are shown in Table 36 and Figure 16 (Table 25 and Fig. 5, vol. 90, pp.D-5708 -5709).

Table 36. Mean percent change from baseline in trochanter BMD at Month 36.

Table 25 ††

Trochanter BMD (g/cm²)
Analysis of Percent Change From Baseline at Month 36
(Intention-to-Treat Approach)

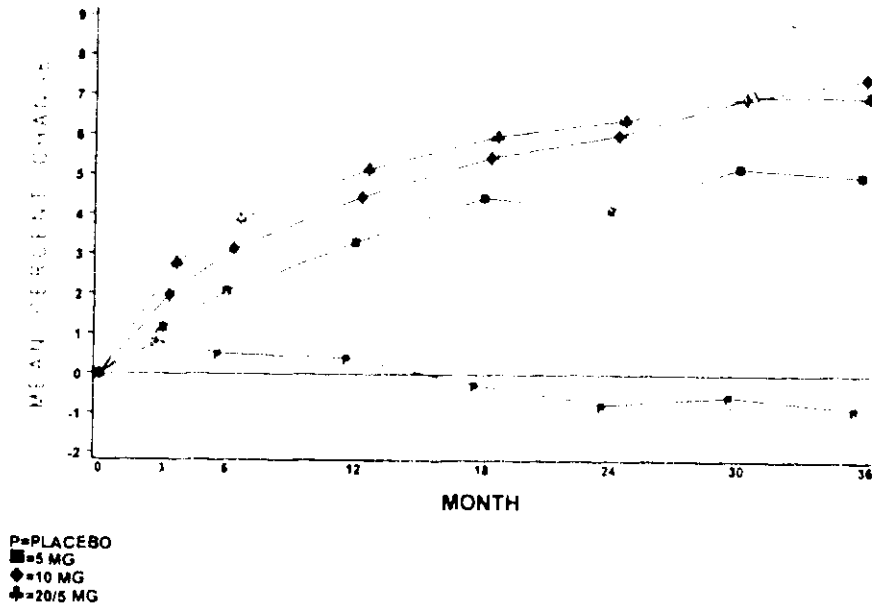
Treatment	N	Means (Observed)		Percent Change From Baseline			
		Baseline	Month 36	Mean	S.D.	Adjusted Mean	LSD Interval
Placebo	174	0.55	0.54	-0.85*	5.63	-0.77	(-1.37, -0.18)
5 mg	88	0.54	0.56	5.00***	6.38	5.10	(4.28, 5.93)
10 mg	86	0.53	0.57	7.45***	5.36	7.39	(6.55, 8.23)
20/5 mg	85	0.54	0.57	6.99***	5.52	6.94	(6.09, 7.79)

Within-treatment test of mean = 0 ***: p 0.001 *: p 0.05
Treatment-by-center interaction p-value: 0.912

Adjusted Trend-Test		Overall p-Value		Comparison Between Doses			Pooled S.D.
Dose Included	p-Value			Placebo	5 mg	10 mg	
Placebo through 20/5 mg	<0.001	<0.001	5 mg	<0.001			5.57
Placebo through 10 mg	<0.001		10 mg	<0.001	0.007		
Placebo through 5 mg	<0.001		20/5 mg	<0.001	0.031	0.601	

Figure 16. Mean percent change in trochanter BMD over 3-year treatment period.

Figure 5 †††
Trochanter BMD (g/cm^2)
Mean Percent Change S.E. of the Mean
(Intention-to-Treat Approach)



Trochanter BMD increased from baseline by 5%, 7.45%, and 6.99% ($p < 0.001$) at ALN 5, 10, and 20/5 mg doses, respectively at Month 36. In the placebo group, trochanter BMD decreased from baseline by 0.9% ($p < 0.05$) over the corresponding period. Increase in trochanter BMD at 10 mg dose was significantly greater than that observed at 5 mg dose. The effect of ALN on trochanter

BMD at doses 5 and 20/5 doses appeared to level off after the second year of treatment. The results of per-protocol analysis were similar to those of ITT analysis.

d. Total body BMD the results are shown in Table 37 and Figure 17 (Table 28, and Fig. 6, vol. 90, pp. D-5713-5714).

Table 37. Mean percent change from baseline in total body BMD at Month 36.

Table 28 ††

Total Body BMD (g/cm³)
Analysis of Percent Change From Baseline at Month 36
(Intention-to-Treat Approach)

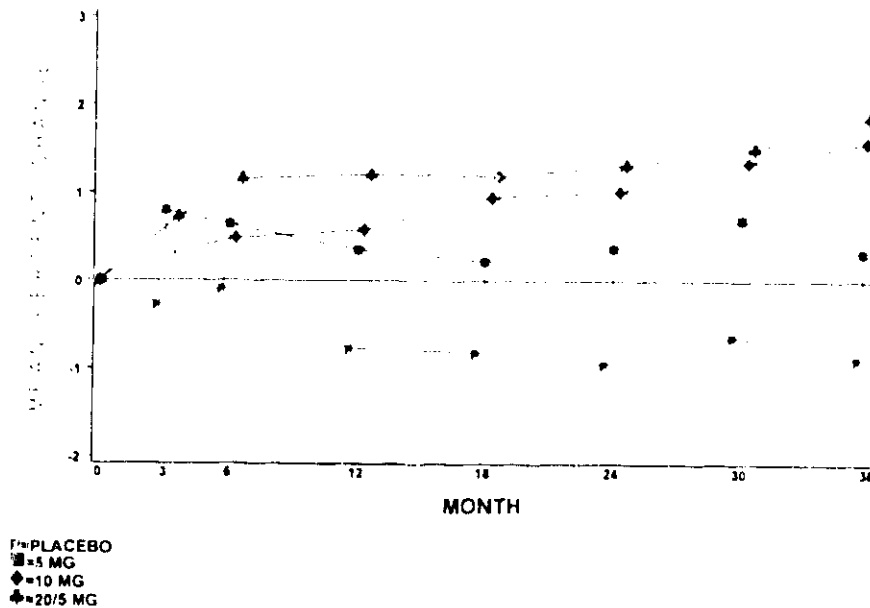
Treatment	N	Means (Observed)		Percent Change From Baseline			
		Baseline	Month 36	Mean	S.D.	Adjusted Mean	LSD Interval
Placebo	114	0.95	0.94	-0.89***	2.69	-0.87	(-1.23, -0.51)
5 mg	57	0.94	0.94	0.32	3.85	0.35	(-0.15, 0.86)
10 mg	59	0.94	0.95	1.58***	2.43	1.61	(1.12, 2.10)
20/5 mg	57	0.94	0.95	1.87***	2.87	1.74	(1.24, 2.24)

Within-treatment test of mean = 0 ***: p < 0.001
Treatment-by-center interaction p-value: 0.997

Adjusted Trend-Test		Overall p-Value	Dose	Comparison Between Doses			Pooled S.D.
Dose Included	p-Value			Placebo	5 mg	10 mg	
Placebo through 20/5 mg	<0.001	<0.001	5 mg	0.005			2.68
Placebo through 10 mg	<0.001		10 mg	<0.001	0.012		
Placebo through 5 mg	0.005		20/5 mg	<0.001	0.007	0.796	

Figure 17. Mean percent change in total body BMD over 36 months.

Figure 6 †††
 Total Body BMD (g/cm²)
 Mean Percent Change S.E. of the Mean
 (Intention-to-Treat Approach)



Significant increases (1.58% and 1.87%) in mean percent change in total body BMD were reported at 10 and 20/5 mg doses of ALN. The placebo group showed a significant decrease (0.9%, $p \leq 0.001$) over three years. The 10 mg ALN group showed a progressive increase in total body BMD over time and a significant increase by 0.6% ($p \leq 0.001$) during the third year.

Data analyzed per-protocol and modified ITT approaches showed similar results.

e. One-third wrist (radius+ulna) BMD

The results are shown in Table 38 and Figure 18 (vol. 90, Table 31 and Fig. 7, pp. D-5718-5719).

Table 38. Mean percent changes in one-third wrist BMD at Months 36.

Table 31 ††

One-Third Wrist (Radius+Ulna) BMD (g/cm^2)
Analysis of Percent Change From Baseline at Month 36
(Intention-to-Treat Approach)

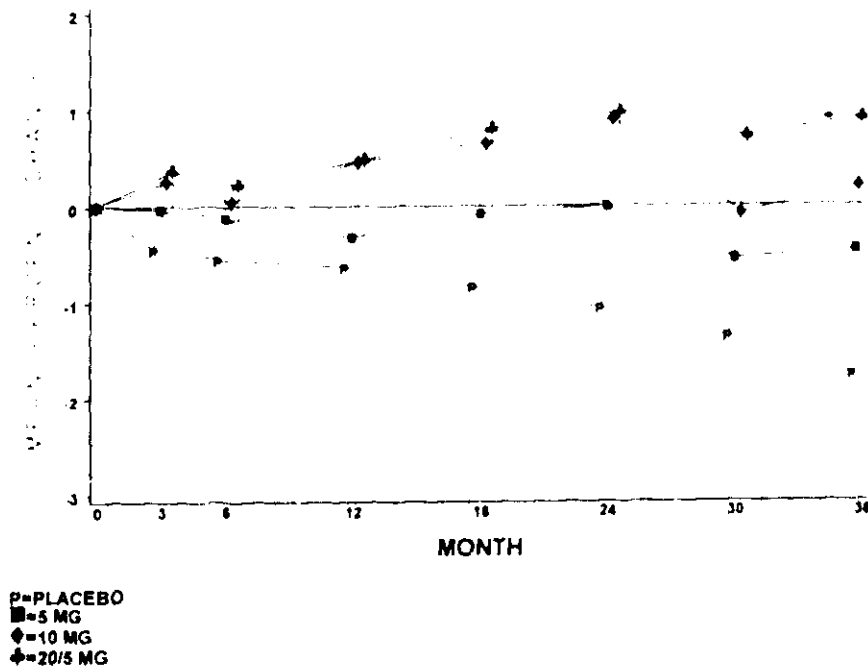
Treatment	N	Mean (Observed)		Percent Change From Baseline			
		Baseline	Month 36	Mean	S.D.	Adjusted Mean	LSD Interval
Placebo	132	0.55	0.54	-1.76***	3.28	-1.73	(-2.08,-1.39)
5 mg	67	0.53	0.53	-0.46	3.19	-0.53	(-1.02,-0.05)
10 mg	65	0.54	0.54	0.21	3.13	0.30	(-0.20, 0.79)
20/5 mg	62	0.55	0.55	0.91**	2.41	0.84	(0.33, 1.35)
Within-treatment test of mean = 0 ***: p 0.001 **; p 0.01							
Treatment-by-center interaction p-value: 0.997							

Adjusted Trend-Test		Overall p-Value		Comparison Between Doses			Pooled S.D.
Dose Included	p-Value			Placebo	5 mg	10 mg	
Placebo through 20/5 mg	<0.001	<0.001	5 mg	0.006			2.86
Placebo through 10 mg	<0.001		10 mg	<0.001	0.097		
Placebo through 5 mg	0.005		20/5 mg	<0.001	0.007	0.289	

Figure 18. Mean percent changes in one-third wrist (radius + ulna) BMD 36 months.

Figure 7 †††

One-Third Wrist (Radius+Ulna) BMD (g/cm²)
 Mean Percent Change, S.E. of the Mean
 (Intention-to-Treat Approach)



The one-third wrist site is made up of cortical bone by more than 95%. The placebo group showed a progressive decrease in BMD over 36 months. At Month 36, the decrease was by 1.8% from baseline (p ≤ 0.001). Compared to change in the placebo group, all ALN-treated groups showed significant increases at Month 36. However, compared to baseline mean values changes, in ALN groups ranged from -0.5% to 0.9% at Month 36. Only significant increase was observed at a dose of 20/5 mg. No significant treatment-by-center interaction was reported. Analysis of data by P-P and modified ITT approaches showed minor variations, but the overall outcome was similar to that of ITT analysis.

2. Stature Sponsor states that a separate stature will be performed that will include and 037.

definitive" evaluation of effect of ALN treatment on pooled data from studies carried out under protocols 035

A summary of results from this study is presented in Table 39 and Figure 19 (vol. 90, Table 33 and Fig. 8, p. D-5722-5722).

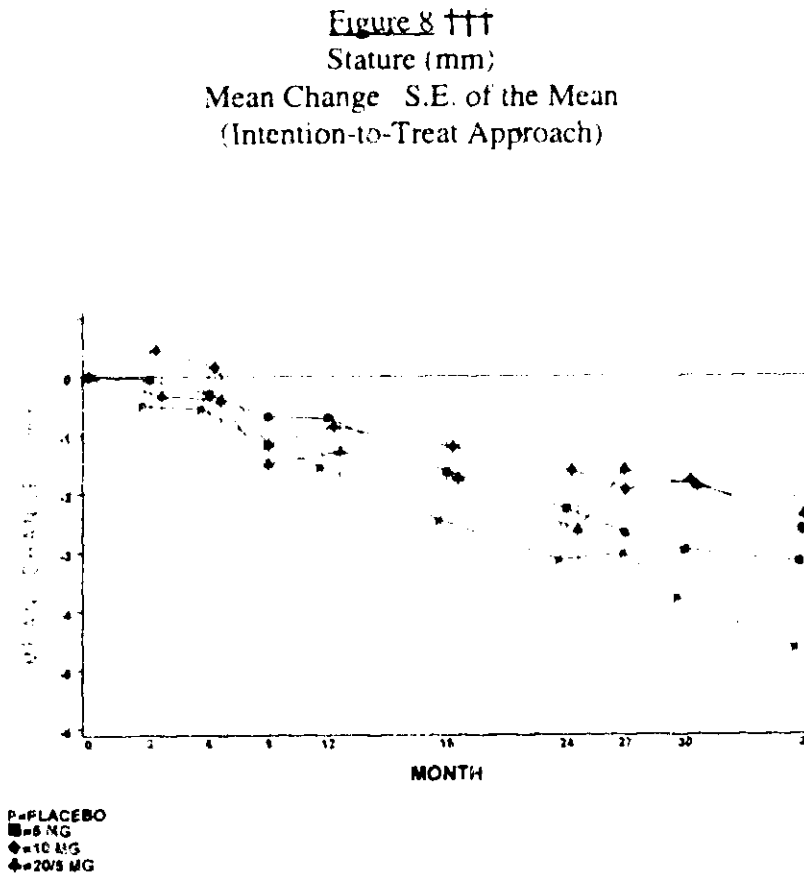
Table 39. Summary of stature analysis (ITT).

Table 33 ††

Summary of Stature Analyses
(Intention-to-Treat Approach)

	Change at Month 36 (mm)		Slope ¹
	Mean	Median	
Placebo	-4.6	-4.4	-1.7
5 mg	-3.2	-2.3	-1.3
10 mg	-2.6	-2.3	-1.0
20/5 mg	-2.4	-1.7	-1.0
p-Value: Placebo vs Pooled Alendronate			
	0.011	0.021	0.007
¹ Mean yearly rate of change in mm			

Figure 19. Mean changes in mean stature over 36 months.



The results from all treatment groups showed a progressive decrease in stature over three years. The placebo group lost about 4.6 mm over three years and ALN 10 and 20/5 mg groups showed significantly less (compared to placebo) loss of stature ($p \leq 0.05$, trend test). The mean yearly rate of change was -1.7 mm for the placebo group and 0.9 mm for the 10 and 20/5 mg groups. Slope analysis indicated a significant ($p = 0.007$) difference between the placebo and pooled ALN group. No significant difference was noted in treatment-by-center interaction. Stature data analyzed by P-P and modified ITT approaches produced similar results.

3. Biochemical efficacy parameters

As previously discussed, biochemical parameters were investigated to provide information on the effect of ALN on bone formation, bone resorption, and mineral homeostasis. These endpoints are not adequate surrogate endpoints for BMD effects of ALN.

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Biochemical endpoints have been analyzed:

- i. To determine the area above the ln (fraction of baseline) curve (AAC) during the first year of study, in order to provide an integral effect of treatment in first year.
- ii. To find out by slope analysis, whether the effect seen on first year is maintained through the third year (i.e., parameter neither increases nor decreases further).
- iii. To determine ln (fraction of baseline) at Month 36 vis-a-vis patient's status at the end of the study period.

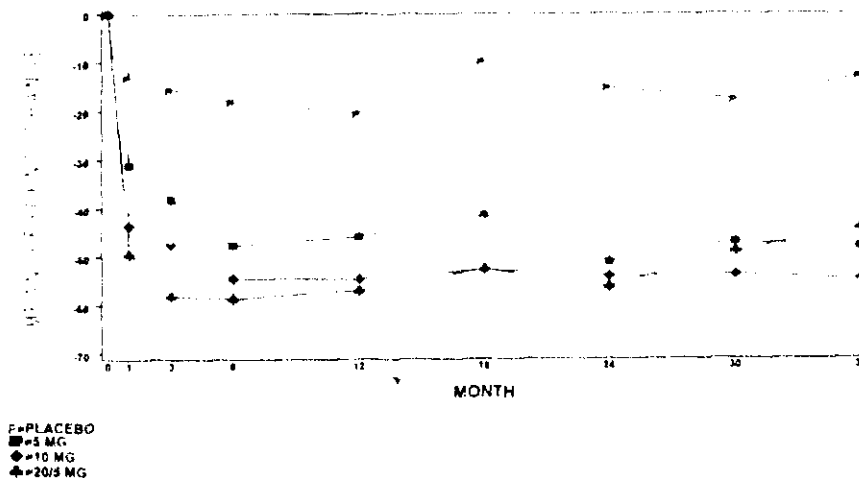
a. Bone turnover markers

1) Urine DPyr (corrected for creatinine)

Figure 19a (Fig.10, vol. 90, p. D-5730) presents the results.

Figure 10 †††

Urine Deoxypyridinoline/Cr (pmol/mg)
 Mean Percent Change S.E. of Mean
 Transformed From Ln (Fraction of Baseline)
 (Per-Protocol Approach)



The results are shown in Table 40.

Table 40. Percent change in DPyr from baseline at 12 and 36 months.

Treatment	No. of Pt.	% Change at Mo 12	% Change at Mo 36	p-Value
Placebo	119	-20.4	-12.9*	* $p \leq 0.001$
ALN 5 mg	61	-45.9	-48.1*	* $p \leq 0.001$
ALN 10 mg	61	-54.7	-54.8*	* $p \leq 0.001$
ALN 20/5 mg	57	-57.5	-44.1*	* $p \leq 0.001$

After 12 months, the response appeared to stabilize in the placebo and ALN 5 mg groups. Response in the ALN 10 mg group was significantly higher than 20/5 mg group at the end of third year ($p \leq 0.023$).

There was no significant treatment-by-center interaction and the results from P-P analysis were similar to ITT analysis.

3) U/Pyr corrected for creatinine U/Pyr is considered to be much less specific marker for bone resorption than DPyr. The results are presented in Appendix 12, Figure 1, Tables 4-7. At Month 36, in the placebo group Pyr did not change much from baseline. Whereas, in all ALN groups, Pyr showed decrease by approx 40%.

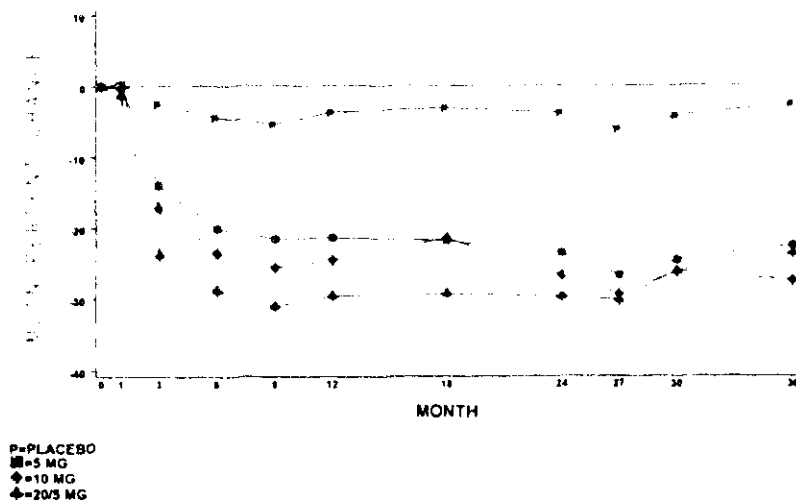
2) Serum alk. phosphatase (SAP)

Figure 20 (Figure 11, vol. 90, p. D-5734) shows the results

Figure 20. Changes in SAP over 36 months (P-P analysis).

Figure 11 †††

Serum Alkaline Phosphatase (U/L)
 Mean Percent Change S.E. of Mean
 Transformed From Ln (Fraction of Baseline)
 (Per-Protocol Approach)



Initially, at the end of 6 months of treatment, SAP levels decreased in all groups and reached a plateau. At Month 36, the SAP in all ALN groups showed decreases from baseline, but sponsor claims that decrease in 10 mg group was greater than that observed in 5 mg group. There was no further decrease in the placebo group from that observed at Month 6 (or from zero). Slope analysis of response in SAP showed 2.2 and 2.6 U/L decreases with ALN at 5 and 10 mg doses during the last two years of treatment. At 20/5 mg dose, there was an increase of 2.8 U/L reported during the final 2 years of treatment. The decrease in SAP appeared to lag behind the decrease in DPyr (a specific marker of bone resorption).

Changes in DPyr and SAP seem to indicate establishment of a new steady-state rate of bone turnover with prolonged treatment with ALN (independent of cumulative amount of ALN incorporated in bone). The important factor in causing suppression of bone turnover is the recently-administered ALN rather than accumulated skeletal load. At ALN 20/5 mg group, SAP decreased after switching to 5 mg in the third year.

4) Serum osteocalcin The results are shown in Figure 21 (Figure 12, vol. 90, 5737). Serum OC reached a new steady-state level at about Month 6 in all ALN groups and this level was maintained throughout treatment period. The percent changes at Month 36 ranged from 37.94% to 51.10% in ALN groups, compared to no change from baseline in the placebo group.

b. Indices of calcium homeostasis and mineral metabolism The results are summarized in Table 41

Table 41. Percent change from baseline in serum calcium, PTH, 1,25 (OH)₂ D, and phosphorus at Month 36.

Treatment	Serum Ca	Serum PTH	Serum 1,25 (OH) ₂ D	Serum Ph
Placebo	+0.9	-4.5	-1.0	1.8
ALN 5 mg	-0.4	-3.5	-0.8	-0.4
ALN 10 mg	-0.8	1.7	12.7	-1.7
ALN 20/5 mg	-0.8	-4.4	2.5	0.9

Urinary calcium excretion in the ALN groups at Month 36 showed no significant difference from that in the placebo group

There was lack of consistency in patterns of changes in these variables. It is difficult to draw any definitive conclusion with regard to the effects of ALN therapy on calcium homeostasis.

4. Correlation analysis There were some weak negative and positive correlations between selected clinical, biochemical and demographic parameters.

5. Subgroup analysis In the following categorical subgroup variables analyses were performed:

- a. Race
- b. Prevalent baseline vertebral fractures (yes or no)
- c. Smoking status (yes or no)
- d. Oophorectomy (yes or no)
- e. Renal insufficiency, creatinine clearance < 54 mL/min (yes or no)

There was no significant treatment-by-subgroup interaction. The relationship between continuous variables (height, weight, body mass index, lumbar spine BMD, etc) and L-spine BMD at Month 36 was also examined. There was no significant treatment-by-covariate interactions.

SAFETY

Safety was evaluated in terms of clinical and laboratory abnormalities.

a. **Overall assessment of clinical AEs**

The results are summarized in Table 42 (Table 39, vol. 90, p. D-5748)

Table 42. Summary of clinical AEs.

Table 39 ††				
Clinical Adverse Experience Summary--Patient Count (%)				
	Placebo (N = 192)	ALN 5 mg (N = 98)	ALN 10 mg (N = 94)	ALN 20/5 mg (N = 94)
Number (%) of patients with one or more adverse experiences	181 (94.3)	92 (93.9)	89 (94.7)	88 (93.6)
With drug-related adverse experiences	42 (21.9)	25 (25.5)	25 (26.6)	29 (30.9)
With serious adverse experiences	35 (18.2)	12 (12.2)	20 (21.3)	14 (14.9)
With serious drug-related adverse experiences	0	0	0	1 (1.1)
Withdrawn from therapy due to adverse experiences	13 (6.8)	3 (3.1)	5 (5.3)	7 (7.4)
Withdrawn from therapy due to a serious adverse experience	5 (2.6)	0	2 (2.1)	2 (2.1)
Withdrawn from therapy due to a drug-related adverse experience	2 (1.0)	3 (3.1)	1 (1.1)	4 (4.3)
Withdrawn from therapy due to a serious drug-related adverse experience	0	0	0	0
Patients who died	0	0	2 (2.1)	0
None of the trend tests performed on this table were 0.1.				

Relatively smaller number of patients in the ALN groups experienced AEs compared to placebo group. The overall results showed no clinically significant differences between various treatment groups with respect to the incidence of clinical AEs, drug-related AEs, and serious clinical AEs. There were 2 deaths in ALN 10 mg dose. These cases will be discussed later on separately. Deaths were either "probably not" or "definitely not" related to ALN.

By body system- Review of the data showed that all treatment groups were similar with respect to occurrence of AEs by body system (Table 40, vol. 90, p. D-5749).

Common clinical AEs- The common reported AEs were respiratory infection, headache, back pain, nausea, and abdominal pain. A trend test was significant ($p \leq 0.05$) with respect to pain, abdominal pain, flatulence, gastroenteritis, and "pain hip" through ALN 20/5 mg dose, and through 10 mg dose with respect to flatulence and abdominal pain.

Serious clinical AEs- One serious AE (abdominal pain) was considered possibly drug-related by the investigator. The patient had a history of upper G-I pain at entry into the study. The pain exacerbated during treatment. An endoscopic examination revealed hiatal hernia. Study drug was interrupted for about three weeks and the patient was treated with ranitidine. After about three weeks the study drug was restarted. Patient experienced acute upper abdominal pain while supine. The drug code was broken. The patient was on ALN 20 mg /day.

The sponsor has provided information on 6 patients who experienced serious G-I AEs (esophagitis, indigestion with hematemesis, gastric erosion, vomiting, pancreatitis) during the course of treatment. Two of these six patients received placebo. In the remaining four patients there was no evidence to indicate a direct causal relationship between G-I AEs and ALN treatment. The overall results tend to indicate a "numerical trend" toward increased incidence of drug-related upper G-I AEs in the ALN 20/5 mg treatment group.

Deaths: Two deaths were reported at ALN 10 mg dose. The cause of death in one case was malignant lung cancer and in other brain neoplasm (probably existed for a long time and slow growing). In both cases, ALN treatment was discontinued. According to the investigators, death due to lung cancer was "probably not" drug-related and death due to brain tumor was "definitely not" drug-related.

Fractures

Table 43 Presents the number of patients by treatment group with vertebral fracture adverse events. Vertebral fracture was evaluated by physician at the study site.

Table 43. Summary of vertebral fracture as adverse event .

	Placebo (N=192)	ALN 5 mg (N=98)	ALN 10 mg (N=94)	ALN 20/5 mg (N=94)
No. (% of Pt. with Vt. Fx.)	27 (14.1)	19 (19.4)	11 (11.7)	7 (7.4)

With regard to proportion of patients with vertebral fractures (T9-L1), the results of a trend analysis indicated significant negative trends "across treatment groups through 20/5 dose at T4 and T 7 levels.

With regard to nonvertebral fracture incidence, all treatment groups were reported to be similar.

Skin rash- About 1.7% of patients had rashes considered possibly, probably, or definitely drug-related by the investigator. There was no clear trend across treatment groups with regard to proportion of patients with "one or more rashes, drug-related rashes, or specific types of rash."

b. Overall assessment of laboratory AEs

Of a total 478 patients who entered into the study, 4 patients (1 in placebo, 2 in 10 mg, and 1 in 20/5 mg groups) were reported to discontinue, before the first visit to the clinic. The results are summarized in Table 44.

Table 44. Summary of laboratory AEs.

	Placebo (N=192)	ALN 5 mg (N=98)	ALN 10 mg (N=94)	ALN 20/5 mg(N=94)
No. Pt. with one lab. test post baseline	191	98	92	93
No. (% of Pt. with one or more AEs	51 (26.7)	24 (24.5)	26 (28.3)	19 (20.4)

No serious drug-related laboratory AEs were reported. A total of 24 patients (5.1%) were reported to have possibly, probably, or definitely drug-related AEs. Ten patients (5.2%),

nine (9.2%), two (2.2%), and three (3.2%) patients in the placebo, 5 mg, 10 mg, and 20/5 mg doses, respectively. One patient in the placebo group was reported to withdraw from the study due to drug-related AEs. Of 14 patients who received ALN 5 mg daily during third year of treatment, none had any "serious or drug-related" AEs.

Laboratory AEs by test abnormalities- The distribution of patients in various treatment groups remains the same. Increases in U/WACS and serum ALT were the most commonly reported laboratory AEs with an incidence of at least 5% in any treatment group. Trend test analysis of data showed no significant trend through 10 mg dose with respect to increase in ALT, AST, or decrease in TSH. But a significant positive trend was reported for changes in AST and ALT through 20/5 mg dose. Also significant positive trend was reported through 20/5 mg dose with respect to U/ protein excretion. The proportion of patients with proteinuria in 10 mg dose did not reach a significant level. Two patients in this group experienced proteinuria, one had a history of bladder prolapse with intermittent hematuria and pyuria (required surgical repair in third year of treatment), and the second patient had prestudy history of proteinuria which did not get worse. Both 10 mg and 20/5 doses showed significant positive trend with regard to decrease in serum calcium level. None of the hypocalcemic episodes were symptomatic.

Laboratory AEs considered drug-related- There was no significant difference among treatment groups regarding the proportion of patients with possibly, probably, or definitely drug-related laboratory AEs.

Vital signs- No significant change (from baseline) in blood pressure and pulse rate was reported at Month 36.

Predefined limits of change during treatment- The 20/5 mg dose of ALN showed a significant trend with regard to proportion patients (12.9%) with a value greater than the upper limit of normal (and $\geq 20\%$) in WBC count. The placebo, 5, and 10 mg groups were reported to show no significant difference.

A significant proportion of patients (55.5%) in 10 mg group experienced decrease (less than lower limit of normal) in corrected serum calcium levels. In the 5 and 10 mg doses significant changes from baseline were reported at the end of Month 36. Treatment groups were reported to be similar with respect to all other predefined limits of change analyses.

Bone biopsy- See review of "special histomorphometry report."

Sponsor's discussion

Osteoporosis is a disease of low bone mass. Therefore, measurement of BMD of lumbar spine by DXA was chosen as the primary efficacy endpoint of the study. Prospective epidemiological studies have shown "good correlation between low bone mass (measured as BMD) and increased risk of fracture." A decrease of 1 SD in total femoral BMD has been reported to increase age-adjusted risk for hip fracture by 2.6 times in elderly postmenopausal women. A

decrease of 1 SD in BMD increases the risk of hip, vertebrae, and skeletal (at any site) fractures by 50% to 160%, 100%, and 50% to 120%, respectively.

Alendronate therapy-induced effect on BMD should therefore, decrease the risk of fracture rate. This study was neither adequately powered nor long enough to assess the efficacy of alendronate for reduction in fracture risk as an endpoint. Fracture intervention trials are ongoing.

Effect of alendronate therapy on BMD- In this study, patients treated with ALN at doses of 5, 10, and 20/5 mg /day for three years showed significant mean increases (from baseline) in lumbar spine BMD (primary efficacy endpoint) by 5.6%, 9.6%, and 7.9%, respectively at Month 36. In contrast, the placebo treated group showed a significant decrease (0.6%) over the corresponding period. The 10 and 20/5 mg doses indicated comparable efficacy (greater than 5 mg dose) during the first 2 years of treatment. The results of this study tend to confirm the "positive effects of alendronate on lumbar spine BMD" in another study carried out in osteoporotic postmenopausal women (Study # 037).

Increase in lumbar spine BMD was very rapid during first 3 to 6 months of alendronate treatment, with a progressive increase over second and third years of treatment. Changes in spinal BMD of placebo group was non-significant during Years 2 and 3. The third year data showed maximum increase in lumbar spine BMD in 10 mg dose, indicating the BMD effect was related more to the current dose of ALN rather than cumulative dose which was about 50% higher in 20/5 mg dose group. Alendronate possibly allowed formation to exceed reduced resorption, thus generating a net positive balance in skeletal mineral content.

The observed difference of about 10.2% increase (relative to placebo) in BMD of L-spine at 10 mg dose at Month 36 is approximately 1 SD, and this magnitude of positive effect is likely to decrease the fracture risk by about 50%. Since increase in BMD occurred gradually over 3 years, the fracture risk should also decrease gradually. The calculated relative risk of incident vertebral fractures over 3-year study should be 20% to 30% lower in patients treated with ALN.

There was no subgroup of ALN-treated patients with "different" response to therapy.

Using the ITT analysis, approx. 94.3% of patients in the 10 mg dose of ALN, demonstrated a $\geq 4.0\%$ increase in spine BMD. This suggests that almost all patients treated at this dose responded positively.

Alendronate treatment increased BMD at all sites of proximal femur. The BMD at femoral neck increased by 4.7% from baseline (6.2% relative to placebo) in 10 mg dose at Month 36. The placebo group lost about 1.5% during the same period. Furthermore, all doses of ALN showed progressive increase in BMD over the second and third years of the study. At the trochanter site, there was about 8.3% difference (increase) in BMD relative to change in the placebo group. This difference was as large as observed with changes in lumbar spine BMD. At all femoral sites 10 mg and 20/5 mg dose exhibited comparable efficacy (both greater than 5 mg dose) over the first two years of study. But at 10 mg, BMD continued to rise during the third year and the response was greater than

that seen with 5 mg dose. If the assumed relationship between loss in hip bone mass and increased fracture risk (2.5 fold relative risk per 1 S.D. loss) holds good as reported in the published studies, then one would expect a 20% to 30% decrease in the risk of hip fracture over three years.

Increase in total body BMD as a result of ALN therapy and a modest decrease in the placebo group over three years seems to indicate that increase in spinal proximal femoral sites did not happen as a result of redistribution of bone from one site to another.

At one-third distal forearm site (> 95% cortical bone), only at 20/5 mg dose there was a significant increase in BMD from baseline over three years. At 10 mg dose, ALN treatment seems to prevent loss of bone as noted in the placebo group.

In summary, ALN treatment resulted in significant increases in BMD at all skeletal sites (spine, total hip, total body, and forearm) investigated. Lumbar spine BMD showed greatest increase. In terms of dose response to ALN treatment, 10 and 20/5 mg doses showed comparable efficacy during the first two years and at both doses response was greater than that observed with 5 mg dose of ALN. At 10 mg dose, progressive increase in BMD was consistently noted during the third year. BMD ALN treatment resulted in preservation of cortical bone BMD at one-third distal forearm site.

With regard to the effect of ALN treatment on stature (measured with Harpenden Stadiometer), there was "statistically significant decrease in loss of stature over 36-month course of the study in both 10 and 20/5 mg alendronate treatment group versus placebo." The rate of loss of height/year (from slope analysis) was 1.7 mm/year in placebo group compared to 1.0 mm/year in pooled population of all ALN groups. Additional data on stature will be presented later along with fracture endpoint studies.

Alendronate treatment resulted in decrease (relative to baseline and placebo) of DPyr (a specific marker for bone resorption) within one month of treatment and reached a nadir at that time point. During the second and third year of treatment there were no "clinically significant" increases or decreases in this parameter in placebo, 5 mg, and 10 mg groups. Serum alk. phosphatase (a marker of bone formation) also showed significant decrease from baseline in all groups and decrease was maximum after 9 to 12 months of treatment. The overall results seem to indicate that the magnitude of suppression of formation and resorption markers due to ALN was similar to that reported following treatment with HRT in postmenopausal women and posttreatment levels are similar to those found in premenopausal women.

Alendronate inhibition of bone resorption resulted in increased urinary excretion of calcium and phosphorus and a small decrease in their serum levels. These changes led to slight increase serum PTH and sustained increase in 1,25 (OH)₂ D levels.

Correlation between baseline demographics or biochemical markers and bone density-

- a. A weak negative correlation between age and BMD.
- b. A weak negative correlation between years after menopause and BMD.

c. A weak negative correlation between baseline biochemical markers (SAP and DPyr/Cr ratio) and L-spine BMD.

d. A weak positive correlation between BMD and body weight, height, and BMI.

e. There was no consistent correlation "between levels of biochemical markers of bone turnover and rates of BMD changes," either in placebo or ALN treated groups. Alendronate seems to increase BMD irrespective of baseline high or low bone turnover.

f. No correlation between baseline level creatinine clearance (≤ 60 mL/min) and response to ALN treatment.

The results of this study did not identify a patient population that would require a smaller or higher than 10 mg of ALN daily for the treatment of postmenopausal osteoporosis.

In general, all doses of ALN used in this study were well tolerated. The frequency of specific clinical AEs observed in ALN groups were similar to those experienced by the placebo group. The frequency of discontinuation from the study because of specific types of AEs was also similar in both ALN and placebo groups.

With regard to proportion of patients with one or more upper G-I problems (e.g., gastritis, esophagitis, and mucosal erosion), there was no significant difference among treatment groups. However, proportionately higher number of patients experienced upper G-I problems (considered drug-related) with increasing doses of ALN. Abdominal pain (mild and transient) occurred with significantly greater incidence in ALN 10 and 20/5 mg doses. One patient discontinued treatment due to abdominal pain at a dose of 5 mg, but none at 10 mg dose. None of these AEs occurred at a significantly higher rate at 10 mg doses compared to placebo group. There was one patient in the ALN 20 mg group, who had interruption of treatment due to late episode of abdominal pain. The patient renewed treatment without recurrence of abdominal pain.

About 2.2% to 3.3% of patients in ALN groups experienced mild form of hypocalcemia (transient and asymptomatic). There was a significant trend in the ALN treated groups with respect to number of patients with WBC count exceeding predefined upper limit. These changes were not sustained.

From a safety point of view, there were no significant trends in the incidence of fractures (vertebral or nonvertebral) among various treatment groups of this study. There were some fractures, but none considered to be drug-related.

Sponsor's conclusion;

1. This study provides evidence for "good" safety and tolerability of alendronate at doses of 5, 10 and 20/5 mg / day for three years in postmenopausal women with osteoporosis. At 10 mg dose, there was significantly greater incidence of abdominal pain relative to placebo group. However, abdominal pain did not lead to discontinuation of treatment in this group.

2. Daily administration of ALN at doses of 5, 10, and 20/5 mg for three years resulted in significant and clinically important increases in BMD of L-spine, proximal femur, and total body in the study.
3. Both 10 and 20/5 mg doses of ALN demonstrated comparable efficacy in terms of BMD increase. The effects of 5 mg dose were less compared to the other two doses at most skeletal sites tested.
4. Annual increases in BMD continued at most skeletal sites tested during the second year of treatment and both during second and third years at 10 mg dose. The cumulative dose of alendronate was greater with 20/5 mg dose than 10 mg dose, but BMD increase in the third year with the former dose was less than that observed with 10 mg dose. This shows that "continuous dosing at the same level is required for progressive increases in BMD."
5. Alendronate therapy decreases the loss of stature relative to placebo treated patients.
6. Patients' age ($\geq$ or $\leq$ 56 years) and baseline creatinine clearance values ($\geq$ or $<$ 60 mL/min) showed no difference in the BMD response (efficacy) to alendronate.
7. Daily alendronate administration (at all doses) resulted in inhibition of bone turnover as determined by studying changes in biochemical markers over three years. Inhibition reached "a stable, dose-dependent plateau." The observed changes in biochemical parameters of calcium and mineral metabolism were as expected with a "specific inhibitor of bone resorption."
8. **"Of all doses studied, 10 mg alendronate sodium appears to be the most appropriate dose for the treatment of osteoporosis in postmenopausal women."**

Reviewer's comments and conclusion:

This multicenter controlled study was well designed to demonstrate the safety and efficacy of alendronate sodium at daily doses of 5, 10, 1 and 20/5 mg for up to 3 years in the treatment of postmenopausal osteoporosis.

Selection of lumbar spine BMD as the primary efficacy endpoint was appropriate. As previously discussed, invitro studies have reported good correlation between BMD and bone strengths (Esses et al. J. Bone Min. Res. 1989;4:715-22; Lotz et al. J. Comput.Assist.Tomogr. 1990;14:107-14). The clinical importance of increased BMD depends on its ability to reduce the risk of vertebral fractures. Measurement of BMD at proximal femur has been reported to be a "stronger predictor" of hip fracture than measurements at other skeletal sites. According to our Osteo-Guidelines, the BMD is considered to be a reasonable surrogate provided the study shows increased BMD at axial and appendicular sites, a positive trend in fracture efficacy, and evidence of normal bone strength and quality in preclinical studies.

Bisphosphonates (other than alendronate) have been reported to increase BMD at various skeletal sites including lumbar spine. Based on the mode of action of these compounds, one can reasonably assume that increase in BMD results from filling in of remodeling spaces. Since, bone

formation is coupled with bone resorption in the remodeling process, the effect of any antiresorptive agent on BMD is expected to be self-limiting even at a higher BMD level.

The present study seems to provide evidence of increased BMD of lumbar spine, proximal femur, and total body relative to baseline and placebo over three years. There are considerable variations with regard to the rate of bone loss at various skeletal sites after menopause. In the literature, there are data from both cross-sectional and longitudinal studies. In recent years, two longitudinal studies (Harris and Dawson-Hughes, *Bone Miner.* 1992;17:87-95; Pouilles et al. *Calcif. Tissue Int.* 1993;52:340-3) have reported loss of lumbar spine BMD of about 3% in the first year after menopause, followed by a decrease of about 2% during the second year and thereafter, < 1% by 4 years after menopause. For loss of bone mass at the hip, one longitudinal study (Harris and Dawson-Hughes, *Bone Miner.* 1992;17:87-95) has reported 0.2%/year for the first 2 years after menopause and thereafter, 0.5%/year by 5 years after menopause. Based on results of many epidemiological studies one may expect that preservation of bone mass or an increase in bone mass in this study population is likely to reduce the risk of osteoporotic fractures. At 10 mg ALN dose, a difference of 10.2% from placebo (Approx. 1 SD) after three years of treatment may result in about 50% reduction in the risk of vertebral fracture. With ERT/HRT therapy of postmenopausal women, "an increment of 2-7%" in bone mass has been reported in many prospective controlled studies over $\geq$ 3 years. One study has suggested that if all postmenopausal women at age 65 are treated with estrogens and further bone mass loss could be prevented, and hip fracture incidence reduced by about 73% (Geelhoed et al. *Aust. J. Public Health* 1994;18:153-60).

The increase in BMD of lumbar spine was rapid during the first 6 months of treatment. At 10 mg dose, BMD increase in spine was maximum at Month 36 and that reflected the effect of current dosing of ALN, rather than cumulative exposure to the drug. Increase in BMD continued during the second and third years of treatment. This pattern of response to ALN on BMD is different from that observed with estrogens and salmon calcitonin in similar patient population. With these drugs, BMD changes stabilized after about 24 months. About 94% of patients treated with ALN at 10 mg dose, showed a rise in BMD by $\geq$ 4%.

The BMD at proximal femur (including femoral neck, trochanter, and Ward's triangle) and total body BMD also showed significant increases (although less than spine in % change) over three years of treatment compared to placebo. The response (increase in BMD) to 10 mg ALN was maximum at these sites (similar to lumbar spine site), compared to 5 and 20.5 mg doses. The increase in BMD of proximal hip was progressive over three years similar to lumbar spine BMD.

Both at 10 and 20.5 mg doses, ALN treatment resulted in significant decrease in loss of stature (height) over three years compared to loss in placebo treated patients.

The effects of ALN treatment on biochemical markers reflect two considerations, one related to its mode of action and the other concerning changes in bone metabolism. Initially, all biochemical markers of bone resorption (U/Ca, hydroxyproline, and pyridinolines) decreased as a result of ALN treatment, consistent with antiresorptive action of the drug. The bone formation markers (SAP, OC) showed similar decreases; maximal in 9 to 12 months. During the second and third years of

treatment there was no further decrease in these parameters, indicating a lack of progressive change and a lack of cumulative effect. The magnitude of suppression of these parameters was similar to that reported with estrogen treatment in similar patient population (Lufkin et al. Ann. Intern. med. 1992;117 (1): 1-9).

Changes (decrease due to increased accretion into bone) in serum calcium and phosphate levels are in agreement with the mechanism of action of ALN. Decrease in serum calcium showed a secondary rise in serum PTH level. There were no consistent correlations between biochemical parameters and rates of changes in BMD, either in placebo or ALN treated groups.

Proportionately more upper G-I AEs were (considered drug-related) seen with increasing doses of ALN. About 20.2 % of patients treated with ALN 10 mg dose experienced abdominal pain, but none discontinued treatment due to pain. Among the laboratory AEs noted in this study, decrease in serum calcium level occurred with increased frequency in ALN treated patients. Both the clinical and laboratory AE profiles for ALN in this study appeared to be reasonably well tolerated and benefits seem to outweigh the risks involved.

This study was not designed to assess fracture efficacy of ALN therapy. Nevertheless, there were significant trends noted among treatment groups with respect to vertebral or nonvertebral fractures. The fracture data from this and other pivotal study will be pooled and analyzed also.

From both safety and efficacy point of views, 10 mg/day ALN appears to be the most appropriate dose for the treatment of osteoporosis in postmenopausal women. The study has demonstrated the safety and efficacy (in terms of increases in BMD of lumbar spine, proximal femur, and total body) in the treatment osteoporosis in postmenopausal women.

7.3 Trial #3 (Sponsor's Ref.# D-16)/Protocol # 037

7.3.1 Title: A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to evaluate the safety and effect on bone density of daily oral alendronate for 3 years in osteopenic postmenopausal women.

7.3.2 Objective/rationale and design:

The primary objectives of this study and design are the same as of the controlled study carried out under protocol # 035 (U.S. pivotal study).

7.3.3 Protocol:

7.3.3.1 Investigators/ centers: This is a multicenter study involving a total of 19 centers in 15 countries outside U.S.A. Table 45 lists the investigators and their country.

Table 45. The list of investigators and country.

Investigators	Country
Dr. A. Romanowicz	Buenos Aires, Argentina
Dr. E. Seeman	Victoria, Australia

Table 45 (continued). The list of investigators and country.

Investigators	Country
Dr. H. Broll	Vienna, Austria
Prof. J. DeQuejer	Diepenbeek, Belgium (Site 1)
" "	Pellenberg, Belgium
Prof. A. vermeulen	Ghent, Belgium
Prof. C Nagant de Deuxchaisnes	Bruxelles, Belgium
Dr. M Leite	Sao Paulo, Brazil
Dr. D.C. Cumming	Alberta, Canada
Dr. I. Rodriguez	Santiago, Chile
Dr. J. Leon	Bogota, Columbia
Prof. C.J. Menkes	Paris, France
Prof. P. Meunier	Lyon, France
Prof. R. Ziegler	Heidelberg, Germany
Prof. U. Liberman	Tel Aviv, Israel
Dr. J.C. Peana/Dr. Correa-Rotter	Tlalpan, Mexico
Dr. I. Reid	Auckland, New Zealand
Dr. P. Jaeger	Berr., Switzerland
Dr. D. Hosking	Nottingham, U.K.

All investigators are qualified.

Protocol summary: The protocol for this study was virtually identical to protocol #035. For this report, all data (including the Month 36) received by the sponsor by August 29, 1994 were included (for protocol # 035, data received by July 29, 1994) in the final evaluation. The evaluation criteria, statistical planning and methods for efficacy and safety parameters were almost identical to those of protocol # 035.

7.3.3.2 RESULTS:

Table 46. Number of patients entered into study by treatment groups.

Protocol #	No. of Centers	Placebo	ALN 5 mg	ALN 10 mg	ALN 20/5 mg
Internat. 037	19	205	104	102	105

Baseline patient characteristics are summarized in Table 8 (Vol. 93, pp 7003-7006). The same baseline characteristics were evaluated as in protocol #035. Except for significant differences in number of years since menopause, body mass index, and baseline serum OC levels, treatment groups were similar with respect to other variables.

Table 47. Baseline patient characteristics that were significantly different between treatment groups.

Variable	Treatment	Mean (S.D.)	Median	p-Value
No. Yrs, since menopause	Placebo	15.2 (3.1)	14.0	0.010
	ALN 5 mg	13.3 (7.0)	13.0	
	ALN 10 mg	16.0 (7.7)	15.0	
	ALN 20/5 mg	16.6 (8.8)	15.0	
Body Mass Index (Kg/m ²)	Placebo	24.4 (3.5)	24.1	0.038
	ALN 5 mg	25.0 (3.9)	24.5	
	ALN 10 mg	24.0 (3.2)	23.4	
	ALN 20/5 mg	25.2 (3.4)	25.2	
Osteocalcin (ng/mL)	Placebo	1.76 (1.49)	1.53	0.041
	ALN 5 mg	1.75 (1.66)	1.22	
	ALN 10 mg	1.50 (1.36)	1.03	
	ALN 20/5 mg	2.19 (1.92)	1.87	

The mean number of years since menopause in the ALN 5 mg dose level was much less than those of the other treatment groups. It is unlikely that this difference and other differences with respect to baseline BMI and serum OC had any clinically significant effect on the primary efficacy endpoint of the study.

With respect to baseline demographics, no significant differences between various treatment groups were reported except for the number of patients who reported smoking cigarettes on a daily basis and the proportion of patients with ≥ 1 prevalent vertebral fracture in the placebo and ALN 20/5 mg groups. Cigarette smoking probably will have no significant effect on the primary efficacy endpoint of the study.

Baseline BMD values- No clinically significant differences between treatment groups were reported with respect to lumbar spine, femoral neck, trochanter, total body, L3 lateral spine, Ward's triangle, total hip, ultra-distal wrist, one-third distal wrist (radius and ulna). Densitometric (Lunar and Hologic) measurements were calibrated differently and reported separately (Vol. 93: Table 10, pp.7009-7011).

Baseline biochemical parameters- There was no significant difference between treatment groups with respect to biochemical markers of bone turnover and mineral metabolism.

Secondary diagnosis- Review of all treatment groups showed similar distribution of patients with each of the secondary diagnoses reported. The most common secondary diagnoses included hypertension and a history of hysterectomy.

Prior drug therapy- Calcium carbonate, levothyroxine sodium, and ibuprofen were the most common drugs that any treatment groups received prior to initiation of this study. There was no significant difference between various treatment groups with respect to % of patients with prior drug treatment.

Concomitant drug therapy- All patients received calcium carbonate, 500 mg daily as required by the protocol. A host of concomitant medications were used by the patients of all treatment groups and there was no difference among them with respect to common concomitant medications (anti-infectives, anti-inflammatories, cardiovascular, and CNS drugs).

Patient accounting- Table 48 (Table 15, vol. 93, 15, p. D-7020) shows patient accounting.

Table 48. Patient accounting in the study.

Table 15 ††

Patient Accounting

	Total	Placebo	ALN 5 mg	ALN 10 mg	ALN 20/5 mg
ENTERED: Total (age range)	516 (44 to 84)	205 (44 to 79)	104† (45 to 77)	102 (46 to 84)	105 (48 to 80)
DISCONTINUED: Total	98	38	24	14	22
Clinical adverse experience	32	12†††	8	3	□
Laboratory adverse experience*	2	0	2	0	0
Patient withdrew consent	37	15	9	6	7
Lost to follow-up	13	5	3	3	2
Protocol deviation	6	2	1	2	1
Other	9	4	2	0	3
COMPLETED: 36 months***	418	167	80	88	83

† AN 2005 (5 mg group) inadvertently received drug supplies intended for patient AN 2004 (placebo group). The patient took these placebo tablets for 66 days from Study Days 664 to 730. Although this interruption in treatment has been clearly documented, this patient's data are still all captured in the 5 mg group.

†† Includes one patient, AN 2162 who was randomized to placebo and then switched to open-label 5 mg in Year 3.

* Includes one patient, AN 2195, from the 5 mg group who had associated clinical adverse experiences and is also captured under discontinued due to laboratory adverse experience.

** Includes eight patients discontinued from Center No. 037020.

*** Includes 12 patients who elected open-label treatment during Year 3.

Of total 516 patients who entered the study, 418 (83%) patients completed 36 months of

treatment. Twelve, 8, 3, and 9 patients were reported to discontinue study for clinical AEs. More patients in the placebo group withdrew consent for continuation in the study. Eight patients from one study center (#037020) were discontinued (prior to Month 24) from the study by MAL for protocol-nonadherence, patient noncompliance, and "lack of adequate source documentation to support the case report form." Data from all patients at this center were excluded from the overall efficacy analysis, but included in the safety analysis.

Since all patients did not come for their clinical visits on the exact day, "relative day ranges" were established along the same line as in protocol for the U.S. study (protocol # 035). For this study the same reasons were followed as in the latter study for exclusion of patients in the per-protocol analysis.

Table 49 (modified from Table 17, vol.93, p.D-7024) summarizes the number of patients used in the lumbar spine BMD analysis.

Table 49. Summary of patients analyzed for lumbar spine BMD.

	Placebo N=205	ALN 5 mg N=104	ALN 10 mg N= 102	ALN 20/5 mg N=105
Total No. included				
ITT analysis	188	89	92	92
P-P analysis	136	65	71	69
Mod. ITT analysis	188	89	92	92

Efficacy:

1. BMD Changes- The primary (lumbar spine BMD) and key secondary (femoral neck, trochanter, and total body BMD) efficacy endpoints of this study were similar to those of the study carried out in the U.S. (protocol # 035). In addition, BMD of L3 lateral spine, Ward's triangle, total hip, ultra-distal forearm (radius and ulna), and one-third distal forearm (radius and ulna) was also determined at designated time intervals. Percent changes in BMD from baseline at different time points as in protocol # 035 were evaluated.

a. Lumbar spine BMD (L-spine BMD)- The results are shown in Table 50 (Table 18, vol. 93, p. D-7029) and Figure 21 (Figure 1, vol. 93, p. D-7028).

in the U.S. (protocol # 035). In addition, BMD of L3 lateral spine, Ward's triangle, total hip, ultra-distal forearm (radius and ulna), and one-third distal forearm (radius and ulna) was also determined at designated time intervals. Percent changes in BMD from baseline at different time points as in protocol # 035 were evaluated.

a. Lumbar spine BMD (L-spine BMD)- The results are shown in Table 50 (Table 18, vol. 93, p. D-7029) and Figure 21 (Figure 1, vol. 93, p. D-7028).

Table 50. Percent change in L-spine BMD from baseline to Month 36 ITT analysis).

Table 18 ††

Lumbar Spine BMD
 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	188	0.75	0.75	-0.31	5.54	-0.05	(-0.61, 0.51)
5 mg	89	0.76	0.80	4.87***	4.68	5.15	(4.35, 5.96)
10 mg	92	0.75	0.80	6.84***	5.43	7.16	(6.37, 7.95)
20/5 mg	92	0.75	0.81	7.77***	6.66	8.12	(7.33, 8.91)

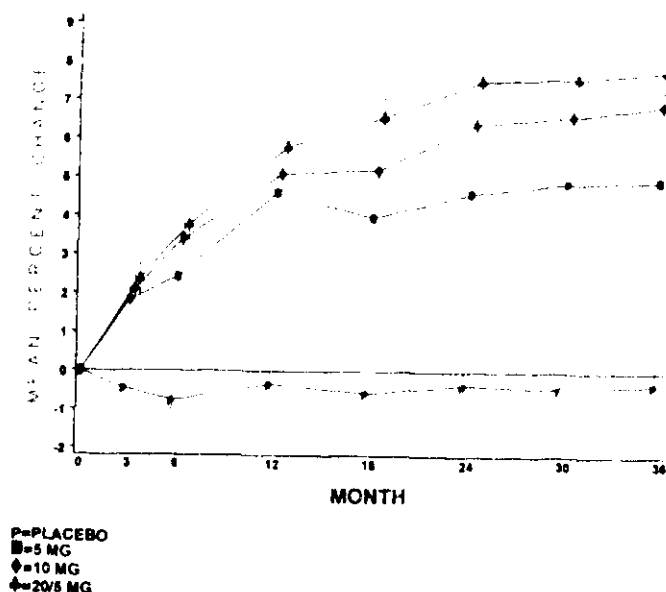
Within-treatment test of mean = 0 ***: p 0.001; **: p 0.01 *: p 0.05
 Treatment-by-center interaction p-value: 0.660

Adjusted Trend-Test		Overall p-Value		Comparison Between Doses			Pooled SD
Dose Included	p-Value			Placebo	5 mg	10 mg	
Placebo through 20/5 mg	<0.001	<0.001	5 mg	<0.001	.	.	5.37
Placebo through 10 mg	<0.001		10 mg	<0.001	0.013	.	
Placebo through 5 mg	<0.001		20/5 mg	<0.001	<0.001	0.226	

Figure 21. Mean Percent change from baseline in L-spine BMD at Month 36.

Figure 1 †††

Lumbar Spine BMD
 Mean Percent Change From Baseline S.E. of the Mean
 (Intention-to-Treat Approach)



The mean increases in BMD from baseline were reported to be 4.9%, 6.8%, and 7.8% at ALN 5, 10, and 20/5 mg doses at Month 36. The placebo group over the same period showed a mean nonsignificant decrease of about 0.3%. The changes in BMD in ALN groups were significant, relative to both baseline ($p < 0.001$) and placebo (< 0.001). In all 3 ALN groups, increases in BMD were significant at Month 12. With 5 mg dose, after 12 months there was practically no further increase during the second and third years of treatment. At 10 and 20/5 mg doses, during the second year there were significant increases in BMD from Month 12. However, during the third year there were nonsignificant increases (range 0.1%-0.6%) in all treatment groups. Though changes between treatment groups showed no significant differences, at 10 mg ALN dose maximum increase in numerical mean (0.56%) was noted. The annual rate of change in BMD is shown in Figure 22 (Figure 2, vol. 93, pad-7032).

In the ALN group more than 92% of patients were reported to manifest an increase in BMD at Month 36, compared to 46.3% in the placebo group. Approximately, 38% and 41% of patients in 10 and 20/5 mg doses achieved almost 8% increase over three years compared to about 7% of

patients in the placebo group. Analyses of spinal BMD data by P-P and modified ITT approaches revealed similar results as seen with ITT analysis. No significant treatment-by-center interaction was reported.

b. Femoral neck BMD- The results are summarized in Table 51 (Table 22, vol.93, p.D-7037) and Figure 22 (Figure 4, vol. 93, p.D-7036).

Table 51. Percent change in femoral neck BMD at Month 36.

Table 22 ††

Femoral Neck BMD
Analysis of Percent Change From Baseline at Month 36
(Intention-to-Treat Approach)

Treatment	N	Means (Observed)		Percent Change From Bas. line			
		Baseline	Month 36	Mean	SD	Adjusted Mean	LSD Interval
Placebo	156	0.67	0.66	-0.53	5.31	-0.55	(-1.13, 0.03)
5 mg	78	0.69	0.71	2.87***	4.90	2.85	(2.04, 3.66)
10 mg	72	0.65	0.68	4.76***	4.96	4.73	(3.89, 5.57)
20/5 mg	83	0.67	0.69	3.60***	6.00	3.57	(2.79, 4.36)

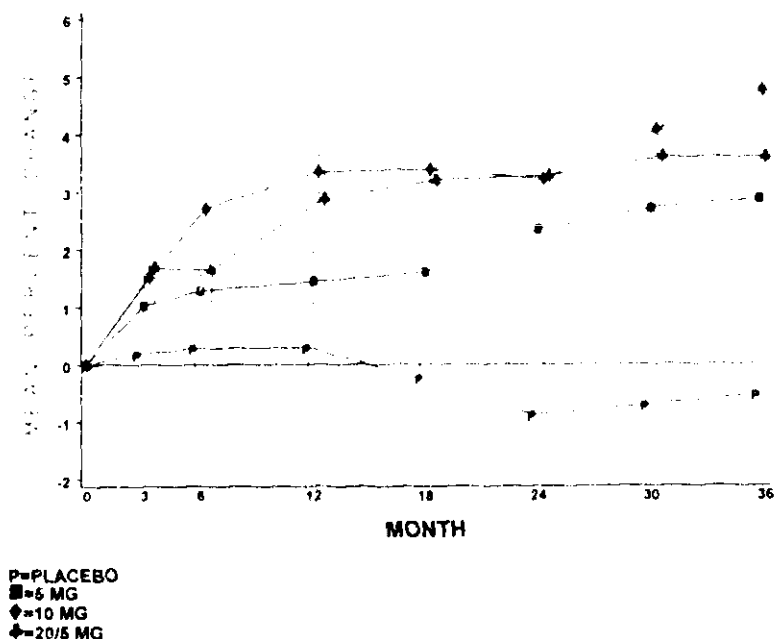
Within-treatment test of mean = 0 ***: p 0.001: **: p 0.01 *: p 0.05
Treatment-by-center interaction p-value: 0.410

Adjusted Trend-Test		Overall p-Value		Comparison Between Doses			Pooled SD
Dose Included	p-Value			Placebo	5 mg	10 mg	
Placebo through 20/5 mg	<0.001	<0.001	5 mg	<0.001			5.05
Placebo through 10 mg	<0.001		10 mg	<0.001	0.024		
Placebo through 5 mg	<0.001		20/5 mg	<0.001	0.365	0.158	

Figure 22. Mean percent change in femoral neck BMD over 3 years (ITT analysis).

Figure 4 †††

Mean Percent Change (S.E.) From Baseline
in Femoral Neck BMD
(Intention-to-Treat Approach)



Femoral neck BMD showed increases (relative to placebo and baseline) as a result of ALN treatment (at all doses) over a 3-year period compared to a nonsignificant decrease from baseline of about 0.5% in the placebo group. The mean increase in 10 mg dose level was greater (4.8% vs 3.6%) than 20/5 mg dose of ALN and significantly more than 5 mg dose. During the third year of the study, ALN 10 mg also showed greater increase (0.9%) compared to 0.5% and 0.3% increases in ALN 5 and 20/5 mg doses.

Analysis of data regarding the proportion of patients who "attained a particular threshold of response at Month 36" revealed an 88% of patients in the ALN 10 mg group with an increase in femoral neck BMD compared to about 47% in the placebo group. However, 44% of patients of ALN 10 mg group and 14.1% of the placebo showed an increase about 5% in BMD (actual increase of 4.8% with 10 mg dose) at Month 36 (see Appendix 21, Table 1, vol.94, p.D-7426).

Per-protocol and modified ITT analysis of data on femoral neck BMD produced similar results as discussed above. No significant difference in treatment-by-center interaction was reported.

c. Trochanter BMD- The placebo group manifested a nonsignificant decrease in BMD from baseline of about 3% over three years. In contrast, the ALN groups showed significant increases in BMD from baseline ($p \leq 0.001$) and placebo (< 0.001) at Month 36. At 10 and 20/5 dose, the increases were 6.8% and 6.9%, respectively. Response was significantly greater than 5 mg dose. During the third year of the study, both 10 and 20/5 mg doses showed increases in BMD by 1.9% and 1.1%, respectively. Whereas, in the placebo and 5 mg ALN groups increases in BMD were not significant. Also, third-year increase in ALN 10 mg was greater than that observed in the second year.

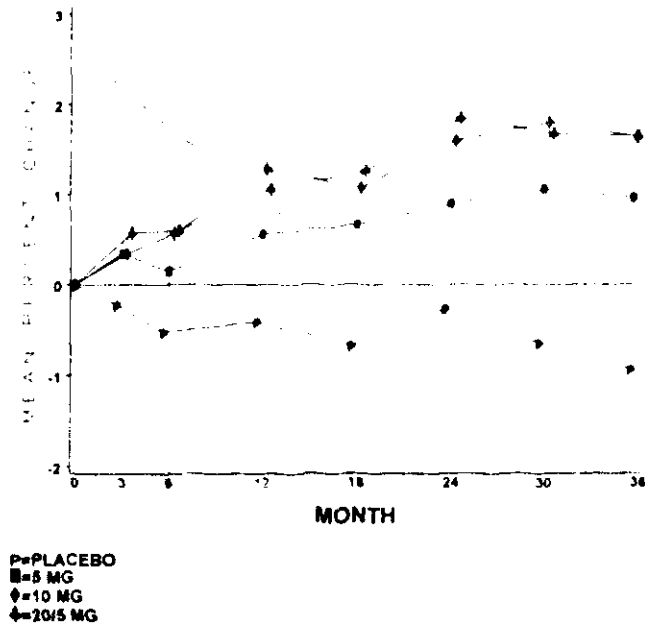
The results were similar with P-P and modified ITT analyses of the data. No significant difference due to treatment-by-interaction was reported.

d. Total body BMD-The results are summarized in Figure 23 (Figure 6, vol. 93, p. D-7046).

Mean percent change in total body BMD from baseline over 36 months.

Figure 6 †††

Mean Percent Change (S.E.) From Baseline
in Total Body BMD
(Intention-to-Treat Approach)



The placebo group was reported to lose total body BMD by about 0.9% over 3 years. The ALN treated groups showed significant increases in BMD from baseline ($p < 0.001$) and placebo ($p < 0.001$) over the same period. The maximum increase of 1.7% was observed in both 10 and 20/5 mg doses. Moreover, increase at latter doses was significantly more than 5 mg. The difference between 5 and 20/5 mg dose was not statistically significant by P-P analysis of data.

All dose of ALN showed significant increases in BMD during the third year of the study compared to a significant loss in the placebo group. There were no differences among ALN groups during the third year of the study.

e. One-third forearm (radius and ulna) BMD (comprised of cortical bone >95%)- The placebo group was reported to lose BMD by about 1.9% at Month 36, and compared to placebo (but not to baseline) all ALN groups showed significant increases over the same period. The overall results seem to indicate preservation of cortical BMD at this site as a result of ALN treatment.

2. Changes in stature: Table 52 and Figure 24 (Figure 8, vol. 93, p.D-presents the results.

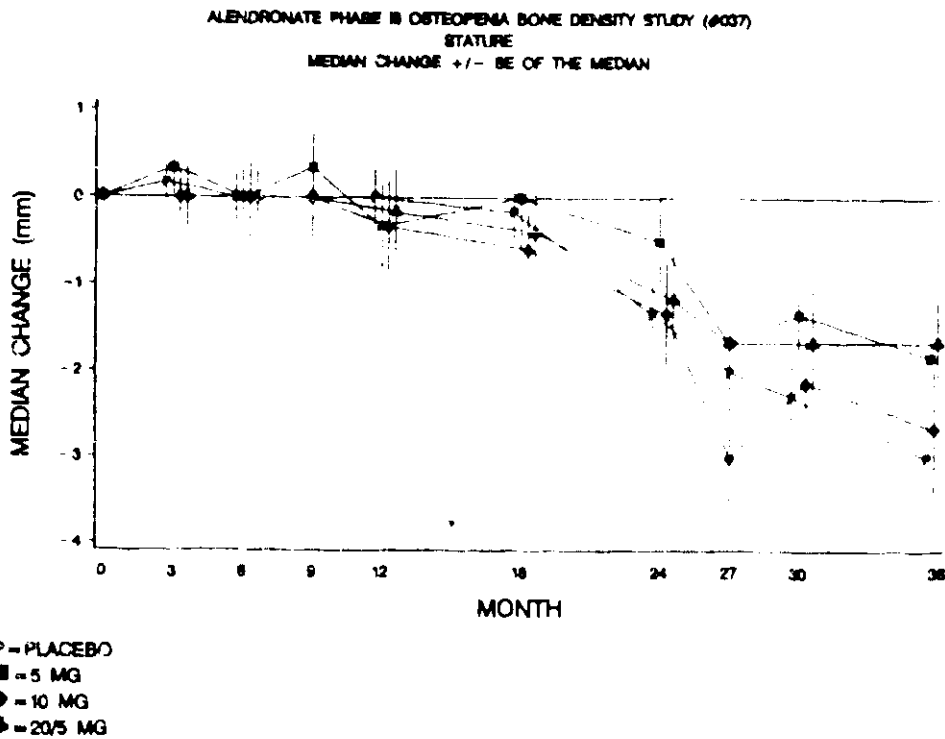
Table 52. Summary of results regarding stature changes.

Treatment	Change From Baseline at Month 36(MM)		Slope (mm/Year)
	Mean	Median	Mean
Placebo	-4.2	-3.0	-1.8
Pooled ALN	-2.8	-2.0	-1.1
p-Value(Placebo vs pooled ALN)	0.108	0.050	0.030

Figure 24. Median values (mm) for stature ±S.E. (ITT analysis).

Figure 8 †††

Stature (mm)
 Median Change S.E. of the Median
 (Intention-to-Treat Approach)



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Serum phosphate-Initial significant decreases from baseline at all doses of ALN during Month 1 and Month 18 and thereafter, returned toward zero at Month 36.

Urinary calcium/creatinine ratio-At Month 1 decreased significantly in all ALN groups. The decreases were of 36.8% and 47.0% at 10 and 20/5 mg doses, respectively. In the placebo group there was a nonsignificant increase at Month 1. At the end of Month 36, the mean changes returned towards zero in all groups including placebo.

4. Correlation analysis

Association between selected clinical, demographic, and biochemical parameters (Tables 1-3, appendix 36, vol. 94)- At baseline lumbar spine BMD was negatively associated with patient's age and number of years since menopause. Lumbar spine BMD was positively associated with patient's body weight, height, and BMI. The correlation analysis showed expected correlation between lumbar spine BMD and clinical, demographic, and biochemical parameters. Within each of the treatment groups, no consistent correlations between baseline values in BMD and biochemical markers and subsequent changes at Month 36.

5. Subgroup analysis

a. Interaction between treatment and prevalent vertebral fracture status- ALN treatment caused increase of lumbar spine BMD from baseline by about 6% to 11% at Month 36 in patients with previous fractures, compared to 5% to 7% increase in the subgroup with no prevalent vertebral fractures. No separate subgroup analysis was done because of small number of patients with prevalent vertebral fractures.

b. Interaction between treatment effect and baseline BMD- There were no consistent treatment effects on lumbar spine BMD at Month 36 among patients with different baseline BMD values. Treatment effects were compared with respect to baseline values below or above the medians. Baseline medians obtained by using Hologic and Lunar machines were evaluated separately. The placebo, ALN 5 and 10 mg had similar effects in both subgroups. The 20/5 mg dose group showed greater effect than 5 and 10 mg doses in patients with baseline BMD $\leq$ median and less effect than 5 and 10 mg doses in patients with baseline BMD $>$ median.

c. Lumbar spine BMD effects in patients with baseline body weight $\leq$ 56 Kg or $>$ 56 Kg- The subgroup of patients who had baseline body weight $\leq$ 56 Kg, the maximum increase in BMD was noted at 20/5 mg dose level. However, for the subgroup of patients with body weight $>$ 56 Kg, there was no difference in response between 10 and 20/5 mg doses. This subgroup analysis however, does not indicate that patients with low body weight require larger dose of ALN.

The overall results of subgroup analyses indicate no clinically significant inconsistency with respect to effect on BMD.

Safety

The safety of ALN therapy was evaluated in the same way as performed in the study carried out under protocol # 035.

1. Adverse experiences (AEs)-clinical- The summary of clinical AEs is presented in Table 53 (Table 46, vol. 93, p. D-7086).

Table 53. Summary of clinical AEs.

Table 46 ††

Clinical Adverse Experience Summary--Patient Count (%)

	Placebo (N = 205)	ALN 5.0 mg (N = 104)	ALN 10 mg (N = 102)	ALN 20/5 mg (N = 105)
Number (%) of patients with one or more adverse experiences	177 (86.3)	89 (85.6)	84 (82.4)	89 (84.8)
With drug-related adverse experiences	59 (28.8)	31 (29.8)	28 (27.5)	33 (31.4)
With serious adverse experiences	34 (16.6)	14 (13.5)	7 (6.9)	18 (17.1)
With serious drug-related adverse experiences	1 (0.5)	1 (1.0)	1 (1.0)	5 (4.8)*
Withdrawn from therapy due to adverse experiences	11 (5.4)	8 (7.7)	3 (2.9)	9 (8.6)
Withdrawn from therapy due to a serious adverse experience	7 (3.4)	2 (1.9)	1 (1.0)	3 (2.9)
Withdrawn from therapy due to a drug-related adverse experience	4 (2.0)	5 (4.8)	2 (2.0)	2 (1.9)
Withdrawn from therapy due to a serious drug-related adverse experience	0	0	1 (1.0)	0
Patients who died	3 (1.5)	1 (1.0)	0	0

This table does not include those adverse experiences that occurred during pretreatment.
* p < 0.05 by trend test through dose.

Table 55. Serious drug-related AEs in 8 patients.

Group	Serious AEs/Drug-related	Comments
Placebo	Diverticulitis	Pt. was on cal. carbonate, AE possibly drug-related
ALN 5 mg	Epigastralgia, nausea, vomiting/antral gastritis with erosive duodenitis	Possibly drug-related
ALN 10 mg	Gastri ulcer with mild hemmorrhage	Probably drug-related
ALN 20/5 mg	AN2624- Abd. pain/cholecystitis	Possibly drug-related
	AN2001- Esophagitis/dysphagia	Esophagitis possibly drug-related
	AN2569-Esophageal spasm	Possibly drug-related
	AN2133-Pyrosis	Possibly drug-related
	AN2008-Gastritis	Possibly drug-related

Deaths- there were four deaths reported in this study. Three in the placebo group and one in 5 mg dose. Causes of death in the placebo group include mediastinitis, (complication of bronchial cyst), MI, septic shock and subdural hematoma and MI in the ALN 5 mg group. None of these deaths were considered as drug-related.

Discontinuation of treatment due to clinical AEs-A total of 31 patients (6.0%) discontinued therapy due to a clinical AEs. Of these 31 patients, 13 discontinued treatment because of possibly, probably, or definitely drug-related clinical AEs. Table 56 summarizes these events.

Table 56. Summary of drug-related AEs that led to discontinuation of treatment.

Group	Clinical AEs N (% of Pt.)	Comments
Placebo	4 (2%) Dyspepsia, nausea, abd. pain, or headache	All possibly drug-related
ALN 5 mg	5 (4.8%) Dyspepsia, acid regurg.,abd. pain,esophagitis,, or nausea	Possib./prob. drug-related
ALN 10 mg	2 (2%) Peptic ulcer/hemorrhage Flatulence	Probably drug-related Definitely drug-related

Upper G-I AEs- Significantly greater number of patients experienced upper serious upper G-I experiences with 20/5 mg dose. Two patients experienced esophagitis, 2 patients experienced dysphagia, and 4 patients experienced odynophagia in the latter group.

Fractures-Fifty-one patients (of total 516 patients) were reported to experience at least one vertebral fracture as an adverse event. Twenty (9.8%) in the placebo, 9 (8.7%) in 5mg, 7 (6.9%) in 10 mg, and 15 (14.3%) in the 20/5 mg groups. The clinical significance of these events are not clear because of small numbers. With regard to nonvertebral fractures there was no clinically relevant trend observed.

Rash-There was no clinically relevant information that need comments.

2. Laboratory AEs

a. An overall assessment of laboratory AEs-The results are summarized in Table 57 (Table 58, vol. 93, p. D-7123).

Table 57. Summary of laboratory AEs.

Table 58 ††

Laboratory Adverse Experience Summary--Patient Count (%)

	Placebo (N = 205)	ALN 5 mg (N = 104)	ALN 10 mg (N = 102)	ALN 20/5 mg (N = 105)
Number of patients with at least one laboratory test post baseline	205	102	99	105
Number (%) of patients with one or more adverse experiences	76 (37.1)	42 (41.2)	40 (40.4)	38 (36.2)
With drug-related adverse experiences	27 (13.2)	18 (17.6)	10 (10.1)	13 (12.4)
With serious adverse experiences	0	0	0	0
With serious drug-related adverse experiences	0	0	0	0
Withdrawn from therapy due to adverse experiences	0	2 (2.0)	0	0
Withdrawn from therapy due to a serious adverse experience	0	0	0	0
Withdrawn from therapy due to a drug-related adverse experience	0	1 (1.0)	0	0
Withdrawn from therapy due to a serious drug-related adverse experience	0	0	0	0

This table does not include those adverse experiences that occurred during pretreatment.

Sixty-eight patients (of total 511 evaluated) were reported to experience drug-related (possibly, probably, or definite) laboratory AEs. All treatment groups were similar with regard to proportion of patients with laboratory AEs. No patients were reported to experience serious AEs. Only one patient in 5 mg group was reported to withdraw from the study due to drug-related AEs (decreased leukocytes).

3. Clinical safety measurements-There were no clinically significant AEs related to body weight, blood pressure, and pulse rate.

4. Laboratory safety measurements

a. Predefined limits of change- The changes (above or below limit) and comparisons were reviewed for hematology (Hbg, Hct, WBC, neutrophils, lymphocytes, monocytes, platelets) and biochemical (serum albumin, creatinine, calcium, phosphorus, sodium, glucose, BUN, AST, ALT) parameters.

Higher proportion of patients in 10 and 20/5 mg groups were reported to experience low (below lower limit of normal) serum phosphorus level.

The overall results showed no clinically significant changes in any treatment groups.

Sponsor's discussion:

The results of this 3-year controlled study demonstrated statistically significant increases (relative to baseline as well as placebo) in lumbar spine (primary efficacy endpoint), femoral neck, trochanter, and total body BMD in postmenopausal osteoporotic women. The effect of ALN 10 mg/day on BMD was greater than 5 mg and was comparable to 20/5 mg dose. The results are in agreement with those observed in studies carried out under protocols # 026 and 035.

Prospective epidemiological studies have reported "strong relationship" between decreased bone mass and increased risk of osteoporotic fractures. It is generally recognized that a 1 S.D. decrease in vertebral and hip BMD approximately doubles the vertebral fracture risk, and a 2.5-fold increase in hip fracture. The patient population of this study at baseline had vertebral BMD ≥ 2.5 S.D. (i.e., $\geq 25\%$) below the mean peak bone mass of premenopausal white women. The observed 6.8% increase (relative to baseline) in lumbar spine BMD at Month 36 with 10 mg dose is likely to reduce the risk of fracture. The results of preclinical studies with alendronate seem to support this expectation. Preclinical bone biopsy data indicated preservation or an increase in bone mass and bone strength in animal osteoporosis models as a result of alendronate treatment. Bone formed during alendronate treatment is normal in quality. Bone histomorphometric data from clinical trials (protocol # 035) also showed "normal bone structure and mineralization" in alendronate-treated patients.

Increases in BMD at both trabecular and cortical (femoral neck) skeletal sites tend to indicate that BMD increase at trabecular site did not occur at expense of cortical bone. The total body BMD also increased simultaneously as a result of alendronate treatment.

Increase in BMD was marked during the first year of treatment and progressively increased thereafter, at spine, femoral neck, and trochanter. At all skeletal sites, the effect of ALN 10 mg dose daily on BMD was found to be greater than two other doses during the third year of treatment. Thus, suggesting that 10 mg ALN dose is most appropriate for the treatment of osteoporosis. The 20/5 mg dose group though received 50% higher cumulative amount of the drug, the 10 mg dose showed better response in terms increase in BMD. This suggest "continuous administration" of optimal dose of the drug in order to achieve expected result on bone mass.

The loss in stature in pooled ALN groups was significantly less than that observed in placebo group after three years of treatment.

The effect of ALN treatment on biochemical markers of bone turnover and parameters of calcium homeostasis and mineral metabolism are consistent with mechanism of action bisphosphonates (antiresorptive agents). Most of initial changes in these parameters returned toward baseline level at Month 36.

With regard to safety of ALN therapy, the drug was well tolerated and the safety profile was similar to that of the placebo.

Sponsor's conclusion.

1. The daily oral alendronate therapy at doses of 5, 10, and 20/5 mg for up to 3 years was generally well tolerated by the postmenopausal osteoporotic women and the safety profile was similar to that observed in the placebo group.

2. Relative to placebo group, all ALN treated groups showed "statistically significant and clinically important" increases in BMD of the lumbar spine, proximal femur, and total body in postmenopausal osteoporotic women. The efficacy of 10 mg dose of ALN was equal to that of the 20 mg. The 5 mg dose was less effective than 10 and 20 mg doses. Alendronate-induced increases in BMD were "progressive over the entire "three-year duration of the study."

3. The efficacy of ALN was similar in all subgroups with respect to age, race, cigarette smoking, oophorectomy status, renal status, baseline calcium intake, number of years after menopause, height, and BMI.

4. The observed changes in biochemical indices of bone turnover were in agreement with the expectations for "a specific inhibitor of bone resorption."

5. The 10 mg dose of ALN produced "greatest increase" in BMD at most sites. Therefore, this dose is the most appropriate dose for the treatment of osteoporosis in postmenopausal women.

Reviewer's comments and conclusion:

The design of this study was almost identical to the 3-year U.S. Study carried out under protocol # 035. This study was conducted in 19 centers involving 15 countries.

Like the U.S. Study, the objectives of this study were to obtain data on the safety and efficacy of ALN at doses of 5, 10, and 20 mg/day for up to three years in postmenopausal osteopenic women. A total of 516 patients enrolled into this study and 418 completed 36 months of treatment. The larger sample size (compared to estimated sample size) at completion of the study increased the power (> 95%) of the study to detect smaller changes from baseline and differences between treatment groups.

The primary and secondary efficacy endpoints were the same as study # 035. The percent changes (increase) from baseline as well as from placebo at Month 36 in BMD of lumbar spine, femoral neck, trochanter, and total body were all statistically significant in all ALN groups from placebo. There was no significant differences between 10 and 20/5 mg ALN groups with regard to percent change from baseline at Month 36 at these four sites. However, these two groups showed statistical difference in response (BMD changes) from 5 mg group. The overall magnitude of response (percent change from baseline at Month 36) to ALN therapy at 10 mg dose at most sites (except for lumbar spine BMD) was very similar to those reported in Study # 035. At the lumbar spine site the percent increase from baseline at Month 36 was slightly less than that reported in the U.S. study (9.6% vs 6.84%). The 6.8% increase in the BMD of lumbar spine at Month 36 as a result of ALN therapy is still clinically significant.

The loss of stature was significantly less in pooled ALN groups compared to placebo.

The biochemical indices of bone turnover started to decrease during the first three months of treatment with ALN. Urinary Dpyr, Pyr, and serum osteocalcin showed an unexpected increase during the second and third year of the study. The sponsor has stated that assay standardization changes, and improper handling of samples (for serum osteocalcin) probably caused such variations. The serum alk. phosphatase level after an initial decrease after 3-6 months of treatment appeared to stabilize at a level with a mean changes of -6.4% to -14.2% from baseline in the ALN treated groups. The results of biochemical endpoints of this study provided information on the effect of ALN on bone turnover. These endpoints provided no evidence for their consideration as surrogate endpoints for BMD effect of ALN.

The safety profile of ALN observed in this study is quite similar to that of the Study # 035. There were no clinically significant differences between placebo and ALN groups with respect to several categories of AEs (e.g., clinical, laboratory), and AEs resulting in discontinuation of treatment. Abdominal pain, headache, and back pain were the most common clinical AEs.

The 20/5 mg ALN group showed a highest proportion of patients with "serious drug-related upper G-I experiences." There was a significant trend ($p \leq 0.5$) in this group with regard to the proportion of patients with dysphagia, esophagitis, and odynophagia.

In conclusion, this controlled study has provided adequate evidence of safety and efficacy (increase in BMD of lumbar spine, femoral neck, trochanter, and total body) of alendronate in the treatment

of osteoporosis in postmenopausal women. The 10 mg daily dose of alendronate appears to be the most appropriate dose for this indication. The occurrence of serious upper G-I AEs, such as dysphagia, esophagitis, and odynophagia should be incorporated in the labeling. Based on our current Osteo-Guidelines, this reviewer feels that the results of these two 3-year controlled trials along with demonstrated preclinical safety data regarding bone quality (comprised of architecture, mass, and strength), provide adequate evidence in support of consideration of its marketing for the proposed indication.

Supportive fracture endpoints

The primary objectives of two pivotal studies (protocols # 035 and # 037) were: a) to demonstrate efficacy in terms of improvement in BMD of lumbar spine, and b) to demonstrate normal quality (histomorphometrically and by the absence of increased fractures due to qualitative defects) of bone during ALN therapy. Neither study alone had adequate power to detect a significant effect of ALN therapy on the incidence of fractures. Therefore, the data from these two identical studies have been pooled for analyses of vertebral fractures, Spine Deformity Index (SDI), and loss of stature.

For vertebral fractures and deformity, lateral spine x-rays at baseline and after 1, 2, and 3 years of treatment were analyzed by computer-assisted digitized method. Changes in vertebral body heights from "first available film to the latest follow-up x-ray" was analyzed blindly (in terms of patient identity and film sequence) at a single radiology center. Six points (3 along superior edge and 3 along inferior edge of each vertebral body) were marked for each of the 14 vertebrae (T4-L5) in order to describe the anterior (Ha), middle (Hm), and posterior (Hp) heights of each vertebral body. These six points represent the 4 corners of the vertebral body and the midpoints of the end plates (See Figure 10).

Prevalent vertebral fracture was defined by comparing patient's baseline vertebral heights with those from a reference population. Change in any vertebral height ratio (Ha/Hp, or Hm/Hp) by more than 3 SD below its corresponding population reference was defined as a prevalent fracture. An incident vertebral fracture was defined as a reduction in vertebral height by at least 20%, or an absolute decrease of a 4 mm (in any vertebral body) between baseline and follow-up.

Vertebral deformity was evaluated by the Spinal Deformity Index (SDI). In measuring the SDI, each vertebral height from T5 through L5 was divided by the "corresponding T4 height (anterior, middle, or posterior)." A maximum 39 vertebral height ratios were obtained. Each height ratio was then compared to population norms. The "absolute differences for those ratios that fall below the minimum population norm are added to express the total SDI." The two treatment groups were compared with respect to the proportion of patients with increased SDI over 3 years.

Stature was measured at baseline and at designated intervals as mentioned earlier with Harpenden Stadiometer.

A post hoc analysis of combined nonvertebral fractures was performed with the data from all Phase IIb/III Treatment Studies.

Results:

Patient accounting in the vertebral fracture and SDI analyses is presented in Table 58 (Table DO-16, vol. 76, p.D-115).

Table 58. Patient accounting in categorical vertebral fracture and SDI analyses.

Table DO-16 ††

	Placebo	Alendronate	Total
Number randomized	397	597	994
Number included in fracture analysis	358	526	881
Number included in SDI analysis	333	502	835
Number (%) excluded from fracture analysis	42 (10.6)	71 (11.9)	113 (11.4)
Number (%) excluded from SDI analysis	64 (16.1)	95 (15.9)	159 (16.0)

Of total 994 patients randomized in two pivotal studies 881 (=88%) and 835 (=84%) of patients were included in the pooled analyses of vertebral fracture and SDI. The patients were excluded from fracture and/or SDI analyses, because of lack of follow-up spine x-rays due to discontinuation from the studies. A small number of patients though remained in the study, but refused follow-up x-rays.

There was no difference between placebo and alendronate groups with respect to baseline patient characteristics (e.g., mean BMD,% with prevalent fractures, mean and median SDI, etc).

Table 59 (Table DO-18, vol. 76, p.D-117) presents the number and percentage of patients with incident categorical vertebral fractures.

Table 59. The number and percentage of patients with incident categorical vertebral fractures.

Table DO-18 ††

Comparison	Placebo *	Pooled Alendronate	RR (95% CI)
Overall	22/355 (6.2%)	17/526 (3.2%)	0.52 (0.28, 0.95)†
Women with prevalent fractures*	13/68 (19.1%)	13/97 (13.4%)	0.70
Women without prevalent fractures*	5/253 (2.0%)	4/384 (1.0%)	0.52
Age <65	9/190 (4.7%)	11/294 (3.7%)	0.79
Age ≥65	13/165 (7.9%)	6/232 (2.6%)	0.33
* The sum of the N for these two subgroups will not equal the overall N, as only subjects with evaluable pretreatment films were included in the baseline demographic analysis for prevalent fractures			
† p = 0.034			
RR = Risk in alendronate-treated patients relative to placebo			

The results indicate a significant ($p=0.034$) reduction in proportion of patients with at least one vertebral fracture in the pooled ALN group compared to placebo. See statistical review for consistency of the results reported by the sponsor. In Study #035 a statistical trend (Table 8 of statistical review) of $p=0.06$ was noted in the ALN group relative to placebo. Such a trend was not seen with the Study #037.

Subgroup analyses of data by the presence or absence of a prevalent fracture and by age ($\geq$ or $\leq$ 65 years) showed qualitatively favorable response in the ALN group.

Table 60 (Table DO-19, vol. 76, p.D-118) shows the fracture results by dose.

Table 60. The number and percentage of patients with incident categorical vertebral fracture.

Table DO-19 ††

Treatment	N Patients With Fracture/Total	Percent	RR
Placebo	22/355	6.2	--
Alendronate 5 mg	5/175	2.9	0.47
Alendronate 10 mg	5/178	2.8	0.45
Alendronate 20/5 mg†	7/173	4.1	0.66
RR = Risk in alendronate-treated patients relative to placebo			
† 20 mg/day for two years followed by 5 mg/day for one year			

The number of patients with incident vertebral fracture was low in all ALN groups relative to placebo. Reanalysis of data (see Table 15 of statistical review) by our statistician also indicated a statistical trend $(p=0.06)$.

All 5 patients in the ALN 10 mg group had one incident categorical vertebral fracture. Table 61 (Table DO-20, vol. 76, p. D-120) shows the number of fractures per 100 patients.

Table 61. The numbers of incident categorical vertebral fractures per 100 patients.

Table DO-20 ††

	Placebo	Alendronate
Number of patients	355	526
Number of vertebral fractures	40	22
Fractures per 100 patients	11.3	4.2

The ALN favored over the placebo group with respect to number of fractures/100 patients: 2.8 vs 11.3.

Spinal deformity index (SDI)-

The results are shown in Table 62 (Table DO-21, vol. 76, p. D.121).

Table 62. The number and percent of patients with increased SDI.

Table DO-21 ††

Study	Placebo	Pooled Alendronate	RR (95% CI)
U.S. Phase III Study	8/177 (4.5)	4/258 (1.6)	0.34 (0.11, 1.06)
International Phase III Study	14/178 (7.9)	13/268 (4.9)	0.62 (0.30, 1.27)
RR = Risk in alendronate-treated patients relative to placebo			

The results indicated higher percent of placebo-treated patients with increased SDI (worsening of existing deformity) over the ALN group (40.5% vs 33.1%). Older patients (≥ 65 years) had higher proportion of patients with increased SDI scores. Analysis of data by utilizing the Wilcoxon Rank Sum Test also showed "a near significant" ($p=0.054$) improvement in SDI change from baseline (see Table 10 of statistical review).

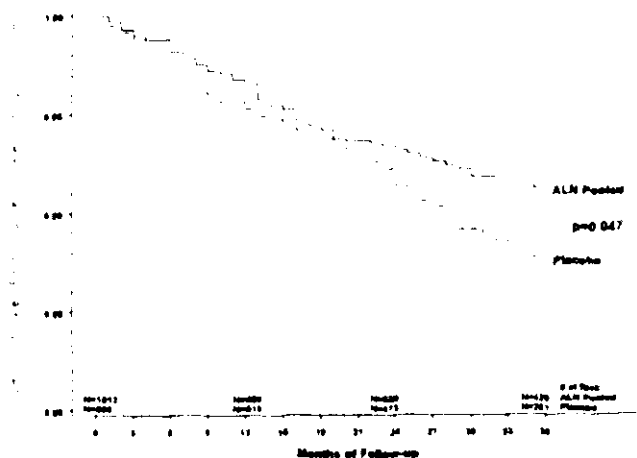
Stature: The results are summarized in Table DO-22 (vol. 76, p. D-123) of this submission and Table 18-23 of our statistical review. In the pooled ALN groups, the mean decrease in the stature was 3.0 mm over 36 months as opposed to 4.6 mm in the placebo ($p=0.005$). Percent change (from baseline at Month 36) in medians, also showed significant ($p < 0.01$)

less decrease in the ALN groups at Month 36, compared to placebo group. The results of slope analysis showed a mean -1.07 mm loss of stature/year in the ALN groups, compared to -1.69 mm/year in the placebo group ($p < 0.001$).

Nonvertebral fractures: In the Primary Phase II studies (#035 and #037), about 7.5% of ALN-treated patients were reported to experience nonvertebral fractures as opposed to 9.6% in the placebo group ($p=0.295$). The results of five Phase IIb/III Studies (lasting for 2-3 years) were pooled and evaluated for cumulative fracture-free survival as a function of time to nonvertebral fracture, using survival analysis method. A total 1012 patients were in the ALN groups and 590 in the placebo. Patients who received ALN at doses of 1, 20, or 40 mg/day were excluded from the analysis. Figure 25 (Figure DO-14, vol. 76, p.D-132) presents the results.

Figure 25. Survival analysis of nonvertebral fractures from five 2 or 3 year trial:

Figure DO-14 ††† Cumulative Fracture-Free Survival as a Function of Time to First Nonvertebral Fracture Phase IIb/III Studies [Refs. D-12; D-15; D-16; D-19; D-23]



The sponsor claims a significant relative risk reduction for nonvertebral fractures in the ALN (pooled) group relative to placebo with a large 95% confidence intervals. The absolute rates of nonvertebral fractures are lower in the ALN than placebo.

7.4 Trial (Sponsor's JO-51)/ Protocol # 054

Protocol summary:

The study design was similar to that of Primary Phase III Studies. Three hundred fifty-nine patients with low spine BMD were randomized to receive, placebo, ALN 1, 2.5, or 5 mg daily for 2 years. In contrast to Phase IIb and Primary Phase III Studies, ALN was administered 30 minutes before breakfast, first food, or medication. In former studies, ALN was administered 1-2 hours before breakfast.

The primary efficacy endpoint of this study was similar to studies # 026,035, and 037. It was also intended to "fully characterize" the dose-response relationship of ALN at lower doses, as well as to examine whether "elderly" osteoporotic patients would require smaller dose, or otherwise respond differently from relatively younger subjects. About two-third of patients enrolled into this study were ≥ 70 years.

The results indicated significant increases (from baseline) in lumbar spine and femoral neck BMD at Month 24. The placebo group showed slight increase (0.5%) in spine BMD during the same period. There was no difference between placebo and ALN groups with respect to occurrence of clinical and/or laboratory AEs.

The results of this study provided supportive evidence for efficacy and safety of ALN at a dose of 5 mg/day. The ALN 1 mg was found to be an ineffective dose, and at 2.5 mg the effect on spine BMD was less than that of 5 mg.

7.5 Trial #5 (Sponsor's Ref. D-191)/Protocol # 041

Protocol summary: A two-year, randomized, placebo-controlled, comparison study in which intranasal calcitonin (sCT) spray was administered to one of the randomized group without blinding. In general, the study population was similar to that of Phase IIb Study (protocol # 026). A total of 286 postmenopausal women (mean age 59.5 years) with baseline lumbar spine BMD of 0.83 g/cm² were randomized. ALN was administered at doses of 10 and 20 mg daily for 2 years and sCT (nasal spray) at a dose of 100 I.U daily. ALN was administered 1 hour before breakfast.

The results indicated increases (from baseline) at 24 months, in spine, femoral neck, trochanter, and total body BMD, comparable to mean values observed in other controlled studies (protocols # 026, 035, and 037) at 10 mg dose. The increase in spine BMD at this dose (10 mg) was less than that reported in other Phase IIb and Phase III Primary Studies. Intranasal sCT group did not increase BMD at any of these sites relative to placebo. The study provided supportive evidence of efficacy and safety of ALN in osteoporotic postmenopausal women.

7.6 Effects on bone quality:

Summary-

Transiliac bone biopsies were obtained at 2 and 3 years from about 133 patients on ALN in Primary Phase III Studies. Additional biopsies were obtained from patients in the Elderly Study. Approximately, 120 biopsies from Phase III Studies were assessed qualitatively and/or quantitatively. For quantitative histomorphometric assessment, the biopsy samples were needed to include adequate trabecular tissue area (i.e., $\geq 20 \text{ mm}^2$ of trabecular area if ≥ 2 trabecular labeled surfaces were present). The important purpose of evaluation of bone biopsy materials was to demonstrate that alendronate has no adverse effect on bone quality.

The results indicated qualitative abnormalities in 24 cases in Phase III Osteoporosis Studies (17 in the U.S. and 7 in the International Study). About 13 of 24 patients in the placebo group had qualitative abnormalities. In the ALN groups, there was no difference between different doses (5, 10, and 20/5 mg) with respect to the occurrence of pathological abnormalities. The following pathological abnormalities were noted: endocrine osteopathy, sarcoidosis, microcallus, Paget's disease, probable hyperparathyroidism, and possible metastatic bone disease. A higher proportion of patients in the placebo group (13.5%) had qualitative pathological abnormalities

compared to ALN groups (8.3%).

The quantitative histomorphometric parameters evaluated for the safety point of view, included osteoid thickness (mean thickness of osteoid seams; OTh), mineral apposition rate (the average rate of progression of active mineralization front; MAR), and osteoid volume (% of bone volume that is unmineralized osteoid; OV).

At Year 2, the mean OTh values (μm) were 11.1, 8.13, 7.73, and 7.56 for the placebo, 5, 10, and 20 mg groups, respectively. At Year 3, the values were not significantly different from those of the Year 2. The OTh values decreased with ALN treatment relative to placebo. OTh values would have shown an increase, if ALN had impaired the mineralization of newly formed bone.

The mean MAR values at Year 2 were 0.61, 0.56, 0.56, and 0.51 $\mu\text{m}/\text{day}$, for the placebo, 5, 10 and 20 mg ALN groups, respectively. At Year 3, the pattern of change in MAR values was not consistent with that of the Year 2. The mean MAR values in the ALN groups were greater than the mean of the placebo group. There was no clear evidence of suppression of MAR by the ALN treatment.

At Year 2, the median values for the OV were 1.42, 0.15, 0.10, and 0.09% for the placebo, 5, 10, and 20 mg groups, respectively. At Year 3, the respective values were 1.12, 0.46, 0.12, and 0.27%. The median values decreased with increasing doses of ALN as expected based on its mechanism of action (in the absence of impairment of mineralization).

Mineralizing surface (% of total bone surface with tetracycline label; MS) is an efficacy related histomorphometric parameter. At Year 2, the median values were 7.57, 0.68, 0.58, and 0.16% for the placebo, 5, 10, and 20 mg groups, respectively. At Year 3, the respective values were 6.37, 2.30, 0.25, and 0.62. Decreases in MS in ALN-treated groups (relative to placebo) could be explained on the basis of its mechanism of action on bone turnover.

The limited bone biopsy data obtained from Primary Phase III Osteoporosis Studies showed lack of adverse effect of ALN on bone mineralization. Additional histomorphometric data from ongoing Fracture Intervention Trial are likely to provide important information on the effect of long-term ALN effects on bone microstructure.

7.7 Proposed package insert

The proposed labeling needs revisions based on comments of the EMDAC. Qualifying statements should be added to the Indications and Usage section to indicate that the efficacy of ALN treatment (in terms of a reduction in the risk of vertebral and nonvertebral fracture) was based on pooled data from the Primary Phase III osteoporosis Studies. Labeling revisions will be undertaken after presentation of the NDA before the EMDAC on July 13, 1995.

7.8 Reviewer's final comments and recommendation

The results from controlled clinical trials of alendronate sodium have provided substantial evidence of efficacy (in terms of significant improvement in spine, hip, and total body bone mass) and safety of the drug for the treatment of osteoporosis in postmenopausal women. The efficacy of the drug in terms of reduction in the risk of vertebral and nonvertebral fractures need to be confirmed by prospective, randomized, controlled studies. See also this reviewer's discussions and comments on each of these controlled studies (Protocols # 026, 035, and 037).

The NDA 20-560, which provides substantial evidence of efficacy and safety of alendronate 10 mg daily for the treatment of osteoporosis in postmenopausal women is approvable. The proposed labeling requires further revisions.


S.N. Dutta, M.D.
Gloria / Hoewle
8-21-95

CC: Orig. NDA 20-560
HFD-340
HFD-510/SND/7.7.1995

NDA 20-560
Alendronate (Fosamax)

Merck Research Laboratories
Review written August 25, 1995

Medical Officer's Review of Safety Update

This safety update was submitted 7-31-95. It contains information on 1942 patients with osteoporosis and 177 with **Paget's Disease**. 660 osteo and 23 Paget's patients were in the core studies and had continued exposure to alendronate beyond that reported in the NDA. There were no newly enrolled patients, but the update includes patients who received placebo during the core studies and then began alendronate for the first time. Cutoff dates for the March 31, 1995 NDA differed with the individual studies as reported in the NDA. The cut-off for data to be included in this update was January 31, 1995. Spontaneous adverse event reports (foreign marketed) and serious adverse experience reports between the NDA cutoff of October 31, 1994 and March 31, 1995 are also reported. Most of the safety data are, therefore, in **osteoporosis patients**. Because Dr. Dutta will review this data, I will be concerned primarily with review of the ADRs in Paget's patients. Also, since Dr. Lutwak will review the safety data presented in the NDA, I will concentrate on additional adverse experiences during the update period. While core osteoporosis studies included 611 patients treated for 3.5 years, only 86 Paget's patients were treated for 6 mo double blind and continued on open-label drug for at least 6 mo. It would be useful to have the ADEs/patient month, because of the wide range of exposure duration.

In one Paget's study (059), it was planned that one group receive 40 mg alendronate and the other group receive placebo for 6 months, then the placebo patients were to receive open-label 40 mg alendronate, and the treated patients were to be followed off drug. However, the treatments were erroneously given to the **wrong groups**, so 22 patients received alendronate 40 mg for more than 9 months and up to 369 days.

Only the 40 mg dose was used during the update period. The 177 Paget's patients (160 continued from NDA) were 43 to 85 years old, and 97 were male, 80 female; 5 were black, 2 other. Concomitant therapies most commonly used were CNS agents (58%), vitamins and minerals (44%), anti-infective agents (41%), cardiovascular drugs (35%), GI agents (21%), anti-inflammatories (18%), water balance agents (18%), endocrine drugs (15%), and autonomic drugs (15%).

In the update period, there was 1 death (esophageal cancer), 5.6% reported serious adverse events, and 7.3% withdrawals due to an adverse event. The death on day 439 of the study followed discontinuation of alendronate therapy at day 389 and diagnosis of esophageal cancer at day 407. He had not received drug from day 183 to day 379. This single death is not informative.

70% reported at least one clinical adverse event (same as NDA).

The most commonly reported events (cumulative, NDA and update) were musculoskeletal pain (32%), abdominal pain (8%), dyspepsia (7%), diarrhea (6%), headache 5.5%, flatulence (5.5%), nausea (5%). None of these were markedly increased in the update period, but musculoskeletal pain increased from 27 to 37%. Abdominal pain, headache, flatulence, and nausea were zero in the update, diarrhea decreased, and dyspepsia increased slightly. It seemed that tolerance might have developed for GI complaints (all digestive system complaints without the abdominal pain were 15 vs 28%). Hypertension increase was reported 1 time in the NDA and 3 post NDA, 0.9 vs 7.5%. Musculoskeletal pain did not increase during the update period (37.5 vs 36.4% of patients). So the only things that even suggest an increased problem with prolonged use are musculoskeletal pain and blood pressure. The osteoporosis population did not show an increase in blood pressure, but used 1/4 the dose used by Paget's. It seems unlikely that this very small number of reports is indicative of any problem.

4/110 (4%) patients had non-fatal serious events in the NDA and 4/40 (10%) in the update. The serious events in the update were 2 episodes of anaphylaxis in one patient, leg pain (lasting 91 days and still present), fracture of femur (fell from ladder), and hypesthesia (still present). The leg pain is probably included in the musculoskeletal pain (See above).

Four patients withdrew from therapy due to adverse experiences, including the cancer death and the serious leg pain. Another had a gastric ulcer, and the fourth had acid regurgitation and dyspepsia.

Laboratory adverse experiences were reported at least once for 34 of the 177 patients; 10 of these reports were in the update period (26% vs 18% in the NDA). No patient in the update period had a serious adverse laboratory experience, or withdrew from therapy because of an adverse laboratory experience. Decreased lymphocytes occurred at slightly higher frequency in the update (5.1 vs 2.8% = 2/39 vs 3/108). Blood urea increased in 4/34 (12%) vs 1/27 (3.7%). All 4 had elevated urea at baseline.

Nonfatal, serious clinical adverse experiences are also reported in 7 patients following the update cutoff: heart failure, malignancy of the pancreas, arthritis, contusion, cataract, skin neoplasm, and prostate neoplasm.

There are no results from this review that indicate any additional safety concerns.

J. Maria T. Spindle
8-30-75

AUG 29 1995

NDA 20-560
Fosamax (Alendronate Sodium)
Merck Research Laboratory

Rev. Completed: 8/25/95

Review and Evaluation of Clinical Data

1. **Name of drug:** Trade: Fosamax
Generic: Alendronate sodium
2. **Dosage form and route of administration:** 10 mg tablets for p.o. use.
3. **Category or use of drug:** For use in the treatment of osteoporosis in postmenopausal women.
4. **Reason for submission:** Safety update report (SUR) to original NDA (Four volumes).
5. **Date of submission:** 7/31/95
6. **Summary review** (This review covers SUR concerning osteoporosis indication):

6.1 Background information:

The NDA 20-560 for Fosamax was submitted on March 31, 1995. The MOR of the NDA was completed on July 7, 1995. On July 13, 1995, the NDA was presented before the Endocrine and Metabolic Drugs Advisory Committee. The Committee recommended approval of Fosamax for the proposed osteoporosis indication.

6.2 This Safety Update Report (SUR) contains the following:

- a. The overview
- b. Integrated summary of safety (Core osteoporosis studies, COS)
- c. Integrated summary of safety (Paget's disease studies)
- d. Adverse experiences from sources other than Case Report Forms
- e. References

a. The overview:

The safety update reporting period was defined as the time between the individual study cutoff dates (See Table 2) through January 31, 1995. This report contains safety data for additional 660 patients "who received continuing alendronate (ALN) therapy for periods up to 2 years." One hundred twenty-six additional patients received ALN under extension studies. These patients previously received placebo in the COS. This report contains data on cumulative ALN experiences in a total of 1942 osteoporotic

patients for up to **3.5 years**. In addition, serious and spontaneous adverse experiences (AEs) from sources other than CRFs were submitted for a period between October 31, 1994 (NDA cutoff date) and March 31, 1995 (SUR cutoff date).

The SUR is divided into following sections:

- Section I - Provides the scope and organization of this report.
- Section II and III - Provides the safety data collected on CRFs from 8 COS.
- Section IV- Provides a summary of serious AEs obtained from sources other than CRFs in the COS. Spontaneous AEs from MRL's postmarketing data were also included in this section.

The patient accounting for the SUR is presented in Table 1 (p.9, vol. 1 of this submission).

Table 1. Patient accounting for the SUR from core osteoporosis studies.

Protocol #	No. of Pt. (ALN only) Reported in NDA	NDA/SUR Duration	No. of Pt. (ALN Only) With SUR Data/ Double Blind	No. of Pt. (ALN Only) With SUR Data/Open Label	Cumulative
035	286 (291*)	3yr/0.5yr	0	25	299
037	311 (320*)	" "	5	0	320
026	157	2vr/0.5yr	0	118	177
029	357	1yr/2yr	327	0	360
038	234	0.5yr/1.5 yr	115	0	235
041	140	2yr/0.5yr	0	194	234
054	268	2yr/0.5yr	0	2	268
062	49	0.25yr/0 yr	0	0	49
Total	1802		447	339	1942

*1816 patients received ALN (including 1802 initially assigned to ALN plus 14 patients who crossover from the placebo group during the 3rd year of the study).

The numbers in the Cumulative data column do not equal the sum of patients in the NDA and SUR columns. The patients who contributed data in both the NDA and SUR periods were counted only once in the Cumulative column.

There were five studies (Protocols 026, 035, 037, 041, and 054) in the COS. Most of the new information for SUR was derived from 786 patients enrolled in these studies. Of these 786 patients, 447 patients received ALN in double-blind studies, and 339 patients received ALN in open-label studies. Six hundred sixty of the 786 patients received ALN during the NDA period and continued to receive ALN in the SUR reporting period. One hundred twenty-six patients who previously received the placebo during the NDA period were switched to ALN in the extension studies.

The majority of safety data in the SUR were derived from 442 patients of postmenopausal osteoporosis prevention studies (Protocols 029 and 038). These patients were exposed to ALN 1 to 20 mg/day for up to 2 and 1.5 years in studies 029 and 038, respectively. A total of 339 patients from osteoporosis treatment studies (Protocols 026, 035, 041, and 054) were exposed to ALN (5 or 10 mg/day) for up to 6 months in the SUR reporting period.

Demographic and AE data were presented "as the pooled alendronate experience incidence." Serious AEs and treatment discontinuations were presented by dose of ALN .

Clinical and laboratory AEs were considered drug-related if the investigators assessed the drug causality as definitely, probably, or possibly.

6.2.1 Summary of safety-COS

Table 2. NDA and SUR CRF cutoff dates.

Protocol No.	Cutoff Dates	
	NDA	SUR*
026	5/2/94	
029	9/10/92	
035	7/29/94	
037	8/24/94	
038	10/22/92	
041	9/28/93	
054	7/13/94	
062	8/5/94	

* The SUR cutoff date for protocol 029 was 12/8/94. The cutoff date for all other studies was 1/31/95.

In the COS, patients received ALN for > 36 months, with a longest duration of treatment for 3.51 years (1280 actual days). The mean duration of exposure was about 705 days. In the NDA, the longest duration oral ALN in 1816 patients was 3.17 years (1157 actual days). Table 4 (p. 15, vol. 5.1 of this submission) presents the number of ALN-treated patients by dose and actual months of treatment in the COS. The demographic characteristics of cumulative 1942 patients were "identical" to those for the 1816 ALN-treated patients reported in the NDA.

The demographic characteristics of 442 ALN-treated patients in osteoporosis prevention studies (Protocols 029 and 039) were the following:

Mean age = 51.8 years (range 41 to 60 years).
Race = 87% (386) white, 0.7% (3) black, and 12% (53) of other racial origin.

Regarding secondary diagnoses in the 1942 patients reported in the cumulative database, data were very similar to those for patients in the original NDA. For 126 patients who previously received placebo and crossover to ALN during the SUR period, there were some "minor" differences between two databases about secondary diagnoses.

About 80% of patients in both databases received concomitant therapy. There was no significant difference between two databases regarding the use of "frequent" therapies that included CNS agents, anti-infective agents, vitamins and minerals, anti-inflammatory agents, and G-I agents. All patients received concomitant calcium carbonate.

6.2.2 The incidence of clinical AEs:

Table 3 (Table 8 of this submission, p. 24, vol. 5.1) presents the summary of clinical AEs in ALN-treated patients (COS).

	NDA Data N=1816	SUR Data Doub.-Blind N=447	SUR Data Open Label N=339	Cumulative Data N=1942
No. (%) of Pt. with one or more AEs	1422 (78.5)	351 (78.5)	91 (26.8)	1549 (79.8)
With drug-related AEs	406 (22.4%)	59 (13.2%)	4 (1.2%)	434 (22.3%)
With serious drug-related AEs	12 (0.7%)	0	0	11 (0.6%)
Withdrew from therapy due to serious drug-rel. AEs	61 (3.4%)	5 (1.1%)	0	66 (3.4%)

Because of longer duration of exposure to ALN in the SUR (double-blind) columns, the percentage of patients with AEs or withdrawals was greater in this period than open-label period. The SUR database during the double-blind period was similar to that reported in the NDA.

Analysis of AEs by body system showed "slightly higher frequency" of AEs in the cumulative database compared to the NDA database (see Table 9 of this submission, pp.26-28, vol. 5.1). The cumulative database included 660 of 1860 osteoporotic patients in the NDA who continued to receive ALN for up to 2 additional years. This resulted in increased incidence of AEs in the cumulative database compared to NDA database.

Both in the NDA and cumulative databases the highest frequencies of AEs were about musculoskeletal, respiratory, and digestive systems. The most common AEs reported in the NDA and cumulative databases are presented in Table 4.

Table 4. The most common AEs in the NDA and cumulative databases.

Common AEs	NDA Database (%)	Cumulative Database (%)
Musculoskeletal pain	31.3	33.4
Up. Resp. Infection	18.3	20.7
Headache	13.7	13.7

For the COS, AEs reported during the SUR, and off-drug periods are presented in References 31 and 32 of this submission (pp. 1089-1792, vol. 5.2). These References contain many tables. Review of tables in Reference 32 (presented AEs that occurred during drug-off period) showed no clinically significant AEs which were different from drug-on period covered in the SUR.

6.2.3 The incidence of drug-related clinical AEs:

Table 10 (pp. 30-31, vol. 5.1 of this submission) presents the number of ALN-treated patients with drug-related clinical AEs (with an incidence $\leq 1\%$ in any database category of COS). The drug-related AEs in NDA and Cumulative databases were 22.4% and 22.3%, respectively. The most common AEs reported in these databases include abdominal pain (5.5% and 5.7%, respectively), and musculoskeletal pain (2.7% and 3.0%, respectively).

6.2.4 Serious AEs from case report forms:

a. Deaths- There was no death during the SUR reporting period.

b. Nonfatal serious AEs:

Table 11 (p.34, vol. 5.1 of this submission) presents the number of nonfatal AEs in ALN-treated patients by body system and drug-relationship in the COS. There were no drug-related (considered by the investigators) serious AEs during the SUR (double-blind and open label) databases. All serious AEs (by body systems) during SUR (double-blind and open label) databases were listed in Tables 12 and 13 of this submission (pp.35-40, vol. 5.1). The serious AEs reported in SUR databases were consistent with the AEs reported in the NDA.

In the SUR double-blind database, 5 patients stopped therapy due to serious AEs, but none were considered drug-related. The

serious AEs included the following: fever and arthritis in one patient, fractured radius and ulna (following a fall from bicycle) in one patient, psychotic depression in one patient, and "a retinal defect" in one patient.

6.2.5 Patients discontinued due to clinical AEs:

Table 5. Number (%) of patients discontinued therapy in the SUR databases.

	SUR Database Double-blind N=447		SUR Database Open label N=339	
Discontd. due to AEs	No. of Pt. 16	(%) (3.6)	No. of Pt. 2	(%) (0.6%)

6.3.1 Laboratory AEs in ALN-treated osteoporosis study population:

In the NDA, the laboratory AEs at ALN 10 mg/daily dose were similar to those of the placebo group. The percentages of ALN-treated patients in the NDA and cumulative databases with at least 1 laboratory AE were 27.3% in the NDA and 32.3%, respectively. There were no clinically significant differences between the NDA and cumulative databases with respect to a) drug-related laboratory AEs, b) incidence of serious nonfatal AEs, c) withdrawals due to AEs, and d) withdrawals due to drug-related AEs.

Table 17 (pp.50-53, vol. 5.1 of this submission) presents the number and percentages of ALN-treated patients with laboratory AEs in the NDA and SUR (double-blind and open-label) databases. The following laboratory AEs occurred in increased percentage of patients for the SUR (double-blind) database compared to NDA and cumulative databases: increased serum ALT and AST, increased calcium, increased creatinine, increased GGT, decreased phosphate, and presence of blood in the urine. 5.3). The rates of these AEs in ALN-treated patients were very similar to those of the placebo-treated patients (see Reference 45, pp. 1886-87, vol. 5.3). Additionally, increased blood WBC, increased urine protein, increased urine RBCs, and increased urine squamous cells were reported in the SUR (double-blind) database, compared to NDA and cumulative databases. Increased blood WBCs was not considered drug-related by the investigators.

A total of 42 patients had AEs of increased urine RBCs, urine protein increased, and/or urine squamous cells increased. Most of these patients had experienced these AEs while on placebo during the run-in period, or noticed without a clinical adverse

experience. Review of patients with urinary AEs suggested no possible renal or bladder effects of ALN.

6.3.2 Incidence of drug-related laboratory AEs:

Table 18 (pp.54-56, vol. 5.1 of this submission) presents the number (%) of ALN-treated patients of COS with drug-related AEs. There was no clinically significant difference between the NDA and cumulative databases with respect to percentages of patients with drug-related (considered by the investigators) laboratory AEs.

6.3.3 Serious laboratory AEs:

a. Deaths - There were no deaths attributable to laboratory AEs in either the NDA or in the SUR.

b. Nonfatal laboratory AEs- There were no new nonfatal AEs.

6.3.4 Patients discontinued due to laboratory AEs: One patient was discontinued from the study due to "an increased IgG test" (on Day 95 of the study) during the SUR period. The patient was on ALN 5 mg, and the investigator felt AE "probably not related to" ALN.

6.4.1 Specific safety evaluation:

a. Fractures- There were 4 patients (2 in the SUR double-blind database and 2 in the SUR open-label database) with vertebral fracture AEs. The vertebral fracture AEs were 5.3% and 5.1% in the cumulative database and in the original NDA, respectively. These vertebral fractures were not considered serious or drug-related. One patient fell off her bicycle and fractured her forearm and the other suffered a hip fracture because of a fall "from a ledge while gardening." In the former case, ALN therapy was discontinued about 3 weeks after the fracture. The forearm fracture healed completely over a 9-month period.

b. Upper G-I AEs-The upper G-I AEs (abdominal pain, nausea, vomiting, dyspepsia, and acid regurgitation) occurred at "similar or lower rates" during the SUR databases compared to the NDA database (see Table 9, pp. 26-28, vol. 5.1).

Of 339 patients who received open-label ALN during the SUR period, one patient developed esophagitis while on ALN (10 mg/daily) for about 3 months. The event resolved about 4 weeks after interruption of treatment. The patient resumed ALN therapy without recurrence of esophagitis. Two additional patients discontinued ALN therapy, one developed "severe dyspepsia" and the other had "moderate acid regurgitation."

These G-I AEs were considered "drug related" by the investigator.

6.5.1 Sponsor's conclusion on safety of Fosamax therapy: The overall safety profile of ALN in cumulative database is very similar to that previously reported in the NDA.

6.6.1 Reviewer's comments:

The SUR reporting period was defined as the period between the individual study cutoff dates noted in the NDA through January 31, 1995. There were 660 patients of COS who had continued exposure to ALN beyond that reported in the NDA. In addition, 126 patients who received placebo in the NDA, entered the extension studies to receive ALN. Therefore, a total of 786 patients provided new data in the SUR. Of a total 786 patients, 447 patients received ALN in double-blind studies, and 339 patients received ALN in open-label studies. The longest treatment with ALN was for 3.51 years (1280 actual days). The SUR presented the cumulative clinical and laboratory AEs profiles for a total of 1942 patients (including 1156 patients on ALN with no new data since the NDA). There were no new patients enrolled in the COS since the NDA.

The demographic characteristics of the 1942 patients in the cumulative database were similar to those for 1816 ALN-treated patients in the NDA. There were no major differences between the cumulative and NDA databases about secondary diagnoses and concomitant therapy.

The overall safety profile of ALN for the cumulative database was similar (based on clinical AEs) to that of the NDA. In the NDA and cumulative databases similar percentages of patients experienced at least one AE (78.3% vs 79.8%). Drug-related AEs were 22.4% vs 22.3% of patients in two databases, respectively. The serious nonfatal AEs were 10.0% in the NDA and 10.5% in the cumulative database, respectively. The two databases were quite similar with respect to withdrawals due to AEs (6.3% vs 6.9%). The NDA and cumulative databases were also similar with respect to percent of ALN-treated patients with most common clinical AEs: musculoskeletal pain (31.3% and 33.4%, respectively), headache (13.7% and 14.9%, respectively), abdominal pain (13.3% and 13.7%, respectively). The drug-related (considered by the investigator) common AEs (e.g., abdominal pain and musculoskeletal pain) occurred at similar rates in two databases.

Most of the laboratory AEs (hematology, blood chemistry, U/A, and stool analysis) occurred at similar rates in two databases.

The incidence of vertebral fracture in cumulative database was 5.3%, compared to 5.1% reported in the NDA. Two patients (one in

SUR double-blind and the other in SUR open label) experienced nonvertebral fractures (forearm and hip). Both fractures resulted from fall.

Upper G-I AEs such as abdominal pain, vomiting, dyspepsia, and acid regurgitation occurred at similar or lower rates in the SUR databases (double blind and open label) compared to NDA database. A decreased incidence of abdominal pain in the SUR database seems to suggest its association with the first several months of treatment. The overall upper G-I AEs in the SUR databases were not "uncharacteristic or inconsistent" with the drug-related G-I events reported in the NDA. During the open-label phase of SUR reporting period, only one patient experienced esophagitis after about 90 days of treatment with ALN (10 mg/day). Interruption of treatment resulted in resolution of event, and the patient resumed treatment without recurrence of this AE.

In conclusion, the safety profile of ALN reported in the SUR is similar to that described in the NDA.

6.7.1 Adverse experiences from sources other than CRF (this review covers only osteoporosis studies):

Adverse experiences entered in the Merck Worldwide Adverse Experience System (WAES):

The WAES included:

- a. Serious AEs reported from sources other than COS.
- b. New serious AEs from Merck studies in other patient populations.
- c. AEs from non-Merck studies.
- d. "Commercial" postmarketing AEs.

Deaths and serious drug related (considered by the investigator) AEs were presented in a narrative way (see References in vols. 5.2-6.4 of this submission).

None of the new nonfatal clinical AEs (including 4 fracture events) were considered drug-related by the investigator (see Tables 35 and 36, vol. 5.1 of this submission).

Of four reported fractures (pubic ramus, intertrochanteric, hip, and arm), three were associated with fall. None was considered drug-related by the investigator.

The actions taken regarding study drug therapy were altered in 2 patients in the SUR report. In a patient with an episode of chest

pain due to gastritis, previously reported interruption of therapy was changed to discontinuation. In another patient, previously reported uninterrupted treatment was changed to interrupted during "esophageal disorder" (see Reference 68, vol. 5.4 of this submission).

Currently, nine osteoporosis studies (involving about 8000 patients) are ongoing. From these studies, 12 deaths and 405 nonfatal serious clinical AEs (in about 351 patients) were entered in the WAES. The treatment allocation was unblinded if AE was considered drug-related and unexpected. Otherwise, AEs were reported in a blinded fashion. Information on deaths was provided in Reference 70 (vol. 5.4). Most deaths were attributed to the following causes: carcinoma of pancreas, amyotrophic lateral sclerosis, myocardial infarction, colon cancer, cardiac arrest, lung cancer, or brain tumors. In one patient the probable cause of death was unknown.

New reports and follow-ups, provided no new information to change the safety profile of ALN as described in the NDA.

Adverse experiences were entered in the WAES from periodontal study, pharmacodynamic study in pagetic patients, and 15 oncology studies. Two deaths and one serious AE reported from these studies were not considered drug-related. There were additional deaths or follow-up on previously reported deaths in patients from hypercalcemia of malignancy and bone metastases studies. In all cases, deaths were attributed to underlying malignancies or their complications.

The sponsor has changed the drug-relationship of an episode of hyperglycemia from possibly to drug-related in a diabetic male patient treated for metastatic bone pain.

There are two cases with AEs from marketed use of ALN in Italy and Mexico. One patient developed an increased frequency and severity of asthma attacks after using ALN for about one month. The dose of ALN, indication for its use, and drug-relationship to AE were not known to the sponsor. Another patient (59-year-old woman) with a history of retrosternal burning, developed "odynophagia, dysphagia, and severe retrosternal burning" after the seventh dose of ALN (5 mg/daily). The reporting physician considered it drug-related. The patient recovered upon discontinuation of therapy and initiation of treatment with omeprazole. The follow-up information revealed that the patients "reclined into a supine position" after each dose of ALN.

The clinical AEs entered in the WAES provided no new information to alter the safety profile of ALN as described in the NDA.

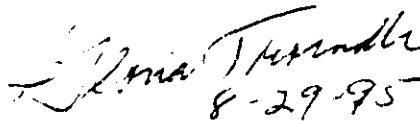
6.8.1 Reviewer's Conclusion and recommendation: Information

provided in the Safety Update Report is consistent with that provided in the NDA. No new clinically significant safety information provided in the SUR for osteoporosis. The safety update report is acceptable.



S.N.Dutta, M.D.

CC: Orig. NDA 20-560
HFD-340
HFD-510/SND/8.24.95.



8-29-95

31

STATISTICAL REVIEW AND EVALUATION

NDA #: 20-560

APPLICANT: Merck Research Laboratories

NAME OF DRUG: Fosamax (alendronate sodium tablets)

INDICATION: Paget's Disease

DOCUMENTS REVIEWED: Volumes 2.1, 2.2, 2.137, 2.138 of NDA 20-560 dated March 31, 1995.

MEDICAL REVIEWER: This review has been discussed with the clinical reviewer, Leo Lutwak, M.D., HFD-510

RELEVANT ISSUES DISCUSSED IN THIS REVIEW

1. Studies 056 and 059 demonstrated that alendronate 40mg daily reduces serum alkaline phosphatase levels significantly more than etidronate 400mg daily and placebo respectively.
2. The safety profile of alendronate was comparable to etidronate and placebo in studies 056 and 059 respectively.

BACKGROUND

The Endocrinologic and Metabolic Drugs Advisory Committee recommended approval of alendronate for the treatment of osteoporosis in postmenopausal women on July 13, 1995.

This approval was based primarily on the results of two multi-center double-blind, randomized, placebo-controlled Phase III studies which were submitted on March 31, 1995.

The sponsor's March 31, 1995 submission also included the results of two multi-center double-blind randomized Phase III studies which were conducted to evaluate the safety and efficacy of alendronate 400mg administered once daily in the treatment of Paget's Disease.

The Division of Metabolism and Endocrine Drug Products (HFD-510) has requested an expeditious statistical review of these studies in order that alendronate may be approved for the osteoporosis and Paget's Disease indications simultaneously.

KEY WORDS: etidronate, geometric mean, logarithmic transformation, Paget's Disease, responder rates, serum alkaline phosphatase, stratification

Study 059

This international multicenter (3 centers) double-blind, randomized, placebo-controlled study was conducted to compare the safety and efficacy of alendronate 40mg administered once daily with that of placebo in the treatment of patients with Paget's Disease of bone.

The primary efficacy parameter was the percent change from baseline in serum alkaline phosphatase levels subsequent to six months of double-blind treatment.

Reviewer's Comments on Study 059

A total of 55 patients (27 alendronate, 28 placebo) were randomized to receive six months of double-blind treatment. Patients were instructed to take one tablet of the study drug each morning at least 30 minutes before breakfast. In addition to the randomized study medication, all patients were provided with daily calcium and vitamin supplements containing 450 to 500mg calcium as carbonate and 400 to 600 IU of Vitamin D. One supplement tablet was taken each evening at mealtime.

Only two patients (both on placebo) failed to complete the six month double-blind treatment phase.

The safety profiles of alendronate and placebo were comparable as 34 patients (16 alendronate, 18 placebo) reported at least one adverse experience during the six month double-blind treatment phase. The most common adverse experience reported by the alendronate patients was headache (4 alendronate, 1 placebo, $p=.28$).

The results of the sponsor's intent-to-treat last observation carried forward primary efficacy parameter analysis are displayed in Table 1. Geometric means are shown as the data was subjected to a logarithmic transformation in order to satisfy ANOVA normality assumptions.

In examining Table 1, one notes that the alendronate patients statistically ($p<.001$) outperformed their placebo counterparts with regard to the primary efficacy parameter. This positive result was consistent across center, gender, and age. All but one patient was Caucasian which of course, prohibits subgroup analysis with regard to racial distinction.

The treatment groups were also compared with regard to protocol-

defined responder rates. In examining Table 2, one notes that the responder rate results are consistent with the primary efficacy parameter results in that there was a highly significant ($p < .001$) difference in favor of alendronate over placebo with regard to these responder rates.

Based on these results, it is apparent that this study was successful in demonstrating that alendronate 40mg administered once daily results in a significantly greater reduction in serum alkaline phosphatase levels than does placebo.

Study 056

This U.S. multicenter (11 centers) double-blind, randomized study was conducted to compare the safety and efficacy of alendronate 40mg and etidronate 400mg administered once daily in the treatment of patients with Paget's Disease of bone.

The primary efficacy parameter was the percent change from baseline in serum alkaline phosphatase levels subsequent to six months of double-blind treatment.

Reviewer's Comments on Study 056

A total of 89 patients were stratified based on prior bisphosphonate or plicamycin use and serum alkaline phosphatase levels. They were then randomized (42 alendronate, 47 placebo) to receive six months of double-blind treatment.

Patients self-administered their study medication orally each morning. In addition, all patients were provided with daily vitamin supplements containing 450mg calcium as carbonate and 400 IU of Vitamin D. One supplement tablet was taken each evening at mealtime.

Fourteen (6 alendronate, 8 etidronate) patients failed to complete the study. All but one of these etidronate patients failed to complete the study due to a clinical adverse experience.

A total of 74 patients (alendronate: 38/42, 90.5%, etidronate: 36/47, 76.6%, $p = .08$) reported at least one adverse experience during the six month double-blind treatment phase. In examining the adverse experience data submitted by the sponsor, only leg pain (1 alendronate, 9 etidronate) yielded a statistically significant ($p < .05$) difference.

The results of the sponsor's intent-to-treat last observation carried forward primary efficacy parameter analysis are displayed in Table 3. Geometric means are shown as the data was subjected to a logarithmic transformation in order to satisfy ANOVA normality assumptions.

In examining Table 3, one notes that the alendronate patients statistically ($p < .01$) outperformed their etidronate counterparts with regard to the primary efficacy parameter. This positive result was consistent across gender, age, and strata. Furthermore, the 79.3% reduction in serum alkaline phosphatase levels experienced by the alendronate patients was comparable to the 70.8% reduction experienced by the Study 059 alendronate patients.

The treatment groups were also compared with regard to protocol-defined responder rates. In examining Table 4, one notes that the responder rate results are consistent with the primary efficacy parameter results in that there was a highly significant ($p < .001$) difference in favor of alendronate over placebo with regard to these responder rates.

Based on these results, it is apparent that this study was successful in demonstrating that alendronate 40mg administered once daily results in a significantly greater reduction in serum alkaline phosphatase levels than does etidronate 400mg administered once daily.

Reviewer's Concluding Comments (may be conveyed to the sponsor)

The results of Studies 056 and 059 indicate that alendronate 40mg administered once daily is statistically associated with a reduction in serum alkaline phosphatase levels. Furthermore, the results suggest that alendronate is generally well tolerated and has a safety profile similar to that of etidronate 400mg/day.

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Concur: Dr. Nevius *SEN 7-30-95*

Dr. Dubey *D 7-31-95*

cc:

Orig. NDA 20-560

HFD-510

HFD-510/SSobel

HFD-510/GTroendle

HFD-510/SDutta

HFD-510/LLutwak

HFD-510 EGalliers

HFD-344-Lisook

HFD-713/SDubey (File 1.3.2 NA)

HFD-713/Group 2 File

HFD-713/DMarticello

Chron.

This review consists of 4 pages of text and 4 pages of tables.

Table 1
 Study 059
 Serum Alkaline Phosphatase (U/L)
 Intent-to-Treat Population

TREATMENT	N	BASELINE MEAN ##	PERCENT CHANGE+
PLACEBO	27#	602.2 (501.0)	8.0 (16.8)
ALENDRONATE	27	680.0 (574.0)	-72.5 (-70.8)*

One placebo patient had no on-treatment data

+ Geometric Mean (adjusted means in parenthesis)

* $p < .001$ in favor of alendronate over placebo. Treatment-by-center interaction p -value=.30

Medians shown in parenthesis

Table 2
Study 059
Responder Rates

TREATMENT	RATE
PLACEBO	0/27
ALENDRONATE	21/27 (77.8%)*

- + A responder is a patient whose alkaline phosphatase has either entered the normal range (as provided by the central laboratory) or has decreased at least 60% from baseline.
- * $p < .001$ in favor of alendronate over placebo.

Table 3
 Study 056
 Serum Alkaline Phosphatase (U/L)
 Intent-to-Treat Population

TREATMENT	N	BASELINE MEAN ##	PERCENT CHANGE+
ETIDRONATE	47	623.1(486.7)	-43.9 (-45.2)
ALENDRONATE	41#	757.4(533.0)	-79.0 (-79.3)*

One alendronate patient had no on-treatment data

Medians shown in parenthesis

+ Geometric Mean (adjusted means in parenthesis)

* $p < .01$ in favor of alendronate over placebo

Table 4
Study 056
Responder* Rates

TREATMENT	RATE
ETIDRONATE	14/47 (29.8%)
ALENDRONATE	36/41 (87.8%)*

- + A responder is a patient whose alkaline phosphatase has either entered the normal range (as provided by the central laboratory) or has decreased at least 60% from baseline.
- * $p < .001$ in favor of alendronate over placebo.

STATISTICAL REVIEW AND EVALUATION

JUN 20 1995

NDA #: 20-560

APPLICANT: Merck Research Laboratories

NAME OF DRUG: Fosamax (alendronate sodium tablets)

INDICATION: Postmenopausal Osteoporosis

DOCUMENTS REVIEWED: Volumes 2.1-2.2, 2.123, 2.125-2.128, 2.134, of NDA 20-560 dated March 31, 1995. Submissions dated May 25, 1995 and June 2, 1995.

MEDICAL REVIEWER: This review has been discussed with the clinical reviewer, Samarendra Dutta, M.D., HFD-510

RELEVANT ISSUES DISCUSSED IN THIS REVIEW

1. The lumbar spine BMD results in Studies 035 and 037 indicate that alendronate is statistically associated with an increase in BMD over 2-3 years of double-blind treatment.
2. The clinical relevance of the alendronate BMD treatment effect needs to be addressed by the clinicians, due to the fact that the placebo patients who received 500mg elemental calcium daily suffered little bone mass loss during double-blind treatment.
3. The pooled fracture-related endpoint results in Studies 035 and 037 indicate that alendronate is statistically associated with a decrease in the new vertebral fracture incidence rate, a decrease in the SDI score, and a reduction in height loss in comparison to placebo.
4. The BMD and fracture-related endpoint results give credence to the sponsor's recommendation to treat patients with alendronate 10mg daily.
5. The results of U.S. Study 035 indicate that alendronate is statistically associated with an increase in flatulence, abdominal pain, hip pain, and pain in general.

KEY WORDS: abdominal pain, calcium, densitometer, digitization, flatulence, hip pain, lumbar spine bone mineral density, new vertebral fracture, nonparametric, open-label, power, spine deformity index, stadiometer, stature

BACKGROUND

The sponsor has submitted the results of five Phase IIb/III studies in support of alendronate in the treatment of postmenopausal osteoporosis.

This submission is scheduled to be discussed at the Endocrinologic and Metabolic Drugs Advisory Committee Meeting on July 13, 1995. At that meeting, a major emphasis will be placed on vertebral fracture-related endpoints.

Consequently, this review will focus on the two primary Phase III Studies 035 and 037 which have fracture data. The remaining 3 studies will be discussed in a subsequent review.

Studies 035 and 037 were double-blind, randomized, placebo-controlled studies which were conducted to "evaluate the safety, tolerability, and effect on bone density and bone and calcium biochemistry, of daily oral alendronate for up to 3 years." Study 035 was conducted in 18 U.S. centers, whereas Study 037 was a 19 center International study.

The original study protocols called for patients to be randomized to receive placebo, alendronate 5mg, alendronate 10mg, or alendronate 20mg for two-years, of double-blind treatment followed by an additional year of alendronate open-label treatment.

During the first year of treatment, it became apparent, that a three-year double-blind study would be necessary to meet certain regulatory requirements for approval in some countries including the U.S. Consequently, the study protocols were amended to allow double-blind treatment to continue for an additional year for all patients who so consented to participate.

Consenting patients who were randomized to receive placebo, alendronate 5mg, or alendronate 10mg continued to receive their randomized double-blind treatment during the third year. However, consenting patients who were randomized to receive alendronate 20mg were blindly switched to receive alendronate 5mg during the third year.

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

The primary efficacy endpoint in Studies 035 and 037 was the

percent change from baseline 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 were included in an intent-to-treat population analysis. The last observation carried forward (LOCF) procedure was utilized for patients who withdrew from the study.

As mentioned above, the original study protocols required all patients to receive open-label alendronate in the third year of treatment. In response to a regulatory request that three-year blinded data should be obtained, patients were asked to consent to enter an amended protocol in which blinded therapy was extended for an additional year. However, it was not considered ethical to withhold open-label treatment to patients who consented to the original study protocol. Consequently, patients had the option of entering a one-year alendronate open-label phase subsequent to the original two-year double-blind treatment phase.

In order to investigate the effect of those patients who decided to receive open-label alendronate 5mg in the third year, the above mentioned LOCF intent-to-treat analysis was also performed (modified intent-to-treat) subsequent to deleting third year data for the open-label patients. The 2 analyses yielded similar results. Consequently, this review will focus on the LOCF intent-to-treat results.

It was recognized prior to the commencement of these studies that they "were not adequately powered singly" and only "moderately powered when pooled" to detect treatment-related differences with regard to the 3 fracture-related endpoints (vertebral fracture, vertebral deformity, stature loss). Therefore, a prospective data analysis plan called for pooling across all active treatment doses, and both studies, for analyses of these 3 fracture endpoints.

Comments on the fracture endpoint results will be made subsequent to discussing the sponsor's BMD results in each of the 2 primary phase III studies.

STUDY 035 BMD RESULTS AND REVIEWER'S COMMENTS

A total of 478 patients (192 placebo, 98 alendronate 5mg, 94 alendronate 10mg, 94 alendronate 20mg) were randomized to receive double-blind treatment. Fourteen of these patients (4 placebo, 3 alendronate 5mg, 3 alendronate 10mg, 4 alendronate 20mg) did not consent to receive an additional year of double-blind treatment and instead chose to receive open-label alendronate 5mg during

the third treatment year. An additional 5 patients declined to participate in the third year of the study in either a blinded or open fashion.

BMD measurements were made with Hologic, Norland, and Lunar densitometers. The Hologic and Norland densitometers provide similarly calibrated measurements whereas the Lunar densitometer measurements are calibrated differently.

A total of 406 patients (including the 14 open-label patients) completed three years of treatment.

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 fact, the alendronate 10mg (sponsor's recommended dose) patients also experienced a significantly greater mean percent lumbar spine BMD increase than did the alendronate 5mg and 20mg/5mg patients.

The above mentioned favorable alendronate BMD results were consistent across center, age group (less than 65, at least 65), race, and densitometer.

The lumbar spine BMD mean percent changes over the 36 month treatment period are illustrated in the graph which follows Table 1 in this review. In examining this graph, one notes that the alendronate BMD increases were most rapid during the first three to six months of double-blind treatment.

However, further annual lumbar spine BMD increases were seen during the second and third years of alendronate treatment. In examining Table 2 which displays the sponsor's annual BMD results, one notes that the sponsor's recommended alendronate 10mg dose statistically outperformed ($p < .001$) placebo in each of the three treatment years. In fact, the alendronate 10mg patients also experienced significantly greater BMD increases in the third year of treatment than did the alendronate 5mg and alendronate 20mg/5mg patients. These results are descriptively displayed in Figure 2 which follows Table 2 in this review.

In the opinion of this reviewer, the clinicians should be aware of the absolute magnitude of the alendronate BMD treatment effect. For example, in examining Table 1, one notes that the placebo mean lumbar spine BMD decreased from $.75\text{g}/\text{cm}^2$ to $.74\text{g}/\text{cm}^2$ whereas the alendronate 10mg lumbar spine BMD increased from $.73\text{g}/\text{cm}^2$ to $.80\text{g}/\text{cm}^2$ over the 36 month treatment period. The clinical significance of the absolute magnitude of the

alendronate treatment effect should of course be addressed by the clinicians.

In this vein, Table 3 which displays percentages of patients who achieved designated lumbar spine BMD changes should be utilized by the clinicians as an aid in interpreting the level of BMD response. For example, in examining Table 3, one notes that 94.3% of the alendronate 10mg patients compared to only 8.1% of the placebo patients experienced at least a 4% increase in lumbar spine BMD. These results are also displayed graphically in the graph which follows Table 3 in this review.

A total of 450 patients (181 placebo: 94.3%, 92 alendronate 5mg: 93.9%, 89 alendronate 10mg: 94.7%, 88 alendronate 20mg/5mg: 93.6%) reported at least one adverse experience during the 36-month treatment period. Twenty-eight (13 placebo: 6.8%, 3 alendronate 5mg: 3.1%, 5 alendronate 10mg: 5.3%, 7 alendronate 20mg/5mg: 7.4%) patients withdrew due to an adverse experience.

Table 4 displays the adverse experiences which were reported by at least 5% of the patients in any treatment group for which a statistically significant ($p < .05$) positive trend was detected across the placebo, 5mg, 10mg, and 20mg/5mg alendronate dosage groups.

Two deaths occurred (brain tumor, lung carcinoma) during the study. Both of these patients were in the alendronate 10mg treatment group.

STUDY 037 BMD RESULTS AND REVIEWER'S COMMENTS

A total of 516 patients (205 placebo, 104 alendronate 5mg, 102 alendronate 10mg, 105 alendronate 20mg) were randomized to receive double-blind treatment. Twelve of these patients (9 placebo, 1 alendronate 5mg, 2 alendronate 10mg) did not consent to receive an additional year of double-blind treatment and instead chose to receive open-label alendronate 5mg during the third treatment year.

BMD measurements were made with Hologic, and Lunar densitometers, which as mentioned above are calibrated differently.

A total of 418 patients (including the 12 open-label patients) completed three years of treatment.

The results of the sponsor's primary efficacy analysis are displayed in Table 5. 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 fact, the alendronate 10mg (sponsor's recommended dose) patients also experienced a significantly ($p=.01$) greater mean percent lumbar spine BMD increase than did the alendronate 5mg patients.

The above mentioned favorable alendronate BMD results were consistent across center, age group (less than 65, at least 65), race, and densitometer.

The lumbar spine BMD mean percent changes over the 36 month treatment period are illustrated in the graph which follows Table 5 in this review. In examining this graph, one notes that the alendronate BMD increases were most rapid during the first year of double-blind treatment.

However, further annual lumbar spine BMD increases were seen during the second and third years of alendronate treatment. In examining Table 6 which displays the sponsor's annual BMD results, one notes that the sponsor's recommended alendronate 10mg dose statistically outperformed ($p<.001$) placebo in each of the first two treatment years. In addition, the alendronate 10mg patients experienced a significantly ($p=.01$) greater BMD mean increase than did the alendronate 5mg patients in the second year. The alendronate 10mg patients also experienced a greater mean BMD increase in the third year than did patients in the other 3 treatment groups although in this case, statistical significance was not achieved. These results are descriptively displayed in Figure 2 which follows Table 6 in this review.

Once again, the absolute magnitude of the BMD response needs to be evaluated by the clinicians. In doing so (by comparing Tables 1 and 5), one should note that the alendronate 10mg 36 month BMD mean is $.80 \text{ g/cm}^2$ in both Studies 035 and 037.

In this vein, Table 7 which displays percentages of patients who achieved designated lumbar spine BMD changes should be utilized by the clinicians as an aid in interpreting the level of BMD response. For example, in examining Table 7, one notes that 62.0% of the alendronate 10mg patients compared to 16.5% of the placebo patients experienced at least a 4% increase in lumbar spine BMD. These results are also displayed graphically in the graph which follows Table 7 in this review.

A total of 439 patients (177 placebo: 86.3% 89 alendronate 5mg: 85.6%, 84 alendronate 10mg 82.4%, 89 alendronate 20mg/5mg: 84.8%) reported at least one adverse experience during the 36 month treatment period. Thirty-one (11 placebo: 5.4%, 8 alendronate 5mg: 7.7%, 3 alendronate 10mg: 2.9%, 9 alendronate 20mg/5mg: 8.6%) of these patients withdrew due to an adverse

experience.

There were no adverse experiences which occurred with an incidence of at least 5% in any treatment group for which a statistically significant ($p < .05$) positive trend was detected across the placebo, 5, 10, and 20mg/5mg alendronate doses.

Four deaths (3 placebo, 1 alendronate 5mg) occurred during the study. The alendronate 5mg patient died due to a myocardial infarction.

Fracture Endpoints

Thoracic and lumbar spine x-rays were collected in Studies 035 and 037 at yearly intervals. To ensure consistency in the evaluation of the films, the available paired x-ray from baseline and the last available follow-up were sent to a central reading laboratory for digitization by technicians blinded to patient identity and treatment allocation. Digitization is a precise measurement of anterior, mid, and posterior vertebral heights using commercially available digitization board and computer software programs. From the height measurements obtained, two forms of analyses for changes in vertebral dimensions were assessed. These were categorical fracture and the spine deformity index (SDI).

In addition, height (stature) was measured using the Harpenden Stadiometer which provides height readings to the nearest mm.

A discussion of the results of each of these 3 fracture related endpoints follows.

Categorical Fracture

A vertebral fracture was defined as a decrease in the anterior, mid, or posterior dimensions of any vertebra by at least 20% and at least 4mm based upon the digitized measurements performed in the central reading laboratory.

As mentioned above, the sponsor's fracture endpoint analysis was based on statistical tests that compared the results of the placebo group with those of the alendronate groups pooled across doses in Studies 035 and 037.

Of the 994 patients whom were randomized to receive double-blind treatment in Studies 035 and 037, 881 had at least 2 x-ray films submitted for digitization. Baseline characteristics of these women were similar to those of the remaining 113 patients.

A total of 39 patients (placebo: 22/355, 6.2%, alendronate: 17/526, 3.2%) had at least one new vertebral fracture as determined from their digitized vertebral heights.

Based on this data, this reviewer derived an odds ratio (alendronate to placebo) of .51 which was statistically significant ($p=.036$) in favor of alendronate over placebo. The corresponding 95% odds ratio confidence interval was (.27, .95).

The new vertebral fracture results discussed above are displayed in Table 8. Results are also shown by study and by age group. In examining this table, one notes that the results numerically favored alendronate over placebo in each case with statistical significance being achieved in the at least 65 age group ($p=.015$). In addition a statistical trend ($p=.063$) was detected in favor of alendronate over placebo in U.S. Study 035.

At this reviewer's request, the sponsor has submitted the vertebral fracture rates by randomized treatment group. These fracture rates are displayed in Table 9. Given that the sponsor's recommended dose is alendronate 10mg once daily, in the opinion of this reviewer, it is critical to examine the alendronate 5mg-placebo and alendronate 10mg-placebo vertebral fracture rate pairwise comparisons. In doing so, one notes the existence of statistical trends (alendronate 10mg versus placebo: $p=.09$, alendronate 5mg versus placebo: $p=.10$) in favor of alendronate 5mg and alendronate 10mg over placebo with respect to the fracture rates pooled over Studies 035 and 037. These results which are displayed in Table 9 indicate that the alendronate 10mg-placebo odds ratio is .44 with a corresponding 95% confidence interval of (.17, 1.15). Each alendronate treatment group in each study has a lower vertebral fracture rate than the corresponding placebo group. However, statistical significance was not achieved due to inadequate power.

Spine Deforming Index

The SDI is a score of spine deformity that evaluates changes in vertebral body dimensions on a continuous rather than a categorical basis. Consequently, the sponsor claims, that this measure may provide evidence of a treatment effect when there are smaller declines in vertebral height than with fracture data.

SDI is obtained by first normalizing each vertebral height to the patient's corresponding T4 height (anterior, mid, or posterior). The height ratios that fall below the minimum value derived from the population norms are summed to express the SDI score. It should be noted that a high proportion of patients (75%) in Studies 035 and 037 do not have any value below the population

norms and, therefore, their SDI is zero. An increase in SDI denotes an increase in deformity.

Of the 994 patients whom were randomized to receive double-blind treatment in Studies 035 and 037, 835 had paired complete x-ray films for which paired SDI values were available. Baseline characteristics of these 835 women were similar to the remaining 159 patients.

As mentioned above, the sponsor's SDI analysis consisted of comparing the alendronate and placebo SDI results pooled over Studies 035 and 037 and over the three alendronate dosage groups.

The sponsor compared the alendronate and placebo results with regard to the proportion of patients who experienced an increase in SDI from baseline. In doing so, the sponsor noted that a significantly ($p=.028$) greater percentage of placebo patients (40.5%) experienced an increase (deformity increased) in SDI than did alendronate (33.1%) patients. In this analysis, the sponsor has merged the "no change" and "decrease" categories. In the opinion of this reviewer, the "no change" and "decrease" categories should not be merged for to do so results in a loss of information. In this case (Table 10), a statistical trend ($p=.075$) was detected in favor of alendronate over placebo.

The sponsor also compared the treatment groups with regard to the change from baseline in SDI by utilizing the Wilcoxon Rank Sum Test as a parametric analysis employing a comparison of arithmetic means was not appropriate due to the high proportion of patients with an SDI value equal to zero. In the opinion of this reviewer, the Wilcoxon Rank Sum Test is more appropriate than the chi-square test as it takes into account the magnitude of the response. In examining Table 10, one notes that the Wilcoxon Rank Sum Test yielded a near significant p-value of .054 in favor of alendronate over placebo with regard to the change from baseline in SDI.

The individual Study 035 and Study 037 SDI results which were submitted at the request of this reviewer are displayed in Tables 11 and 12 respectively. These results are consistent with the new vertebral fracture results (Table 8) in that a statistical trend ($p=.06$) was detected in favor of alendronate over placebo in Study 035.

The results by age group (Tables 13 and 14) which were also submitted at the request of this reviewer are also consistent with the new vertebral fracture results in that alendronate fared relatively better than placebo ($p=.08$) in the at least age 65 group than in the less than age 65 group.

Tables 15-17 display the SDI results by alendronate treatment group as requested by this reviewer. In examining Table 15 (Studies 035 and 037 combined) one notes that the SDI results are consistent with the new vertebral fracture results (Table 9) in that a statistical trend ($p=.06$) was detected in favor of alendronate 10mg over placebo. Statistical significance was achieved in Study 035 Table 16) in favor of alendronate 10mg over placebo ($p=.03$) and in Study 037 (Table 17) in favor of alendronate 5mg over placebo.

Stature

Height was measured in all patients using the Harpenden Stadiometer, which provides height readings to the nearest mm. At each study visit, stature was measured three times, and five times if any of the first three differed by more than 4mm from the other two. All measurements obtained at a visit were averaged.

Of the 994 patients who were randomized to receive double-blind treatment in Studies 035 and 037, 921 had values recorded for stature at both baseline and at least one follow-up visit, and 902 women had values recorded on at least three timepoints.

The results of the sponsor's analysis pooled over Studies 035 and 037 is displayed in Table 18. A nonparametric analysis was performed since the underlying normality and homogeneity of variance assumptions were violated to a significant degree. In examining this table one notes that the alendronate patients experienced a significantly ($p<.01$) smaller median reduction in stature over the 36-month treatment period than did placebo patients. The results were consistent across the 2 studies (Tables 19-20) and a statistical trend ($p<.10$) was detected in favor of alendronate 10mg over placebo in Study 035.

Even stronger results in favor of alendronate over placebo were obtained with regard to a slope analysis which measured the average change per year in height (Tables 21-23).

The alendronate stature treatment effect was more pronounced (as it was for new vertebral fractures and SDI) in the at least 65 age group as statistical significance ($p<.01$) was achieved in favor of alendronate over placebo for each (median change and slope analyses) of the above mentioned analyses. In addition, a statistical trend ($p<.10$) was detected in favor of alendronate over placebo in the slope analysis for the under age 65 population.

Reviewer's Concluding Comments (may be conveyed to the sponsor)

The lumbar spine BMD results in U.S. Study 035 indicate that alendronate is statistically associated with an increase in BMD. The sponsor's proposed 10mg alendronate dose was successful in sustaining a BMD treatment effect over the entire three year duration of the study.

However, the clinical relevance of the absolute magnitude of the alendronate BMD treatment effect should be addressed by the reviewing clinicians as the BMD levels in the placebo patients (who received 500mg elemental calcium daily throughout the study) remained constant during the second and third years of double-blind treatment subsequent to losing less than 1% of bone mass during the first year of double-blind treatment.

In addition, the results of Study 035 indicated that alendronate was statistically associated with flatulence, abdominal pain, hip pain and pain in general.

The lumbar spine BMD results in International Study 037 also indicate that alendronate is statistically associated with an increase in BMD and provide additional statistical evidence in support of the sponsor's proposed alendronate 10mg dosage regimen. However, as mentioned above, the clinical relevance of the ability of 500mg elemental calcium daily (which was administered to the placebo patients) to preserve bone mass over the entire three year duration of the double-blind treatment period needs to be addressed by the reviewing clinicians.

The sponsor's new vertebral fracture rate results pooled across alendronate dosage groups and Studies 035 and 037 indicate that alendronate is statistically associated (odds ratio of .51) with a reduction in the new vertebral fracture rate. This positive result was due primarily to the U.S. Study 035 results where a statistical trend ($p=.063$) was detected in favor of alendronate over placebo (odds ratio of .33). The Study 037 results while not statistically significant were in the right direction (odds ratio of .60). Also, patients at least 65 years of age appeared to benefit (odds ratio of .31, $p=.015$) much more than their less than age 65 counterparts.

Furthermore, the most promising results were achieved by the sponsor's proposed alendronate 10mg dosing regimen which exhibited a statistical trend ($p=.093$) over placebo pooled over Studies 035 and 037 (odds ratio of .44).

The pooled SDI results were highly supportive of the new vertebral fracture rate results in that a strong statistical trend ($p=.054$) was detected in favor of alendronate over placebo. Once again, this positive result was primarily due to the Study

035 results ($p=.06$) as well as to the at least age 65 patient population ($p=.06$). As with regard to the new vertebral fracture results, the most promising results were achieved by the sponsor's proposed alendronate 10mg dosing regimen ($p=.06$).

The pooled stature results were also supportive of the new vertebral fracture rate results in that the alendronate patients lost significantly less height than their placebo counterparts. In particular the alendronate 10mg patients lost significantly less height ($p<.05$) than their placebo counterparts (1.2mm/year versus 1.8mm/year) over the three year treatment period. Once again the alendronate treatment effect was more pronounced (relative to placebo) for the at least age 65 population than for the less than age 65 population.

In conclusion, Studies 035 and 037 were successful in demonstrating the existence of a statistical association between alendronate and a lumbar spine BMD increase as well as a statistical association between alendronate and a positive response with regard to the fracture-related endpoints (new vertebral fracture rate, SDI, stature). Furthermore, the results give credence to the sponsor's recommendation to treat patients with alendronate 10mg daily.

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Mathematical Statistician

Concur: Dr. Nevius *SEN 6-18-95*

Dr. Dubey *6-20-95*

cc:
Orig. NDA 20-560
HFD-510
HFD-510/~~SSobier~~ *RHzelein*
HFD-510/Troendle
HFD-510/Dutta
HFD-510/Lutwak
HFD-510/EGalliers
HFD-344/Lisook
HFD-713/Dubey[File 1.3.2 NDA]
HFD-713/Group 2 File
HFD-713/DMarticello

This review consists of 12 pages of text and 29 pages of tables and graphs.

TABLE 1
STUDY 035

LUMBAR SPINE BMD MEANS (g/cm²)

TREATMENT	N	BASELINE	MONTH 36	MEAN ^a PERCENT CHANGE
PLACEBO	186	.75	.74	-.64 (-.74)
ALENDRONATE 5MG	89	.73	.77	5.60* (5.57)
ALENDRONATE 10MG	88	.73	.80	9.58*+ [#] (9.54)
ALENDRONATE 20MG/5MG	86	.75	.80	7.88*+ (7.79)
				P<.001

* p<.001 in favor of alendronate over placebo. Treatment-by-center interaction p=.63

+ p<.001 in favor of alendronate 10mg and alendronate 20mg/5mg over alendronate 5mg

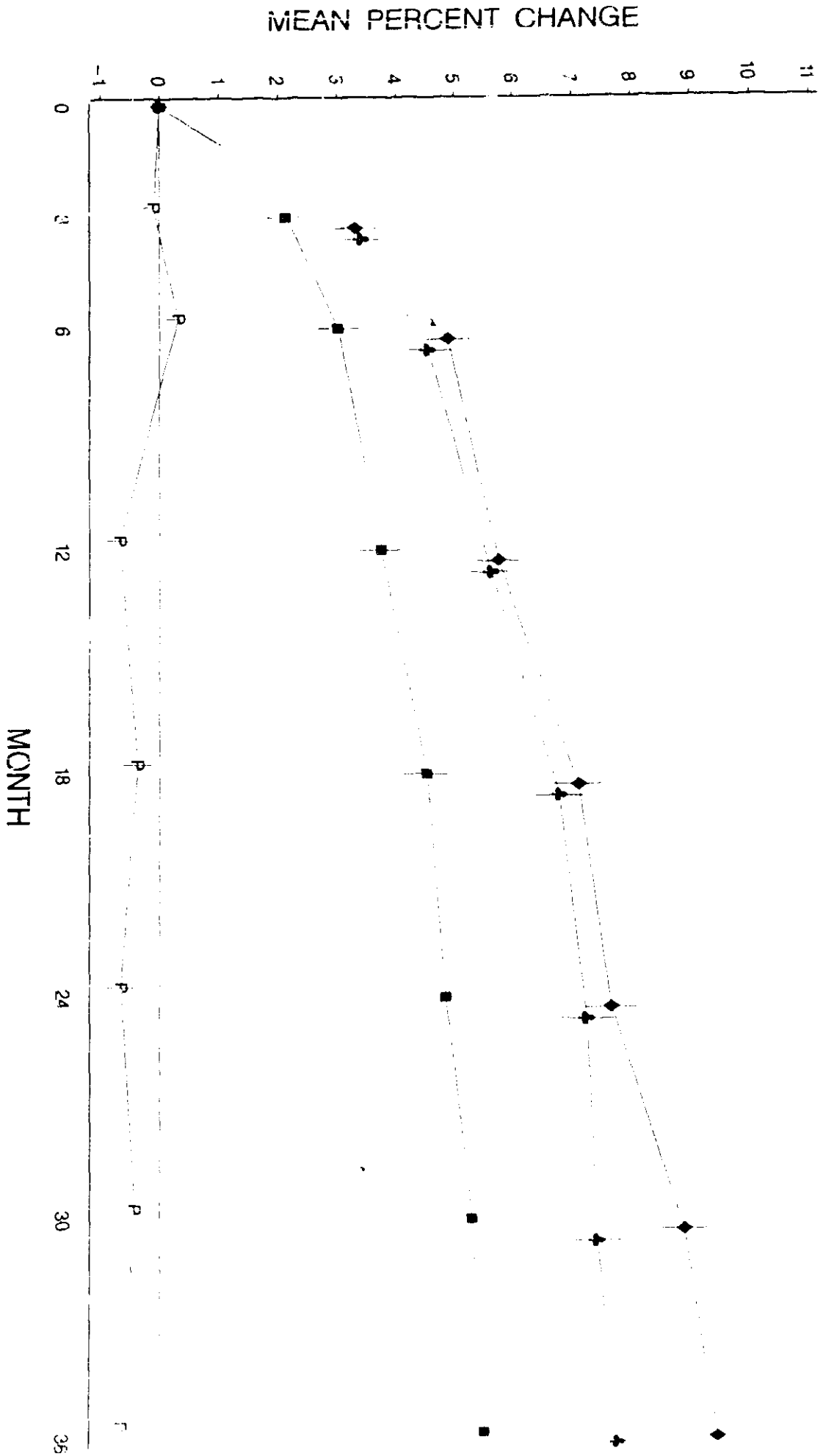
p<.01 in favor of alendronate 10mg over alendronate 20mg/5mg

a Adjusted means in parenthesis

ALENDRONATE PHASE III OSTEOPENIA BONE DENSITY STUDY (#035)

LUMBAR SPINE BMD

MEAN PERCENT CHANGE +/- SE OF THE MEAN
 "INTENTION-TO-TREAT" APPROACH



= PLACEBO

■ = 5 MG

▲ = 10 MG

◆ = 20/5 MG

TABLE 2

STUDY 035

LUMBAR SPINE BMD MEANS
Intent-to-Treat Annual Analyses

MEAN * PERCENT CHANGE

TREATMENT	BASELINE-MONTH 12	MONTH 12-MONTH 24	MONTH 24-MONTH 36
PLACEBO	-.67 (-.79)	.01 (-.04)	.14 (.11)
ALENDRONATE 5MG	3.77** (3.61)	1.25* (1.26)	.75 (.73)
ALENDRONATE 10MG	5.78**++ (5.65)	1.93** (1.92)	1.74**+# (1.74)
ALENDRONATE 20MG/5MG	5.66**++ (5.46)	1.75** (1.73)	.55 (.51)
	P<.001	P<.001	P<.01

* p<.01 in favor of alendronate over placebo

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

+ p<.05 in favor of alendronate 10mg over alendronate 5mg

++ p<.001 in favor of alendronate 10mg and alendronate 20mg/5mg over alendronate 5mg

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

a Adjusted means in parenthesis

C. Efficacy (Cont.)

Figure 2

Lumbar Spine BMD (g/cm²)
Annual Change ± S.E. of the Mean
(Intention-to-Treat Approach)

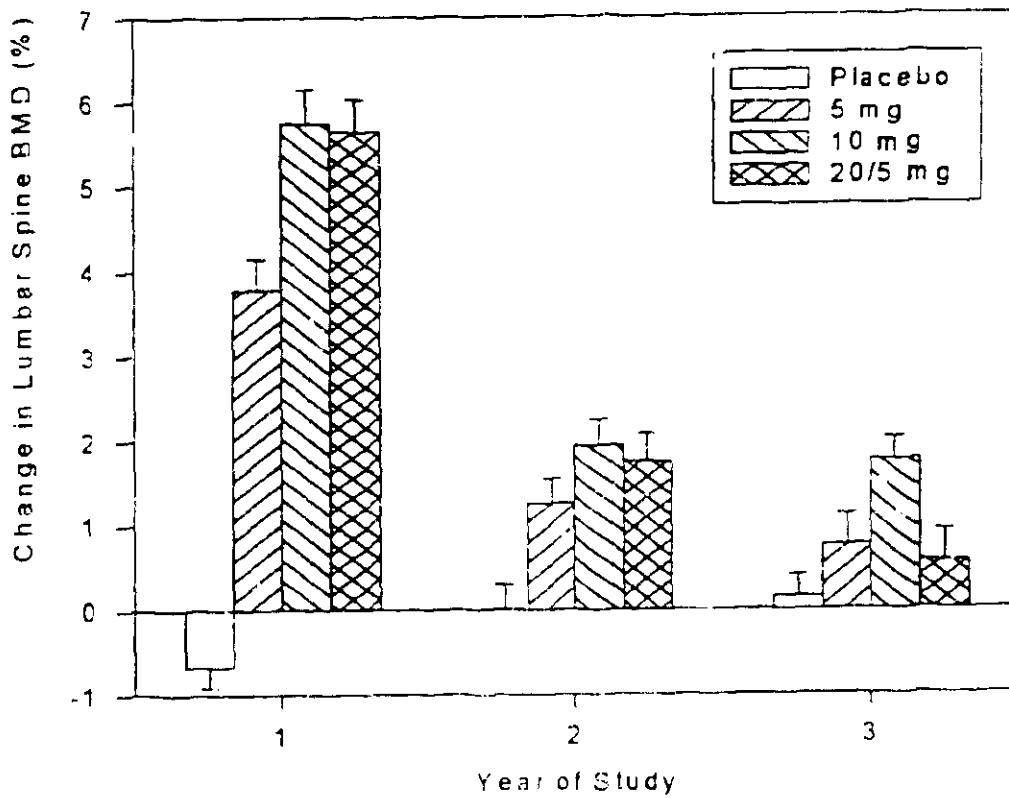


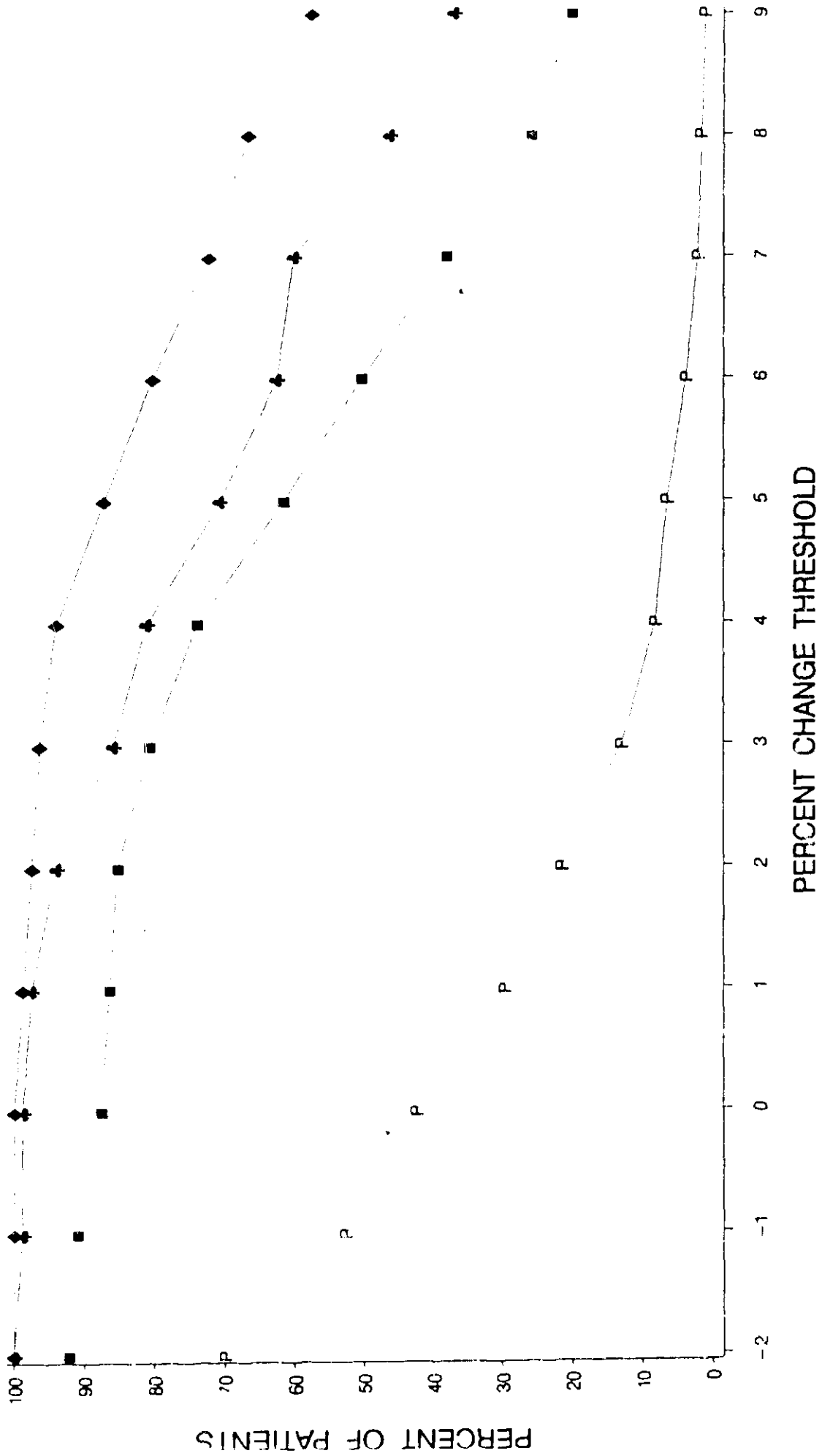
TABLE 3

STUDY 035

PERCENT OF PATIENTS WITH 36 MONTH PERCENT CHANGE IN LUMBAR SPINE
BMD EXCEEDING THRESHOLDS RANGING FROM -2% TO 9%

THRESHOLD	PLACEBO	ALENDRONATE 5MG	ALENDRONATE 10MG	ALENDRONATE 20MG/5MG
-2%	69.9	92.1	100.0	100.0
-1%	52.7	91.0	100.0	98.8
0%	42.5	87.6	100.0	98.8
1%	29.6	86.5	98.9	97.7
2%	21.5	85.4	97.7	94.2
3%	12.9	80.9	96.6	86.0
4%	8.1	74.2	94.3	81.4
5%	6.5	61.8	87.5	70.9
6%	3.8	50.6	80.7	62.8
7%	2.2	38.2	72.7	60.5
8%	1.6	25.8	67.0	46.5
9%	1.1	20.2	58.0	37.2

MK-217 PHASE III OSTEOPENIA BONE DENSITY STUDY (#035)
 PERCENT OF PATIENTS WITH 36-MONTH CHANGE IN LUMBAR SPINE BMD
 EXCEEDING THRESHOLDS RANGING FROM -2% TO 9%
 "INTENTION-TO-TREAT" APPROACH



= PLACEBO
 □ = 5 MG
 △ = 10 MG
 ● = 20/5 MG

TABLE 4

STUDY 035

ADVERSE EXPERIENCE* FREQUENCIES

ADVERSE EXPERIENCE	PLACEBO	ALENDRONATE 5MG	ALENDRONATE 10MG	ALENDRONATE 20MG/5MG
PAIN (SITE UNSPECIFIED)	1 (0.5%)	2 (2.0%)	2 (2.1%)	5 (5.3%)
FLATULENCE	4 (2.1%)	3 (3.1%)	6 (6.4%)	6 (6.4%)
ABDOMINAL PAIN	21 (10.9%)	15 (15.3%)	19 (20.2%)	17 (18.1%)
HIP PAIN	17 (8.9%)	10 (10.2%)	14 (14.9%)	15 (16.0%)

+ Adverse experiences that occurred with an incidence of at least 5% in any treatment group for which there was a statistically significant ($p < .05$) positive trend across the placebo, 5 10 and 20/5mg alendronate doses. P-values were pain: .012, flatulence: .033, abdominal pain: .034, and hip pain: $p = .043$.

TABLE 5

STUDY 037

LUMBAR SPINE BMD (g/cm²)
 INTENT-TO-TREAT ANALYSIS
 36 MONTH ANALYSIS

TREATMENT	N	BASELINE	MONTH 36	MEAN * PERCENT CHANGE
PLACEBO	188	.75	.75	-.31 (-.05)
ALENDRONATE 5MG	89	.76	.80	4.87* (5.15)
ALENDRONATE 10MG	92	.75	.80	6.84** (7.16)
ALENDRONATE 20MG/5MG	92	.75	.81	7.77*** (8.12)
				P<.001

*p<.001 in favor of alendronate over placebo. Treatment by center interaction p=.66

+ p=.01 in favor of alendronate 10mg over alendronate 5mg

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

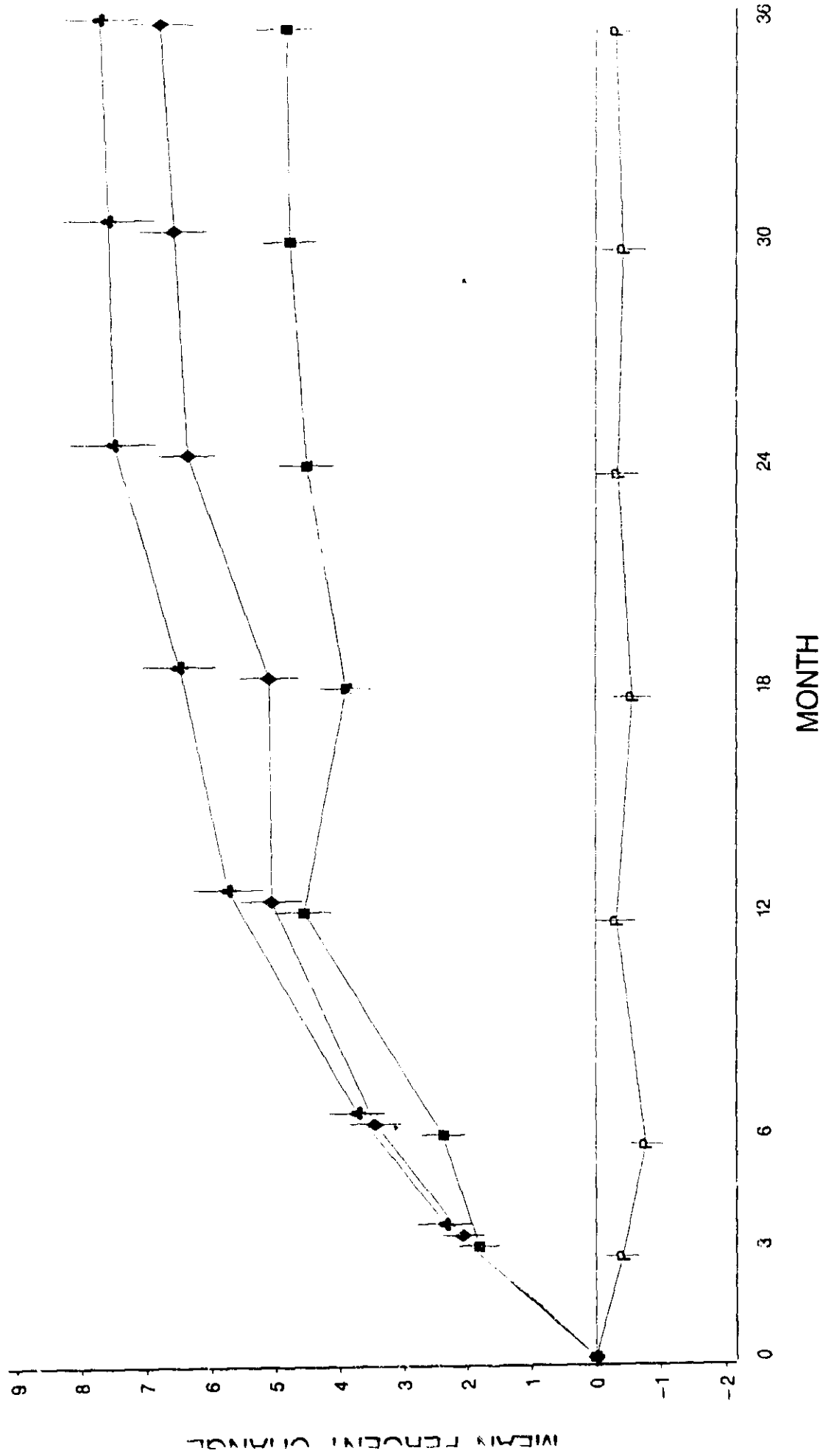
a Adjusted means in parenthesis

ALENDRONATE PHASE III OSTEOPENIA BONE DENSITY STUDY (#037)

LUMBAR SPINE BMD

MEAN PERCENT CHANGE +/- SE OF THE MEAN

"INTENTION-TO-TREAT" APPROACH



PLACEBO
= 5 MG
= 10 MG
= 20/5 MG

TABLE 6
STUDY 037

INTENT-TO-TREAT ANNUAL ANALYSES
Mean ^a Percent Change

TREATMENT	BASELINE-MONTH 12	MONTH 12-MONTH 24	MONTH 24-MONTH 36
PLACEBO	-.32 (-.33)	-.05 (.08)	.06 (.23)
ALENDRONATE 5MG	4.57* (4.53)	.11 (.28)	.18 (.36)
ALENDRONATE 10MG	5.07* (5.06)	1.35*+ (1.48)	.56 (.73)
ALENDRONATE 20MG/5MG	5.75*# (5.87)	1.72*++ (1.76)	.21 (.35)
	P<.001	P<.001	P=.72

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

+ p=.01 in favor of alendronate 10mg over alendronate 5mg

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

p<.05 in favor of alendronate 20mg/5mg over alendronate 5mg

a Adjusted means in parenthesis

MK-217 Prot. No 037
Three-Year Phase III Osteoporosis Bone Density Study (Intl.)
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C. Efficacy (Cont.)

Figure 2

Annual Change in Lumbar Spine BMD
Intention-to-Treat Approach
Mean $\pm$ 1 S.E.

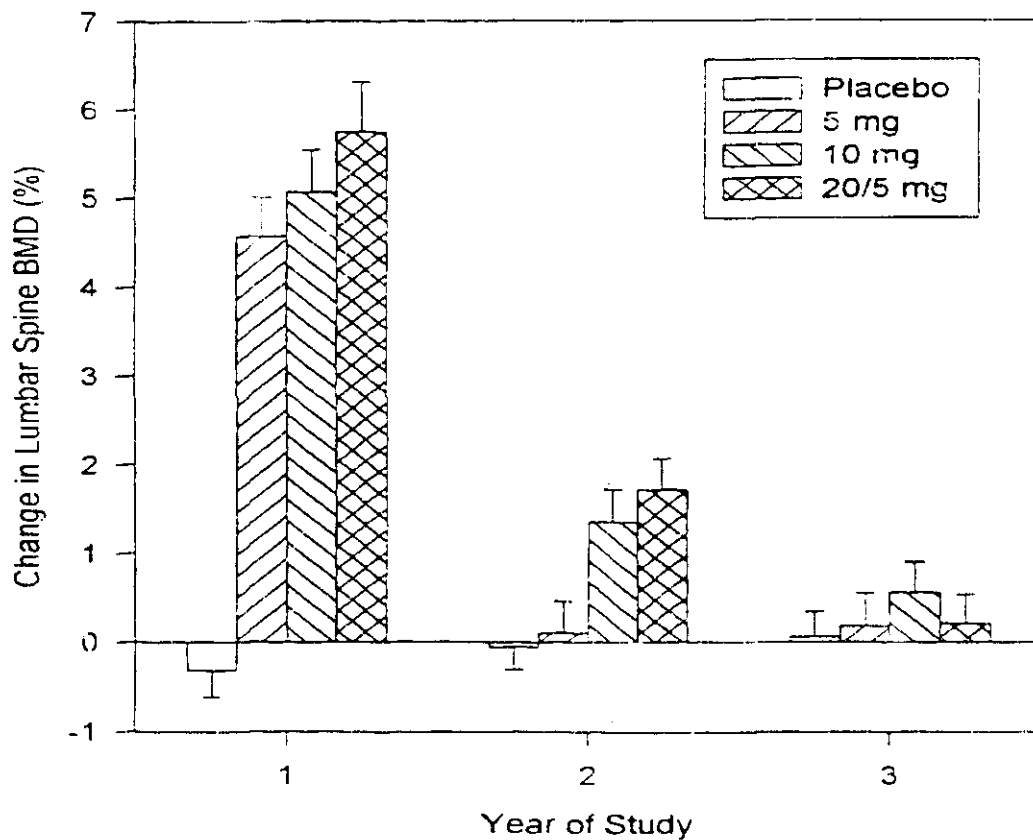


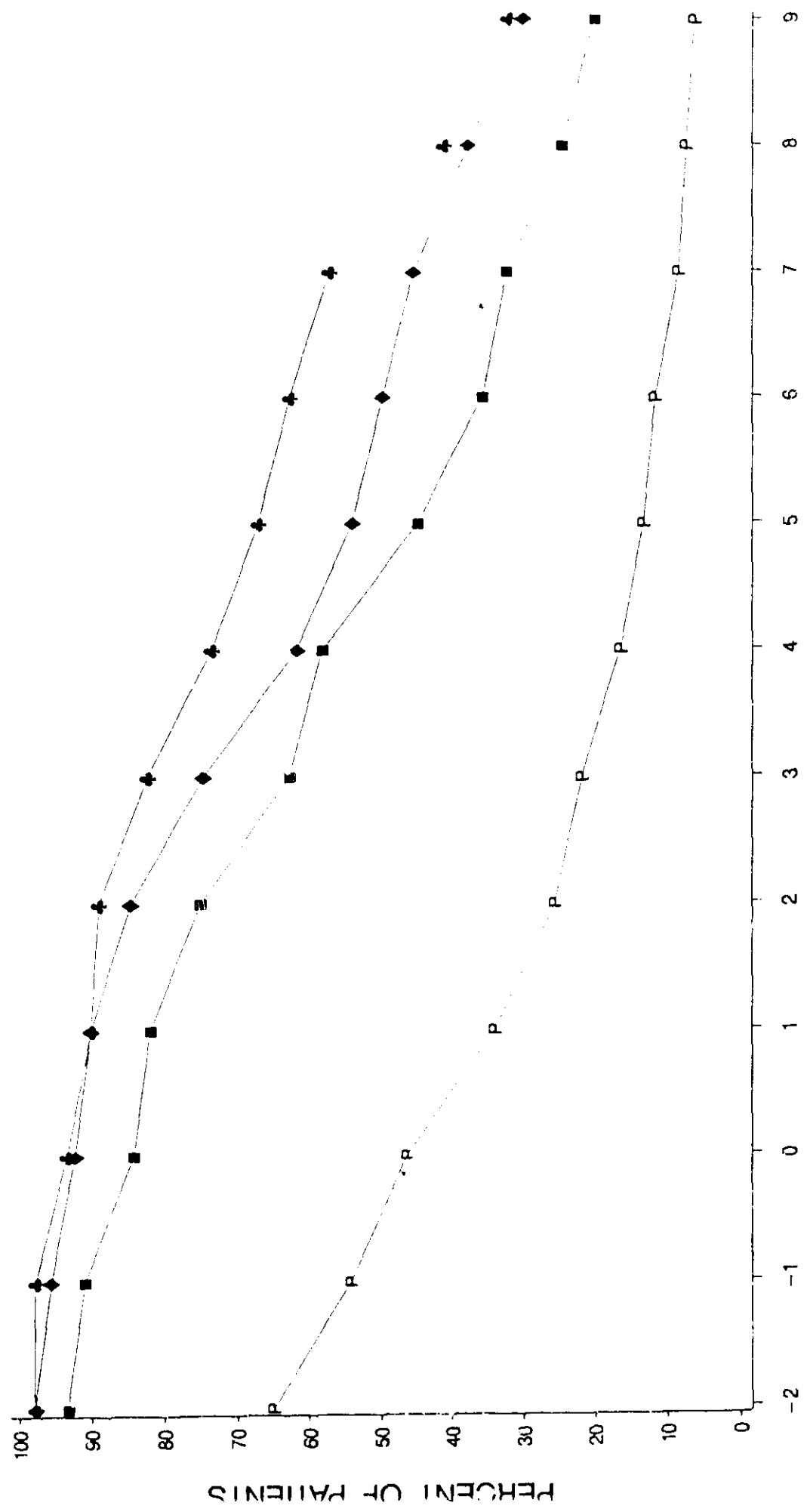
TABLE 7

STUDY 037

PERCENT OF PATIENTS WITH 36 MONTH PERCENT CHANGE IN LUMBAR SPINE
BMD EXCEEDING THRESHOLDS RANGING FROM -2% TO 9%

THRESHOLD	PLACEBO	ALENDRONATE 5MG	ALENDRONATE 10MG	ALENDRONATE 20MG/5MG
-2%	64.9	93.3	97.8	97.8
-1%	54.3	91.0	95.7	97.8
0%	46.3	84.3	92.4	93.5
1%	34.0	82.0	90.2	90.2
2%	25.5	75.3	84.8	89.1
3%	21.8	62.9	75.0	82.6
4%	16.5	58.4	62.0	73.9
5%	13.3	44.9	54.3	67.4
6%	11.7	36.0	50.0	63.0
7%	8.5	32.6	45.7	57.6
8%	7.4	24.7	38.0	41.3
9%	6.4	20.2	30.4	32.6

MK-217 PHASE III OSTEOPENIA BONE DENSITY STUDY (#037)
 PERCENT OF PATIENTS WITH 36-MONTH CHANGE IN LUMBAR SPINE BMD
 EXCEEDING THRESHOLDS RANGING FROM -2% TO 9%
 "INTENTION-TO-TREAT" APPROACH



= PLACEBO
 = 5 MG
 = 10 MG
 = 20/5 MG

TABLE 8

NEW VERTEBRAL FRACTURES
(BY STUDY AND AGE GROUP)

	ALENDRONATE	PLACEBO	ODDS RATIO*	ODDS RATIO 95% CONFIDENCE INTERVAL
OVERALL	17/526 (3.23%)	22/355 (6.20%)	.51 (P=.036)	(.27, .95)
STUDY 035	4/258 (1.55%)	8/177 (4.52%)	.33 (P=.063)	(.10, 1.07)
STUDY 037	13/268 (4.85%)	14/178 (7.87%)	.60 (P=.190)	(.28, 1.29)
AGE <65	11/294 (3.74%)	9/190 (4.74%)	.78 (P=.589)	(.32, 1.93)
AGE AT LEAST 65	6/232 (2.59%)	13/165 (7.88%)	.31 (p=.015)	(.12, .79)

* Alendronate to placebo. Ratio less than 1.0 favors alendronate.

TABLE 9

NEW VERTEBRAL FRACTURES
(BY STUDY AND TREATMENT GROUPS)

	PLACEBO	ALENDRONATE 5MG	ALENDRONATE 10MG	ALENDRONATE 20MG/5MG
OVERALL	22/355 (6.20%)*	5/175 (2.86%)*	5/178 (2.81%)**	7/173 (4.05%)
STUDY 035	8/177 (4.52%)	2/88 (2.27%)	1/87 (1.15%)	1/83 (1.20%)
STUDY 037	14/178 (7.87%)	3/87 (3.45%)	4/91 (4.40%)	6/90 (6.67%)

* p = .101 in favor of alendronate 5mg over placebo. Odds ratio = .45. Odds ratio 95% confidence interval = (.13,1.53).

** p = .093 in favor of alendronate 10mg over placebo. Odds ratio = .44. Odds ratio 95% confidence interval = (.17,1.15).

TABLE 10

SDI
STUDIES 035 AND 037

SDI CHANGE #	PLACEBO (N = 333)	ALENDRONATE (502)
INCREASE	135 (40.5%)	166 (33.1%)
NO CHANGE	149 (44.7%)	260 (51.8%)
DECREASE	49 (14.7%)	76 (15.1%)

CHI-SQUARE: P = .075+

WILCOXON RANK SUM: P = .054+

A decrease in SDI is favorable.

+ p < .10 in favor of alendronate over placebo.

TABLE 11

SDI
STUDY 035

SDI CHANGE #	PLACEBO (N = 173)	ALENDRONATE (N=256)
INCREASE	69 (39.9%)	81 (31.6%)
NO CHANGE	80 (46.2%)	134 (52.3%)
DECREASE	24 (13.9%)	41 (16.0%)

CHI-SQUARE: P = .21

WILCOXON RANK SUM: P = .06+

A decrease in SDI is favorable.

+ p < .10 in favor of alendronate over placebo.

TABLE 12

SDI
STUDY 037

SDI CHANGE #	PLACEBO (N = 160,	ALENDRONATE (N=246)
INCREASE	66 (41.3%)	85 (34.6%)
NO CHANGE	69 (43.1%)	126 (51.2%)
DECREASE	25 (15.6%)	35 (14.2%)

CHI-SQUARE: P = .27

WILCOXON RANK SUM: P = .39

A decrease in SDI is favorable.

TABLE 13

SDI
STUDIES 035 AND 037
AGE LESS THAN 65

SDI CHANGE #	PLACEBO (N = 183)	ALENDRONATE (N=277)
INCREASE	67 (36.6%)	81 (29.2%)
NO CHANGE	84 (45.9%)	156 (56.3%)
DECREASE	32 (17.5%)	40 (14.4%)

CHI-SQUARE: P = .09+

WILCOXON RANK SUM: P = .37

A decrease in SDI is favorable.

+ p < .10 in favor of alendronate over placebo.

TABLE 14

SDI
STUDIES 035 AND 037
AGE AT LEAST 65

SDI CHANGE #	PLACEBO (N = 150)	ALENDRONATE (N=225)
INCREASE	68 (45.3%)	85 (37.8%)
NO CHANGE	65 (43.3%)	104 (46.2%)
DECREASE	17 (11.3%)	36 (15.0%)

CHI-SQUARE: P = .25

WILCOXON RANK SUM: P = .08+

A decrease in SDI is favorable.

+ p < .10 in favor of alendronate over placebo.

NDA 20560

FOSAMAX

5 OF 7

TABLE 15

SDI
STUDIES 035 AND 037

SDI CHANGE #	PLACEBO (N=333)	ALENDRONATE 5MG (N=165)	ALENDRONATE 10MG (N=171)	ALENDRONATE 20/5MG (N=166)
INCREASE	135 (40.5%)	57 (34.5%)	52 (30.4%)	57 (34.3%)
NO CHANGE	149 (44.7%)	78 (47.3%)	93 (54.4%)	89 (53.6%)
DECREASE	49 (14.7%)	30 (18.2%)	26 (15.2%)	20 (12.0%)

WILCOXON RANK SUM P-VALUES

Placebo versus Alendronate 5mg: p = .11

Placebo versus Alendronate 10mg: p = .06+

A decrease in SDI is favorable

+ p < .10 in favor of alendronate 10mg over placebo

TABLE 16

SDI
STUDY 035

SDI CHANGE #	PLACEBO (N=173)	ALENDRONATE 5MG (N=86)	ALENDRONATE 10MG (N=87)	ALENDRONATE 20/5MG (N=83)
INCREASE	69 (39.9%)	35 (40.7%)	23 (26.4%)	23 (27.7%)
NO CHANGE	80 (46.2%)	37 (43.0%)	49 (56.3%)	48 (57.8%)
DECREASE	24 (13.9%)	14 (16.3%)	15 (17.2%)	12 (14.5%)

WILCOXON RANK SUM P-VALUES

Placebo versus Alendronate 5mg: p = .85

Placebo versus Alendronate 10mg: p = .03*

A decrease in SDI is favorable

* p < .05 in favor of alendronate 10mg over placebo

TABLE 17

SDI
STUDY 037

SDI CHANGE #	PLACEBO (N=160)	ALENDRONATE 5MG (N=79)	ALENDRONATE 10MG (N=84)	ALENDRONATE 20/5MG (N=83)
INCREASE	66 (41.3%)	22 (27.8%)	29 (34.5%)	34 (41.0%)
NO CHANGE	69 (43.1%)	41 (51.9%)	44 (52.4%)	41 (49.4%)
DECREASE	25 (15.6%)	16 (20.3%)	11 (13.1%)	8 (9.6%)

WILCOXON RANK SUM P-VALUES

Placebo versus Alendronate 5mg: $p = .035^*$

Placebo versus Alendronate 10mg: $p = .67$

A decrease in SDI is favorable

* $p < .05$ in favor of alendronate 5mg over placebo

TABLE 18
 STUDIES 035 AND 037
 STATURE MEDIANS (MM)
 INTENT-TO-TREAT ANALYSIS

TREATMENT	N	BASELINE	MONTH 36	CHANGE
PLACEBO	375	1587	1581	-3.15
ALENDRONATE 5MG	182	1577	1577	-2.17**
ALENDRONATE 10MG	179	1585	1579	-2.33
ALENDRONATE 20MG/5MG	185	1583	1579	-1.67*
POOLED ALENDRONATE	546	1583	1579	-2.12**

* P < .05 in favor of alendronate over placebo.

** P < .01 in favor of alendronate over placebo.

TABLE 19

STUDY 035

STATURE MEDIANS (MM)
INTENT-TO-TREAT ANALYSIS

TREATMENT	N	BASELINE	MONTH 36	CHANGE
PLACEBO	174	1603	1598 [*]	-4.42
ALENDRONATE 5MG	85	1604	1603	-2.33
ALENDRONATE 10MG	82	1596	1596	-2.25 ⁺
ALENDRONATE 20MG/5MG	84	1604	1600	-1.65 ⁺
POOLED ALENDRONATE	251	1599	1597	-2.17 [*]

⁺ P < .10 in favor of alendronate over placebo.

^{*} P < .05 in favor of alendronate over placebo.

TABLE 20

STUDY 037

STATURE MEDIANS (MM)
INTENT-TO-TREAT ANALYSIS

TREATMENT	N	BASELINE	MONTH 36	CHANGE
PLACEBO	201	1565	1564 [*]	-3.00
ALENDRONATE 5MG	97	1565	1563	-1.83 ^{***}
ALENDRONATE 10MG	97	1570	1567	-2.67
ALENDRONATE 20MG/5MG	101	1570	1570	-1.67
POOLED ALENDRONATE	295	1569	1567	-2.00 [*]

* P = .05 in favor of alendronate over placebo.

** P < .01 in favor of alendronate over placebo.

p < .05 in favor of alendronate 5mg over alendronate 10mg.

TABLE 21
 STUDIES 035 AND 037
 STATURE
 INTENT-TO-TREAT SLOPE ANALYSIS (MM/YEAR)

TREATMENT	N	MEAN ^a
PLACEBO	365	-1.69 (-1.77)
ALENDRONATE 5MG	180	-1.12* (-1.15)
ALENDRONATE 10MG	179	-1.15* (-1.20)
ALENDRONATE 20MG/5MG	178	-.95** (-1.08)
POOLED ANALYSIS	537	-1.07*** (-1.14)

* p < .05 in favor of alendronate over placebo.

** p < .01 in favor of alendronate over placebo.

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

a Adjusted means in parenthesis.

TABLE 22

STUDY 035
 STATURE
 INTENT-TO-TREAT SLOPE ANALYSIS (MM/YEAR)

TREATMENT	N	MEAN ^a
PLACEBO	170	-1.70 (-1.68)
ALENDRONATE 5MG	84	-1.32 (-1.26)
ALENDRONATE 10MG	82	-.94* (-.94)
ALENDRONATE 20MG/5MG	79	-.82* (-.99)
POOLED ANALYSIS	245	-1.03** (-1.07)

* p < .05 in favor of alendronate over placebo.

** p < .01 in favor of alendronate over placebo.

a Adjusted means in parenthesis.

TABLE 23
 STUDY 037
 STATURE
 INTENT-TO-TREAT SLOPE ANALYSIS (MM/YEAR)

TREATMENT	N	MEAN ^a
PLACEBO	195	-1.69 (-1.86)
ALENDRONATE 5MG	96	-.94* (-1.09)
ALENDRONATE 10MG	97	-1.33 (-1.46)
ALENDRONATE 20MG/5MG	99	-1.06+ (-1.20)
POOLED ANALYSIS	292	-1.11* (-1.25)

+ p < .10 in favor of alendronate over placebo.

* p < .05 in favor of alendronate over placebo.

a Adjusted means in parenthesis.

AUG 3 1995

NDA: 20-560
Alendronate Sodium
(FOSAMAX®)
Submission Date: 6/27/95
Sponsor: Merck Research Laboratories
Type of Submission: Response to Request for Information
Reviewer: Michael J. Fossler, Pharm. D., Ph. D.

Background

The submission dated 6/27/95 is in response to a request for information made at a meeting between the Agency and the sponsor on 6/13/95. The Agency requested additional pharmacokinetic and pharmacodynamic data supporting the conclusion that the 30 minute fast post-dose will produce the same therapeutic response as waiting 60 minutes before eating. The present submission presents evidence that the two regimens are therapeutically equivalent.

Analysis

The firm provides both a pharmacokinetic argument and a pharmacodynamic (clinical) argument to support their contention that a 30 minute wait is sufficient.

For the pharmacokinetic argument, the firm cites the results of two food effect studies performed for the original NDA (see the biopharm review dated 6/30/95 for reviews of these studies). Both studies were randomized crossover studies in post-menopausal women given either 10 or 20 mg alendronate either 0.5, 1, or 2 hours before eating the first meal of the day. The firm presents the summary table reproduced below (Table 1).

Table 1: Effect of Meal Timing on Urinary Excretion of Alendronate following Oral dosing

Time of Alendronate Dose before Breakfast	Protocol 053 (n = 49, 10 mg dose)			Protocol 032 (n = 15, 20 mg dose)		
	Geometric Mean Ratio	95% CI	p-value	Geometric Mean Ratio	95% CI	p-value
1 hr vs 2 hr	0.70	0.52, 0.94	-	0.54	0.34, 0.86	-
0.5 hr vs 2 hr	0.54	0.40, 0.74	-	0.64	0.41, 1.02	-
0.5 hr vs 1 hr*	0.76	0.55, 1.06	0.127	1.18	0.74, 1.86	> 0.20

* 90% confidence limits calculated by the reviewer are 0.531, 1.03

The firm claims that in Protocol 32, the 30 minute group demonstrated superior absorption to the 1 hr group, whereas in Protocol 53 it is the other way around. It should be noted, though, that Protocol 32 was a very small study for a drug with such high variability (intra-subject CV% about 50%), so these results must be interpreted with considerable caution. Protocol 53, with considerably more subjects, is considered to be the most reliable study. Although the firm claims that "... the difference in extent of absorption of alendronate was modest and did not reach statistical significance...", in fact the 30 and 60 minute regimens are not bioequivalent by current guidelines, as the confidence limits for the mean ratio of 0.5 hr vs 1 hr fall outside 80-125%.

Further evidence for the conclusion that significantly less drug is absorbed under the 30 minute wait is provided in Table 2. It is noted that nearly one-quarter of subjects dosed a half-hour before the first meal have no quantifiable alendronate in their urine as compared with 6% of subjects dosed 1 hour before the first meal. The Division believes that this comparison provides compelling evidence that significantly less drug is absorbed when the drug is taken 30 minutes before the first meal of the day.

For the pharmacodynamic argument, the firm compares the bone mineral density (BMD) measurements obtained in the two pivotal trials on 5 mg alendronate daily (taken 60 minutes before breakfast) with those obtained in Protocol 54, a study in elderly women who were instructed to take 1, 2.5, or 5 mg alendronate 30 minutes before breakfast. Comparison of the percent change in BMD after 24 months of treatment with 5 mg across the two studies does support the firm's contention that the two dosing regimens are therapeutically equivalent (Table 3). The populations appear to be comparable in terms of baseline spine BMD and creatinine clearance, although the patients in Protocol 54 were older by design.

Table 2: Number (%) of subjects with no quantifiable alendronate in their urine after various dosing regimens. Data from Protocol 53.

Treatment	*Number (%) below Limit of Quantitation of the Assay
Dosed 0.5 hrs before meal	12 (24%)
Dosed 1 hr before meal	3 (6%)
Dosed 2 hrs before meal	2 (4%)
Dosed immediately after meal	41 (84%)
Dosed 2 hrs after meal	32 (65%)

Table 3: Effect of meal timing on BMD gain at 24 months in patients treated with alendronate 5 mg daily.

Protocol	Timing of Dose	Number of Patients	Mean % Change in BMD at 24 months
35/37	≥ 1 hour before breakfast	173	5.22
54	≥ 0.5 hour before breakfast	85	5.57

Recommendation

The Division of Biopharmaceutics (HFD-420) has reviewed the submission dated 6/27/95 thoroughly. Although the Division is still concerned about the decrease in absorption of this compound when dosed 30 minutes before breakfast as opposed to 1 hour before, the pharmacodynamic evidence presented by the firm is compelling. The Advisory Committee (minutes attached) has recommended that the compound be taken no less than 30 minutes before breakfast, with 60 minutes recommended for optimal absorption. The Division considers this recommendation to be a good compromise, which will ensure maximum compliance, yet make certain patients wait a sufficient time for drug absorption to occur.

The sponsor has modified its proposed physician and patient labeling (attached). Please forward the text under Labeling Comments to the firm, as appropriate.

Labeling Comments

- 1) In the *Pharmacokinetics* section under **CLINICAL PHARMACOLOGY**, the text under the heading *Absorption* should be replaced by the following:

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 (0.66%) was similar to that in women when administered after an overnight fast and 2 hours before breakfast.

In a study examining the effect of the timing of a meal on the bioavailability of alendronate in 49 post-menopausal women, bioavailability was decreased when 10 mg alendronate was administered either 0.5 or 1 hour before eating when compared to dosing 2 hours before eating. Bioavailability was also 26% lower when alendronate was administered 0.5 hours before eating as compared to 1 hour before eating. Bioavailability was negligible when 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%.

In a trial in elderly patients given 5 mg of alendronate 30 minutes before breakfast, similar bone mineral density changes were noted when compared to the pivotal trials, in which one of the treatment arms was 5 mg alendronate administered 60 minutes before breakfast.

2) The summary table of pharmacokinetic parameters should be replaced with the following table:

	Mean	90% confidence Interval
Absolute bioavailability of 10 mg tablet, taken 2 hours before first meal of the day	0.74% (females)	(0.54, 1.03)
	0.66% (males)	(0.50, 0.87)
Absolute bioavailability of 40 mg tablet, taken 2 hours before first meal of the day	0.57% (females)	(0.41, 0.79)
Renal Clearance (mL/min) (n = 6)	71	(64, 78)

3) The text under *Drug Interactions* (pg. 5) should be replaced with the following:

Drug Interactions

It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of FOSAMAX. Therefore, patients must wait at least 30-60 minutes after taking FOSAMAX before taking any other drug.

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 H₂-antagonists is unknown.

4) The second sentence under *Information for Patients* (pg. 15) should be modified as follows:

.... Patients should also be instructed that waiting longer than 30 minutes before eating will improve the absorption of FOSAMAX.

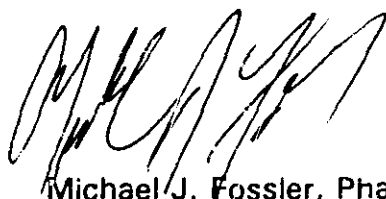
5) Under **DOSAGE AND ADMINISTRATION**, the following sentence should be added after the first sentence in the first paragraph (pg. 15)

Waiting longer than 30 minutes before eating will improve the absorption of FOSAMAX.

6) In the patient labeling, the first "bullet" on page 3 should be modified as follows:

- Take FOSAMAX *no sooner than 30 minutes before your first meal, beverage, or other medication (including antacids, calcium supplements and vitamins) of the day. Waiting longer than 30 minutes before eating will improve the absorption of FOSAMAX into the body.*

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.

 8/2/95

Michael J. Fossler, Pharm. D., Ph. D.
Pharmacokinetics Evaluation Branch II

RD initialed by John Hunt, Section Head 8/2/95

FT initialed by John Hunt, Section Head JPH 8/2/95

cc: NDA 20-560 (pink), HFD-510(Dutta, Hedin), HFD-426(Fleischer), HFD-427(M. Chen, Fossler), HFD-340(Viswanathan), Drug, Chron, Review, FOI (HFD-19)
rev 5/12/95

NDA: 20-560

JUN 30 1995

Alendronate Sodium
10 and 40 mg Tablets
(Fosamax[®])

Submission Date: 3/31/95
5/5/95

Sponsor: Merck Research Laboratories
West Point, PA

Type of Submission: New Drug Application (1P-NME)

Reviewer: Michael J. Fossler, Pharm. D., Ph. D.

Synopsis

Merck Research Laboratories has submitted NDA 20-560 for alendronate sodium, a bisphosphonate compound which is a potent and specific inhibitor of osteoclast activity. The proposed indications are 1) treatment of osteoporosis in post-menopausal women and 2) treatment of Paget's disease of bone in men and women. The recommended doses are 10 mg daily for osteoporosis and 40 mg daily for Paget's disease. The compound will be available in 10 and 40 mg tablets.

The oral bioavailability of alendronate relative to an intravenous injection is low (0.7% in post-menopausal women, 0.6% in healthy men), and is substantially affected by the timing of food intake. Meals 0.5 or 1 hour post-dose reduce the bioavailability of alendronate by 47 and 28%, compared with a meal 2 hours post-dose. Dosing either immediately after eating or 2 hours after eating decreases absorption of alendronate by more than 80%. Alendronate taken with either black coffee or orange juice also shows reduced bioavailability compared with water. Increased gastric pH induced by ranitidine was found to increase the bioavailability of alendronate.

At therapeutic doses, alendronate is present in the plasma at concentrations too low to measure by current analytical methods; therefore cumulative urinary excretion has been used as a measure of drug exposure. Upon iv injection, the drug rapidly distributes to bone with about 50-60% of a given dose binding to bone surfaces. The remaining drug not bound to bone is eliminated in the urine over 36-48 hours. The half-life of bound drug has been estimated at more than 10 years. The percent of an oral dose excreted in the urine over 36 hours was found to be similar from 5-80 mg, indicating dose linearity.

Studies in animals and in breast cancer patients given ¹⁴C-alendronate have revealed no metabolites. The compound is approximately 78% bound to albumin. No studies in patients with severe renal insufficiency (creatinine clearance < 35

mL/min) were performed. Based on the data collected, no obvious relationship was found between either age or renal function (as assessed by creatinine clearance) and the amount of drug excreted over 36 hours. Both men and women show similar urinary excretion profiles. Alendronate is not indicated for use in the pediatric population.

No formal drug interaction studies were performed. Animal studies have suggested that bisphosphonates such as alendronate are excreted via a unique renal transport system, and so are unlikely to interfere with the excretion of drugs by the usual anionic/cationic pathways. It is unlikely that alendronate will interact with hepatically-metabolized drugs. The extent of protein binding seen with alendronate (78%) makes it unlikely to displace other protein-bound drugs from binding sites. Because of the substantial effect that food, calcium supplements and beverages have on the bioavailability of alendronate, it is recommended that other medications should not be administered sooner than 1 hour after dosing. One study suggests that patients taking compounds which raise gastric pH (such as H₂ antagonists) may show increased bioavailability of alendronate. This is not a clinically significant interaction.

The proposed dissolution method is
specification is at 30 minutes.

Recommendation

The biopharmaceutics portion of NDA 20-560 is approved. Please forward the text under X. General Comments (to be sent to Sponsor) and XI. Labeling Comments (to be sent to Sponsor) to the Sponsor as appropriate.

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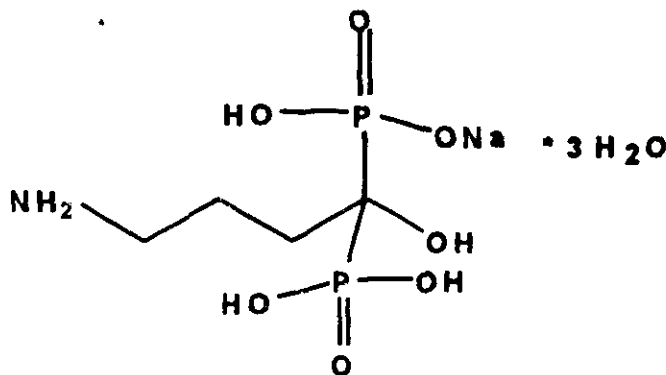
Appendix I: Study Summaries (available from the Division of Biopharmaceutics upon request)

Protocol Number	Title	Page
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39	A Open Study to Investigate the Disposition of a Single Intravenous Dose of ¹⁴ C-Alendronate Sodium in Patients with Metastatic Breast Cancer	28
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60	An Open-Label, Multiple-Dose Study to Investigate the Influence of Repetitive IV Doses on the Pharmacokinetics of Alendronate Sodium in Post-menopausal Volunteers	34
65	An Open-Label, 5-Period Crossover Study in Post-menopausal Female Volunteers to Investigate the Oral Absorption of Alendronate Sodium Final Production Process Tablets	36
66	An Open-Label, 5-Period Crossover Study to Investigate the Influence of Beverages Taken With the Dose on the Bioavailability of Alendronate Sodium (Final Market Composition) in Post-Menopausal Volunteers	38
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Background

Merck Research has submitted NDA 20-560 for alendronate sodium tablets. Alendronate is a potent, orally active bisphosphonate compound which is an inhibitor of osteoclast activity which in turn inhibits bone resorption. The proposed indications are 1) osteoporosis in postmenopausal women, and 2) treatment of Paget's disease of bone. The chemical structure is shown below:

Alendronate sodium ($C_4H_{12}NNaO_7P_2 \cdot 3H_2O$) is a white crystalline solid with a molecular weight of 325.12. It is highly soluble in water (40 mg/mL), but practically insoluble in organic solvents (octanol:water coefficient = 0.003). Alendronate will be marketed as 10 and 40 mg oral tablets.



Summary of Bioavailability/Pharmacokinetics/Pharmacodynamics

I. Bioavailability/Bioequivalence

A. Absolute Bioavailability

The absolute bioavailability of 10 mg alendronate tablets in post-menopausal women was found to be 0.74% (90% confidence interval 0.54-1.03%). Similar values were obtained in normal men (mean 0.66%, 90% CI 0.50-0.87%). The 40 mg tablet shows similar bioavailability in women (mean 0.57%, 90% CI 0.41-0.79%). This low bioavailability is typical of the chemical class, as bisphosphonates are strong chelators of mono and divalent cations.

Two studies examined the effect of meals on the bioavailability of alendronate. In a randomized crossover trial in 15 post-menopausal women, it was found that the absorption of 20 mg alendronate was reduced by eating 1 hour post-dose or eating 0.5 hours after dosing as compared with eating 2 hours post-dose. The meal used was 1 fried egg, 2 pieces of toast, 20 g jelly, 2 strips of bacon, and 250 mL orange juice. Supplemental calcium administered with the meals appeared to have no additional effect on bioavailability (Table 1).

Table 1: Back-transformed geometric means and 90% confidence intervals for mean urinary excretion of alendronate up to 36 hours post-dose in 15 post-menopausal women given 20 mg alendronate under various dietary conditions. All treatments in the table compared to dosing 2 hours before eating. (Protocol 32)

Treatment	Mean	90% confidence intervals
Meal + Ca ⁺⁺ 2 hrs post dose	91	62, 133
Meal 1 hr post dose	54	37, 80
Meal + Ca ⁺⁺ 1 hr post dose	66	45, 97
Meal 0.5 hr post dose	64	44, 94

In a second study in 50 (49 completed) healthy post-menopausal women, administration of 1 x 10 mg alendronate 0.5-1 hour before a meal (FDA Standard meal) significantly impaired absorption as compared with administration 2 hours before a meal. More significantly, it was found that administration of alendronate either immediately or two hours after eating resulted in virtually no absorption of drug. Also noted is that dosing 0.5 hrs before a meal resulted in decreased absorption as compared to 1 hour before eating (Table 2).

The effect of the administration of 1 x 10 mg alendronate with typical breakfast beverages such as coffee and orange juice was investigated in 42 post-menopausal women. Administration with coffee or orange juice as compared to water reduces the bioavailability of alendronate by 60%.

The effect of gastric pH on the absorption of the 40 mg tablet was examined. Intravenous ranitidine was found to more than double the amount of alendronate excreted in the urine, but did not affect the urinary excretion of concomitantly administered iv ¹⁴C-alendronate. This indicates that the increase in the amount of alendronate excreted is likely due to increased absorption rather than inhibition of renal excretion.

In the pivotal clinical trials (Protocols 35 and 37), patients were instructed to wait 1 hour after dosing to eat. In the labeling, it is stated that alendronate should be taken in the morning at least 30 minutes before ingestion of any food. The basis for this dosing recommendation is based on Protocol 54, which was a clinical study of women age 59-85 who were randomized to alendronate 1 mg (n = 86), 2.5 (n = 89), 5 mg (n = 93) or placebo taken 0.5 hours before eating the first meal of the day. The Sponsor claims that since comparable efficacy was seen in this trial compared with the pivotal trials, and compliance with a 1 hour wait before eating may be a problem, the drug should be administered 0.5 hours before meals.

Table 2: Mean relative bioavailability values and 90% confidence intervals in 49 post-menopausal women. All treatments in the table compared to dosing 2 hours before eating except where indicated. (Protocol 53) LOQ = limit of quantitation for the assay (1 ng/mL). Computed by the reviewer.

Treatment	Mean	90% confidence intervals	*Number (%) below LOQ
Dosed 0.5 hrs before meal	53.5	38.4, 74.6	**12 (24%)
Dosed 1 hr before meal	72.4	52.0, 100.9	**3 (6%)
Dosed immediately after meal	17.1	12.3, 23.9	41 (84%)
Dosed 2 hrs after meal	20.9	15.0, 29.1	32 (65%)
Dosed 0.5 hrs before meal using 1 hr before meal as reference	73.9	53.1, 103.0	—

*Refers to the number of subjects with urinary concentrations of alendronate below the LOQ for the assay. For the ANOVA, amount excreted was estimated by multiplying the urine volume by a random number between 0 and 1.

**Compare with 2 subjects (4%) for the reference treatment.

B. Bioequivalence

No bioequivalence studies were performed. The same formulations have been used throughout the development of the compound.

II. Pharmacokinetics

In a study in 15 post-menopausal women given 250 μ g of alendronate as a 2 hour infusion, the urinary excretion rate profile appears polyphasic (Figure 1). The first phase represents rapid distribution to bone and elimination, with the second phase representing elimination of drug not bound to bone (~45% of total dose).

It is known that the drug bound to bone does undergo slow elimination over a period of years as bone remodeling takes place. In an attempt to estimate the half-life of this elimination, 18 post-menopausal women with a diagnosis of osteoporosis received 7.5 mg of alendronate infused over 12 hours for four days. Complete urine collections were performed over 1 week, then 24 hour urinary collections were performed at intervals over the next 36 months. About 70% of

the total dose had been excreted by 18 months. The mean terminal half-life of elimination of alendronate from bone was estimated in these subjects at 10.9 years (range 5.4-19 years).

Because of the long terminal half-life of alendronate, there was concern that crossover-type trials might be impossible to perform if there were significant drug in the urine of volunteers returning for the second phase of a study. To test whether significant carry-over is seen after multiple dosing, ten post-menopausal women were given 125 μg alendronate as a 2 hour infusion on days 1, 4-8, and day 18. Urine was collected up to 36 hours post-dose on days 1 and 18, and alendronate was quantitated by HPLC. The mean amount of drug excreted after the first and last dose were 68.3 and 61.3 μg , respectively ($p = 0.38$). The conclusion is that the release of drug from bone is not a significant cause of carryover effects, thus permitting the use of the crossover design.

One study was performed examining the plasma pharmacokinetics of 10 mg ^{14}C -alendronate infused over 2 hours in women with metastatic breast cancer. Results are shown in Table 3. The difference seen between renal clearance and total body clearance is due to the essentially irreversible binding of about 60% of drug to the bone. It also appears that the percent of dose recovered in the urine is about the same as after a 250 μg injection, even though the dose given is 40 times larger. This indicates that the elimination over the first 36 hours after dosing may be linear over a very large range.

III. Metabolism

Studies in animals as well as a radiolabelled alendronate study in patients with breast cancer have revealed no metabolites of alendronate. Figure 3 shows plasma levels and total radioactivity over time in six women given 10 mg of alendronate by intravenous infusion. The curves are superimposable, suggesting no biotransformation is occurring.

Figure 1: Urinary excretion rate plot for 15 post-menopausal women given 250 μ g of alendronate intravenously. Error bars represent 95% confidence interval about the mean value. (Protocol 17)

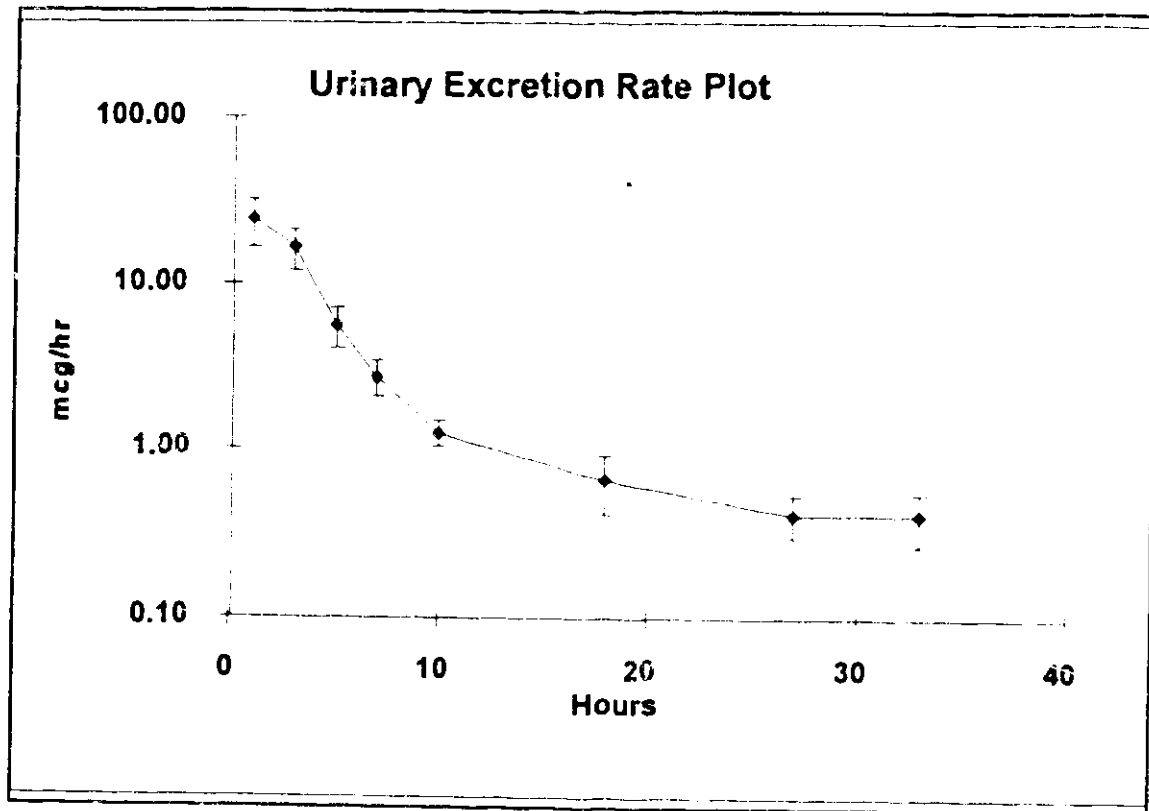


Table 3: Plasma pharmacokinetics of iv alendronate in 6 women with metastatic breast cancer given 10 mg over 2 hours. (Protocol 39).

Parameter	Mean	SD	CV%
AUC (ng*hr/mL)	838	61	7.3
V _{0.5s} (L)	29	8	27.6
Total body clearance (mL/min)	200	14	7.0
Renal Clearance (mL/min)	71	9	12.7
*Percent of Dose recovered in urine (%)	40.14	4.46	11.1

*patients given 250 µg intravenously excreted about 42% (95% CI 36.2, 49.3) over 36 hours.

IV. Dose and Dosage Form Proportionality

Alendronate will be available in 10 and 40 mg tablets. The recommended dose is 10 mg daily for post-menopausal osteoporosis and 40 mg daily for Paget's disease of bone.

A study in 15 post-menopausal women given 5, 10, 40 or 80 mg tablets of alendronate in a crossover fashion was performed to assess dose linearity. The percent of dose excreted in the urine over 36 hours is similar at all doses (Table 4).

V. Special Populations

Renal

Data from two studies in which post-menopausal women were given 10 mg alendronate 2 hours before a meal were used by the reviewer to determine if there is any relationship between renal function (as assessed by creatinine clearance) and amount of drug excreted over 36 hours. No obvious relationship exists between renal function and amount of drug excreted over 36 hours. Intravenous

Figure 3: Plasma concentrations of unchanged alendronate and total radioactivity in 6 women with metastatic breast cancer given 10 mg of ¹⁴C-alendronate over 2 hours. (Protocol 39)

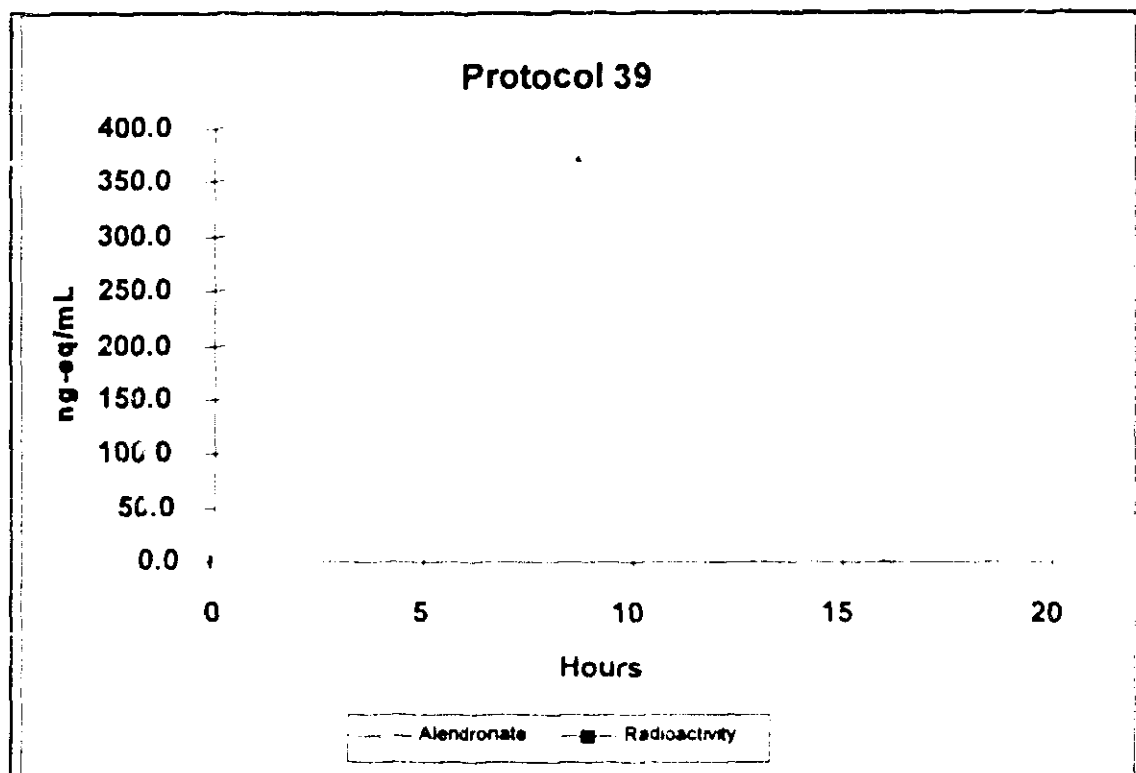


Table 4: Mean total urinary excretion (std dev, cv%) and % dose excreted over 36 hours in 15 post-menopausal women given 5-80 mg alendronate orally. The results indicate linear excretion from 5-80 mg. (Protocol 17)

Dose (mg)	Total excretion over 36 hrs (μ g)	Percent of dose excreted over 36 hours
5	18.6 (14.0, 75.3%)	0.395
10	43.6 (31.6, 72.5%)	0.446
40	170.9 (105.4, 61.7%)	0.429
80	355.4 (366.4, 103%)	0.437

data were also examined, with similar findings.

Age

No effect of age on the amount of alendronate excreted over 36 hours was noted, using the same data as above.

Gender

Both men and women excrete similar amounts of alendronate over 36 hours, suggesting that there is no gender difference in the pharmacokinetics of this compound.

Pediatric

Alendronate is not indicated for use in the pediatric population.

VI. Drug Interactions

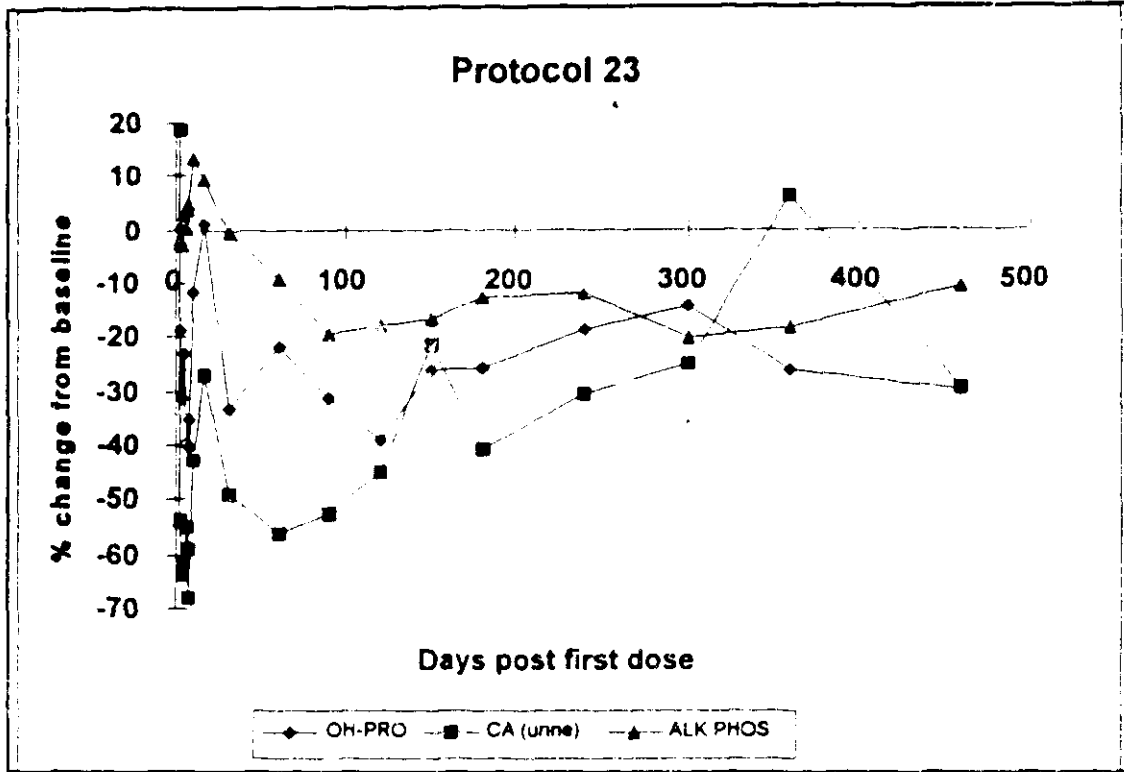
No drug interaction studies were performed in this submission. The very low plasma concentrations seen after administration, and the fact that alendronate is not metabolized by the liver suggests that no interactions with other drugs will take place by metabolic or protein displacement mechanisms. Rats given high doses of cimetidine, quinine, or probenecid along with alendronate showed no decreased urinary excretion of alendronate, suggesting that the usual anionic/cationic transport systems are not involved in its elimination. Etidronate (another bisphosphonate) does inhibit excretion of alendronate in the rat, suggesting that these compounds are secreted through a unique renal transport system.

Because of the substantial effect that food and beverages have on the oral bioavailability of alendronate, other medications (including vitamins and calcium supplements) should not be administered sooner than 1 hour after alendronate.

VII. Pharmacokinetic/Pharmacodynamic Relationships

As alendronate can not be quantitated in plasma at therapeutic doses, no pk/pd data exist. In Protocol 23, 18 post-menopausal women with a diagnosis of osteoporosis received 7.5 mg of alendronate infused over 12 hours for four days. Complete urine collections were performed over 1 week, then 24 hour urinary collections were performed at intervals over the next 36 months. Biochemical markers of bone turnover (urinary hydroxyproline, calcium, serum alkaline phosphatase, calcium and phosphorous) were also collected. The data indicate that significant decreases in urinary hydroxyproline and calcium persisted for nearly two years after administration (Figure 4). Serum calcium and phosphorous did not change significantly throughout the study. The gradual return to baseline of these markers of bone turnover despite the long half-life of the drug in bone reflects the fact that, upon administration, alendronate concentrates at sites of active bone resorption, where it exerts its pharmacological effect (inhibition of osteoclast activity). New bone is then formed over the bound drug, thus rendering it inactive. This suggests that total bone burden of alendronate is not likely to be related to clinical or pharmacological effect.

Figure 4: Some markers of bone turnover in patients given 7.5 mg iv x 4 days. OH-PRO- urinary hydroxyproline corrected for creatinine, CA (urine) - urinary calcium corrected for creatinine, ALK PHOS - serum alkaline phosphatase. Serum calcium and phosphorous did not change significantly from baseline and are not shown.



VIII. Formulation

The components of the tablet formulation are listed in Table 5. The two formulations are not proportionally similar in the ratio of active/inactive ingredients. Table 3 does show that the 10 and 40 mg tablets display dose proportionality

Table 5: Alendronate tablet formulations.

Component (mg)	Amount per 10 mg tablet (mg)	Amount per 40 mg tablet (mg)
Alendronate sodium trihydrate	13.05	52.21
Lactose NF		
Microcrystalline Cellulose NF		
Croscarmellose Na NF		
Mg Stearate		

dissolution specification is in 30 minutes. The data presented on all of the 10 mg clinical lots (batch sizes ranging from 10,000-600,000 tablets) indicate that is dissolved in 30 minutes. One production-sized batch (5.6 million) tested shows similar dissolution behavior. Data for the 40 mg tablet show similar dissolution profiles to the 10 mg tablet. Studies using the 10 mg tablet in simulated gastric fluid and simulated intestinal fluid (both without enzymes) as the dissolution medium showed identical results to water. This is not unexpected, given the high aqueous solubility of the compound.

IX. Assays

Both the urine and plasma assay involves co-precipitation of alendronate with endogenous phosphates by the addition of calcium chloride to the alkalized sample. The sample volume is 5 mL. The drug is then derivatized with 2,3-naphthalene

dicarboxyaldehyde N-acetyl-D-penicillamine (ND/NAP) which is necessary since alendronate does not possess a chromophore. The derivative is then quantitated using HPLC equipped with fluorescence detection.

Limit of quantitation - 1 ng/mL urine, 5 ng/mL plasma.

Linearity - Urine: linear from 1 - 25 ng/mL. Plasma linear from 5-125 ng/mL.

Specificity - no endogenous interferences were found in blank urine or plasma samples.

Precision -Urine: Intraday-6% at 1 ng/mL, 3.9% at 25 ng/mL. Inter-day-7.4% at 2.5 ng/mL, 7% at 25 ng/mL. Plasma: Intraday-4.2% at 5 ng/mL, 3% at 125 ng/mL. Interday-12% at 25 ng/mL, 4.2% at 100 ng/mL

Accuracy - 100% $\pm$ 5 for the whole range of concentrations for both plasma and urine.

Stability - No degradation noted in urine or plasma samples stored at -15° C for 8 months.

Recovery - recovery was high at 90% or greater for both assays.

X. General Comments (to be sent to Sponsor)

1) In the conclusion to Protocol 53 , it is stated by the Sponsor that alendronate absorption is not significantly different when it is given 0.5 or 1 hour before a meal (paired t-test, $p=0.127$). This analysis, along with supporting clinical data, is used to conclude that the compound may be given 0.5 hrs before the first meal of the day. However, it is noted that 24% of the subjects in Protocol 53 did not show quantifiable alendronate in their urine when the drug was given 30 minutes before breakfast, as compared to 6% and 4% when the drug was given an hour or 2 hours before breakfast, respectively. This suggests that the average patient, taking 10 mg alendronate 30 minutes before breakfast might be expected to absorb an amount of drug equivalent to what has been shown efficacious in the clinical trials only 75% of the time. Therefore, it is recommended that the product be dosed 1 hour before the first meal of the day, as in the two pivotal clinical trials.

2) A: of dissolution of both strengths of alendronate has occurred by 10-15 minutes, it is recommended that the dissolution specification be changed to in 15 minutes.

XI. Labeling Comments (to be sent to Sponsor)

1) In the *Pharmacokinetics* section under CLINICAL PHARMACOLOGY, the text under the heading *Absorption* should be replaced by the following:

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 (0.66%) was similar to that in women when administered after an overnight fast and 2 hours before breakfast.

In a study examining the effect of the timing of a meal on the bioavailability of alendronate in 49 post-menopausal women, bioavailability was decreased when 10 mg alendronate was administered either 0.5 or 1 hour before eating when compared to dosing 2 hours before eating. Bioavailability was also 26% lower when alendronate was administered 0.5 hours before eating as compared to 1 hour before eating. Bioavailability was negligible when 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%.

2) The summary table of pharmacokinetic parameters should be modified as follows:

	Mean	90% confidence Interval
Absolute bioavailability of 10 mg tablet, taken 2 hours before first meal of the day	0.74% (females)	(0.54, 1.03)
	0.66% (males)	(0.50, 0.87)
Absolute bioavailability of 40 mg tablet, taken 2 hours before first meal of the day	0.57% (females)	(0.41, 0.79)
Renal Clearance (mL/min) (n = 6)	71	(64, 78)

3) Under **PRECAUTIONS** the text under *Information for Patients* should be replaced with the following:

Information for Patients

Patients should be instructed that the expected benefits of FOSAMAX may only be obtained when each tablet is taken first thing in the morning at least one hour before the first food, beverage, or medication of the day with a full glass of plain water. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of FOSAMAX.

4) Under **PRECAUTIONS** the text under *Drug Interactions* should be replaced with the following:

Drug Interactions

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

Intravenous ranitidine infused to maintain a gastric pH ≥ 4 was shown to double the bioavailability of oral alendronate. The clinical significance of this increased bioavailability is unknown.

5) The first paragraph immediately under **DOSAGE AND ADMINISTRATION** should be replaced with the following:

DOSAGE AND ADMINISTRATION

FOSAMAX must be taken at least one hour before the first food, beverage, or medication of the day with a full glass of plain water only, since other beverages (including mineral water), food, and some medications are likely to reduce the absorption of FOSAMAX (see DRUG INTERACTIONS).



6/30/95

Michael J. Fossler, Pharm. D., Ph. D.
Pharmacokinetics Evaluation Branch II

RD initialed by John Hunt, Section Head 6/19/95

FT initialed by John Hunt, Section Head  6/30/95

Biopharm Day held 6/27/94. Attendees: Ludden, Malinowski, M. Chen, Collins, Hepp, Hussain, Dutta (HFD-510), Hunt, Fossler

cc: NDA 20-560 (pink), HFD-510(Dutta, Hedin), HFD-426(Fleischer), HFD-427(M. Chen, Fossler), HFD-340(Viswanathan), Drug, Chron, Review, FOI (HFD-19)
rev 5/4/95

APR 21 1995

Memorandum

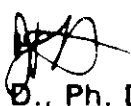
Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

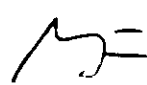
NDA: 20-560

Product: Alendronate Sodium
(FOSAMAX®)
10 and 40 mg tablets

Sponsor: Merck Research Laboratories, West Point, PA

To: Thomas M. Ludden, Ph. D.
Henry Malinowski, Ph. D.
Mei-Ling Chen, Ph. D.

Through: John Hunt, Section Head 

From: Michael J. Fossler, Pharm. D., Ph. D. 

Re: 21 Day Filing Meeting for NDA 20,560 for Fosamax (alendronate sodium), indicated for the treatment of two disorders of bone metabolism; osteoporosis in postmenopausal women and Paget's disease of bone.

Pre-Meeting scheduled for 19 April, 1995 at 11:30 AM in Dr. Chen's office

Date: 4/19/95

Synopsis

Merck Research Laboratories has submitted NDA 20,560 for alendronate sodium (Fosamax). Alendronate is a potent, orally active aminobisphosphonate compound to be indicated for two bone metabolic disorders; osteoporosis in postmenopausal women and Paget's disease of bone. The recommended dose of alendronate will be 10 mg daily for the treatment of osteoporosis and 40 mg daily for the treatment of Paget's disease.

A total of 11 studies have been submitted to the Human Pharmacokinetics

and Bioavailability section of the NDA. The urinary excretion of alendronate after both single and multiple doses was investigated in postmenopausal women (alendronate is present in the systemic circulation in minute quantities at clinically effective doses and can not be detected in the plasma by current analytical methods). Dose proportionality from 5 - 80 mg was also investigated in postmenopausal women. Studies investigating the bioavailability/bioequivalence of capsules and tablets were investigated in both postmenopausal women and healthy male volunteers. The to-be-marketed formulation is the same as that used in the pivotal clinical studies. The effect of ingestion of food and liquids (coffee, orange juice) on the bioavailability of the compound was thoroughly investigated (like all bisphosphonates, bioavailability after oral administration is poor (< 1%) and the absorption of alendronate is severely decreased by co-administration with food). The effect of increased gastric pH on the absorption of alendronate in postmenopausal women was also investigated. Using a extremely high iv dose of 10 mg, plasma pharmacokinetics of ¹⁴C-alendronate was investigated in women with metastatic bone disease secondary to breast cancer. A study in patients suffering from Paget's disease was designed to estimate the terminal t_{1/2} of alendronate and contains pharmacodynamic data. The drug has been studied in both men and women and the urinary excretion is similar in both sexes. No studies were performed in patients with renal impairment (the compound is not metabolized). The compound is not recommended for use in the pediatric population.

Information on the analytical methods and validation data used to quantitate alendronate in body fluids is included in the submission. Also included is a description of the formulations used in all of the studies and the dissolution method.

Recommendation

The Division of Biopharmaceutics (HFD-420) has reviewed the information presented in the Human Pharmacokinetics and Bioavailability section of NDA 20-560. Based on that review, the Division has determined that the application is fileable from a biopharmaceutics perspective. Please forward the **Comments** below to the Sponsor.

Comments (to be forwarded to Sponsor)

1. Currently, the FDA is attempting to standardize the content and presentation of the information that is to be given in the **Pharmacokinetics** section of the **CLINICAL PHARMACOLOGY** portion of the package insert. The **Pharmacokinetics**

section should present information as appropriate under the subheadings of *Absorption, Distribution, Metabolism, and Excretion*. Following this, there should be a section with the heading of *Special Populations*, where pharmacokinetic information, as appropriate, should be included under the sub-heading of *Geriatric, Pediatric, Gender, Race, Renal Insufficiency, Hepatic insufficiency, and Drug-Drug Interactions*. Where relevant information is lacking it should be so stated.

Lastly, a table with pharmacokinetic parameters to include (as appropriate) absolute bioavailability, time to peak, clearance, volume of distribution, half-life, and renal clearance for normals and each special population (including the drug's intended target population). Mean values with the coefficients of variation and 95% confidence intervals should be provided.

Please send the corrected labeling for review in WordPerfect for Windows 6.0 format.

2. Are there any data on the urinary excretion of alendronate in patients with renal impairment? Please submit any studies/analyses that examine the effect of renal impairment on the cumulative urinary excretion of alendronate.

3. Please submit a pH solubility dissolution study for the pure drug substance. In addition, for each tablet lot and strength used in any clinical or biopharmaceutics studies that remains in date, please perform dissolution studies in both simulated gastric and intestinal fluid (both without enzymes) using USP Method II at 50 rpm, using 12 dosage units per study. Please submit the data in ASCII format (space delimited) as well as hard copies.

21 day Filing Pre-Meeting held on 19 April, 1995 at 11:45 AM in Dr. Chen's office. Present: Fossler, Hunt, Chen, M.

cc: HFD-510(Dutta, Hedin, Niu), Drug File, Chron. File

SEP - 1 1995

NDA 20-560

September 1, 1995

Merck Sharp & Dohme
West Point, PA

Submission: March 31, 1995

PHARMACCOLOGY REVIEW OF NDA

DRUG: Alendronate sodium (=monosodium salt, trihydrate; ALN) Fosamax[®]; Aminohydroxybutane Bisphosphonate (AHButBP); alendronic acid. Laboratory codes: MK-217; L-670,452-005Y
Supplied as 10 and 40 mg tablets.

RELATED INDS:

Category: Bisphosphonate (anti-resorptive agent)

Proposed Clinical Indications: The treatment of postmenopausal osteoporosis at a recommended dose of 10 mg/day and Paget's disease at a dose of 40 mg/day.

Elizabeth Barbehenn
Elizabeth Barbehenn, Ph.D.

cc: NDA Arch
HFD-510
HFD-510/Jordan/Barbehenn
Fosamax.#01

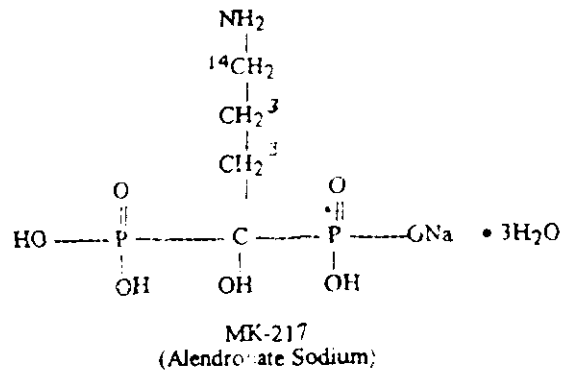
A. Jordan 9/1/95

Volume locations of studies refer to the numbers in IND (a complete set of studies was submitted April 27, 1994.)

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CHEMISTRY
STRUCTURE



Mr: 325; pKs: 0.81, 2.2, 6.3, 10.8, 12.2
 pH aqueous solution of sodium alendronate: 4.4
 pH of free acid: 2.2; pH of disodium salt: 8.7
 No UV absorbance (210-400 nm)

CHEMISTRY METHOD (HPLC of unlabeled drug):

(as 9-fluorenylmethyl chloroformate, FOMC derivative)

Column: 25x4.1 mm (10 μ particle), 35°C, 266 nm UV detection

Linearity/sensitivity: 0.02 to 0.15 $\mu\text{g/ml}$ (p.B-115)

Impurities/selectivity: resolution p.B-117; structures p.B-34

This method (forming a derivative) was only used in humans.

ADME SINGLE DOSE, RADIOLABELED DRUG (vol 27)

G1: METABOLISM IN MALE RATS AND DOGS (vol 27)

January 1990 (report date) Merck, West Point, PA.

TREATMENT: Male rats and dogs were given a **single dose of 1**

mg/kg dose i.v. [^3H -MK-217 (rats) or ^{14}C -MK-217 (dogs)]. Pooled 0-6 hour urine was examined on a Zorbax SAX column; pooled and combusted rat femurs and tibias were fractionated on this column on day 40 postdose. Alendronate was labeled in the butyrate part of the molecule: the 4 position (^{14}C) and the 2 and 3 positions (^3H). Rats received one dose of 1 mg/kg dose of ^3H drug. Urine was pooled, adjusted to pH 8, precipitated with 100% EtOH, dissolved in water and placed on a Bond Elute extraction column (aminopropyl), washed and eluted with 2M HCl. The absorbate was evaporated to dryness, redissolved in water, and put on an HPLC column monitoring radioactivity.

RESULTS: Column profiles of 0-6 hour urine from rats and dogs were similar to that of the original drug. The column profile of

radiolabeled rat bone had an extreme amount of tailing (peak at 5 minutes and >4 minutes more of counts trailing off).

G2: PK/ADME AFTER IV DOSE IN MALE Sprague-Dawley RATS (vol 27)
August 1988 (report date) Merck

STUDY #1)

Treatment: **Single 1 mg/kg i.v. dose of [14C]-MK-217**

Renal clearance 4.9 ml/min/kg (33% of dose in 24 hours)

Urinary excretion: approximately 33%

Biliary excretion: 0.2%

Tissues: "all had positive gradients relative to plasma"

	<u>ug/g</u> (24 H POSTDOSE)
Kidney	0.62
Liver	0.11
Lung	0.10
Brain	0.05
Spleen	0.04
Stomach/sm int	0.03
Testes	0.01
Plasma	0.001
Femur	7
Tibia	8

t_{1/2} in bone: >433 days

AUC 0-24 h (plasma): 67 ug h/ml

AUC 0-24 h (urine): 76 ug h/ml

STUDY #2)

Treatment: **Single oral doses of 1, 5, and 25 mg/kg** with absorption measured by levels in tibia and femur collected 24 hours postdose. Bone levels rose exponentially as a f(dose), more so after oral than iv dosing (see Fig).

METABOLISM: (p.C-52) "The results of the isolation procedure alone preclude the presence of any chemical species other than very polar, very strong anions." "...considerable tailing (on column) a phenomenon characteristic of polyvalent acids on ion-exchange packings."

G6: TISSUE DISTRIBUTION (i.v.) IN MALE SPRAGUE-DAWLEY RATS

September 1992 (report date) Merck (vol 27)

Rats were killed at 0.08, 0.25, 0.5, 1, and 6 h after 1 mg/kg 14C i.v. dose.

ONE MG/KG I.V. IN MALE RATS

TIME POST-DOSE (HOURS)	PERCENT OF DOSE REMAINING IN NON-CALCIFIED TISSUES
0.1	63
0.25	35
0.5	17
6	1

Muscle had 0.3%, liver had 0.2%, and kidney had 0.5% of dose at 6 hr postdose (tibia had 7 ug/g and femur had 9 ug/g).

Part II: 30 MG/KG I.V.

At the last timepoint measured (48 hours after a 30 mg/kg i.v. dose), 23% of the dose remained in the tissues while 31% had been recovered in the urine.

NON-CALCIFIED TISSUE LEVELS

(48 hours post 30 mg/kg i.v. dose)

	ug Eq/g	PERCENT OF DOSE
KIDNEY	240	10
LIVER	63	8
SPLEEN	42	0.4
MUSCLE	0.9	1.5
LUNG	22	0.3
STOMACH	13	0.2
PANCREAS	9	0.2
SM INTEST	6	0.3
URINE		31

G3: FACTORS AFFECTING ORAL ABSORPTION IN MALE RATS (vol 27)

September 1992 (report date) Merck

ABSORPTION: Fasted, male Sprague-Dawley rats were given 0.2 mg/kg 3H drug i.v. and 5 mg/kg 14C drug orally simultaneously. The rats were killed 24 hours later. Plasma levels were "too low to be measured" but no data supporting this.

ORAL ABSORPTION IN MALE RATS

PERCENT IN BONE: 1% of oral dose measured (14C/3H)

SITES OF ABSORPTION (after direct injection into duodenum)
 jejunum>duodenum>ileum> gavage

EFFECT OF FOOD (based on levels in tibia and femur):
 fasted:fed (3H:14C) in bone =4-5x

EFFECT OF DOSE

conc in tibia after 5 mg/kg oral gavage

DOSE (mg/kg)	TIBIA (ug/g)
10	0.2
20	0.2
30	1.5
40	8

(for comparison, 24 h after 1 mg/kg i.v., tibia had 7 ug/g)

EFFECT OF EDTA: no affect on absorption

EFFECT OF pH (ug eq/g tibia): pH 11=2x ug Eq/g pH 2 (po gavage)

G4: UPTAKE INTO BONE IN MALE DOGS AND MONKEYS; PO/IV (vol 27)

September 1992 (report date) Merck

Fasted males (two dogs and two cynomolgus monkeys) received 0.8 mg/kg 14C iv and 8 mg/kg 3H oral simultaneously. Radioactivity in bone was determined after combustion. Oral absorption based on bone levels was about 2% in both species (based on the ratio of 3H:14C).

G7: EFFECTS OF DOSE, SEX, AND AGE ON DISPOSITION (lit ref.)

Uptake into tibia fell off as dose increased (i.v. in male and female rats). There was no evidence of saturation of tibia uptake within 21 days (level in bone after one or 21 days same (37 and 33 ug/g in joint; 11 and 10 ug/g in shaft; and 33% urinary recovery) when tested in 2-month old male rats. There was no sex difference in tibial ALN concentration in old rats.

G9: EFFECT OF AGE AND SEX ON UPTAKE INTO BONE IN RATS

Tibia and femur had similar concentrations (measured after single doses of both 1 and 10 mg/kg i.v.)

ug eq/g
(after 1 mg/kg i.v.)

	<u>TIBIA CONCENTRATION</u>		<u>MALE</u>	
	MALE	FEMALE	TIBIA	FEMUR
2-MONTH	11	8 ^a	11	10
12-MONTH	3 ^b	3 ^b	3	3
24-MONTH	3 ^b	3 ^b	4	4

a: p<0.001 vs males

b: p<0.05 vs 2-month old rats

G8: UPTAKE INTO BONE IN MALE RATS AND DOGS AFTER SINGLE IV DOSE

DOSE (mg/kg i.v.)	DOG (TIBIA) (ug/g)	RAT (TIBIA or FEMUR) (ug/g)
0.2	1	
0.8	7	
1		10
3		20
5		40
10		5
20		125

b: p<0.001 vs 2-month old rats

G12: DOSE DEPENDENT KINETICS IN MALE RATS AFTER I.V. DOSE

Renal clearance **decreased** as dose increased (from 7.4 ml/min/kg at 1 mg/kg to 3.3 ml/min/kg at 20 mg/kg).

<u>I.V. Dose</u> (mg/kg)	<u>% in non-calcified tissues postdose:</u>	
	<u>6 hours</u>	<u>18 hours</u>
1	1	no data
20	30	30

G10: BONE UPTAKE IN EXPERIMENTAL HYPO- AND HYPERCALCEMIC MALE RATS

Models were removal of parathyroid (hypocalcemic) and injection of vit D or infusion of PTH (hypercalcemic). Dose was **one mg/kg i.v. drug**.

	FOSAMAX LEVELS	
	TIBIA (ug eq/g)	FEMUR (ug eq/g)
Control	11	9
Hypercalcemic (+vit D)	9	9
Hypocalcemic (-parathyroid)	8*	7*
Hypercalcemic (+PTH)	5*	5*

*p<0.01 vs control

G14: INTERACTION BETWEEN ETIDRONATE AND MK-217 IN MALE RATS

Renal excretion is both glomerular filtration and tubular secretion (Drug Metab. Disps., 19:926, 1992). Etidronate (which is secreted by the renal tubules) reduced the renal clearance of MK-217 suggesting they compete for the same transport system; etidronate also inhibited the bone uptake of MK-217.

G11: UPTAKE BY BONE IN MALE RATS WITH RENAL FAILURE

Mean concentrations of drug in bone in rats with renal failure were about twice those in control rats when tested at doses of 1, 3, and 5 mg/kg iv. Clearance was lower in renal failure rats.

G15: RENAL FAILURE AND TISSUE DISPOSITION IN MALE RATS

Renal failure was induced in rats by doses of 0.5, 0.75, 1 or 5 mg/kg uranyl nitrate (UN) injected in the tail vein five days before start of the study. MK-217 at 1 mg/kg i.v. (14C) and 3H inulin were injected and rats killed 24 hours post dose.

Uranyl Nitrate (mg/kg)	Renal Cl (ml/min/kg)	GFR (ml/min/kg)	Tibia conc (ug/g)
0	7.4	12	9.6
0.5	8.7	9.5	9.3
0.75	1.7	2.7	12
1	1.5	2.4	14
5	0.7	1.0	15

MK-217 accumulated in plasma (t_{1/2} increased as function of dose)

MK-217 accumulated in kidney (2% after 1 mg/kg uranyl nitrate and 7% after 5 mg/kg uranyl acetate).

MK-217 LEVELS AS % OF DOSE IN HEALTHY AND RENAL FAILURE RATS
(24 h post 1 mg/kg i.v. dose)

TISSUE	HEALTHY	RENAL FAILURE RATS	
	CONTROLS	(1 mg/kg UN)	(5 mg/kg UN)
KIDNEY	0.5	2.0	7.0
SPLEEN	0.02	0.02	0.6
SMALL INT	0.046	0.052	0.072
STOMACH	0.014	0.040	0.067
PLASMA	0.002	0.026	0.077

G16: RENAL HANDLING IN HYPO & HYPER CALCEMIC MALE RATS

Renal secretion of MK-217 was lower in both hypo- and hypercalcemic rats by a factor of 2-3. GFR was normal (hypo) but lower in hyper. Renal secretion of model compounds TEAB and PAH was not affected in hypo but MK-217 was decreased.

G20: EFFECT OF EXPERIMENTAL PEPTIC ULCERS IN MALE RATS

Ulcers were induced with aspirin or indomethacin by oral gavage. Radioactivity of drug in bones was determined after combustion. There was a 4- to 7-fold increase in MK-217 concentration in bone after indomethacin (from 0.46 ug/g in controls to 3.3 ug/g. The increase was thought to be due to gi mucosal erosion. Phenol red in the urine went from 4.3% (controls) to 32% (indomethacin).

G17: PROTEIN BINDING OF DRUG (rat plasma)

MK-217 is about 90% bound in rat plasma; the binding increases with increasing Ca⁺⁺ concentration up to 1 mM.

G18: PROTEIN BINDING (human plasma)

MK-217 is about 70% bound in human plasma; binding increases with increasing Ca⁺⁺ concentration up to 1 mM. EDTA blocks binding completely at 1.3 mM.

G19: PROTEIN BINDING (dog and monkey plasma)

About 20-30% is bound in dog and monkey plasma.

LISTING OF PK STUDIES IN NDA

(RADIOACTIVE PK STUDIES IN MALE RATS WITH IV DOSING)

(unless specified otherwise)

- Ref 1: i.v. (male rats)
- Ref 2: oral and i.v. (male rats; tibia and femur)
- Ref 3: oral vs i.v. (male rats; tibia and femur)
- Ref 4: oral+iv dose (tibia, fibula, mandible 8 days later; male dogs and monkeys)
- Ref 5: iv dosing (journal paper)
- Ref 6: iv dosing (tibia and femur)
- Ref 7: iv dosing rat (journal paper)
- Ref 8: iv dosing dog and rat (femur and tibia)
- Ref 9: iv dosing rat (femur and tibia; tissue distribution as % of dose; female/male; young vs old)
- Ref 10: iv dosing (urine and bone; hyper/hypocalcemia)
- Ref 11: iv dosing
- Ref 12: iv dosing (bones + other tissues as % of dose)
- Ref 13: iv dosing
- Ref 14: iv dosing
- Ref 15: iv dosing
- Ref 16: iv
- Ref 17: protein binding rat plasma

Ref 18; protein binding human plasma (70%)
 Ref 19: protein binding dog (75%) and monkey (30%)
 Ref 20: peptic ulcers and absorption in male rats
 Ref 21,22,23: papers from lit (review, clodrenate, Ca in renal tubule cell injury)

HUMAN PK

"Urinary excretion and retention within the body, presumably in the skeleton, are the primary means of disposition" (40% of i.v. dose and 0.3% of oral dose are excreted in urine).

"The presence of a metabolite in urine cannot be unequivocally excluded." (C-2397)

After a 20 mg dose: 60 ug was recovered in the urine (fed 2 hours postdose); 30 ug recovered (fed 1 hour postdose). (C-1822)

PHARMACODYNAMICS (vols. 25 & 26)

PROPOSED MODE OF ACTION: After injection, radiolabel goes to bone (hydroxyapatite) at sites of bone resorption and prevents osteoclast functioning.

IN VITRO STUDIES:

AFFINITY FOR BONE ($K_d = 1$ mM) with capacity of 100 nmoles/mg dry bone. 50% of drug taken up at pH 7 was released at pH 3.5. Binding to human bone particles (bone powder; 180 um mesh) increased as a function of dose up to the highest dose tested (4 mM).

OSTEOCLASTS ATTACHED TO BONE IN VITRO: Osteoclasts from rat humeri and femora of one- to five-day old rats were plated on bovine cortical bone slices and glued to coverslips. An intracellular fluorescent pH indicator showed that osteoclasts could extrude H^+ ions (unless bone slices were coated with alendronate first). [Ref F-13; vol 34, submitted 3/31/95]

MOUSE NEONATAL CALVARIA-DERIVED CELLS OR RAT OSTEOCLASTS FROM 1-3 DAY OLD RATS were co-cultured with bone marrow cells; intracellular pH was measured using a cation-sensitive fluorescent dye. ALN caused a small rise in intracellular Ca^{++} but it was too small to act as a termination signal. There were different cell types in terms of their pH response to external NH_4 : some increase and some decrease. (Ref F-11)

FRESHLY ISOLATED NEWBORN RAT OSTEOCLASTS: No effect on K⁺ conductance or membrane permeability to other ions (at 1 mM) Preincubation of alendronate with osteoclasts from rat or chick with bone particles inhibits bone resorption. (F-11)

LOCATION IN BONE: 50-70% of resorption surfaces identified by presence of osteoclasts. Ruffled border is flattened (2 days after dose); drug buried in bone (6 days postdose); drug on cement lines (7 weeks postdose).

IN VIVO STUDIES

MALE 9-WEEK OLD MICE (Ref F-7): [³H] Alendronate (ALN; 8 ug P/kg, "the clinically effective dose") or [³H] Etidronate (EHDP; 3 mg P/kg); 3 uCi/mouse, were given given as a series of four i.p. injections. Mice were killed 24 hours after the first injection. Radioactive uptake and autoradiography were done on hindlimbs. The skeletal uptake was estimated to be 2% ALN and 8% EHDP. For ALN, 10% bone surface was covered, for EHDP, 25%. There was more endocortical labeling with EHDP.

EIGHT DAY-OLD RAT PUPS were injected s.c. with both drugs as above. The uptake of tracer into hindlimbs was as below:

DOSE mg P/kg	<u>PER CENT IN BONE</u>		<u>PER CENT ON SURFACE</u>			
	EHDP	ALN	<u>OSTEOCLAST</u>		<u>OSTEOBLAST</u>	
			EHDP	ALN	EHDP	ALN
0.008		6		45		20
0.06		7		50		40
0.08	10		70		60	
0.1		11		50		40
4.5	22		90		90	

MALE MICE: One 0.03 ug/kg s.c. dose to male mice; mice killed 7 weeks later and 1.5 um section of femur exposed to film for 10 weeks at 4°. There was a line of grains as well as scattered grains "on the surface". (ref. F-8)

MALE RATS: Ten daily doses of 0.01, 0.1 and 1 mg/kg s.c. for 10 days; femoral length measured, femora than ashed. Tibia were embedded, sectioned (7 um coronal plane), and stained; trabecular bone volume was measured. Trabecular bone volume increased in all treated groups 34-37% vs 22% in vehicle control (Δ 12-15% but high variability). There was no change in epiphyseal width.

EFFICACY OF BONE RESORPTION (ORAL VS I.V.) (F-17)

Oral: Male Sprague-Dawley rats weighing 80-150 g were given daily gavage doses of 0, 1.25, 2.5, or 5 mg/kg for 14 weeks; rats were killed and one hindlimb fixed in 10% formalin.

I.V.: Male Sprague-Dawley rats weighing 120-200 g were given daily i.v. doses of 0, 0.05, 0.25, or 1 mg/kg for 5 weeks; rats were killed and one hindlimb fixed in 70% ethanol.

The proximal half of the tibia was embedded in methyl methacrylate; 7 um sections cut coronally and stained with Masson's trichrome. One section/rat tibia, from 0.5 mm below epiphyseal growth plate, was analyzed by a Joyce-Loebl Image Analyzer (examining five adjacent metaphyseal fields) in an area where there was trabecular, but not cortical, bone. Both the % trabecular bone area averaged over the 5 fields and the group means were calculated. In growing rats, metaphyseal bone resorption occurs continuously; inhibition in long bones produces an accumulation of trabecular bone that can be quantified.

MEAN TRABECULAR BONE AREA (%)

(Mean +/- S.E.)

DOSE mg/kg	I.V. (5/g)	ORAL (5/g)
0	10.4 (1.1)	15.9 (1.8)
0.05	70.3 (2.2)	
0.25	77.3 (1.3)	
1.0	77.2 (2.4)	
1.25		42.8 (2.4)
2.50		37.2 (1.8)
5.0		70.0 (2.3)

The sponsor's conclusion was that 0.05 mg/kg (i.v) was equivalent to 5.0 mg/kg (oral) and was the basis for their saying that 1% of an oral dose was absorbed.

OVARIECTOMIZED RATS + SUB-CUTANEOUS DOSING (F-16)

Sprague-Dawley rats (200-240 g) were given drug s.c. beginning immediately after ovx and continuing for 12 weeks. There were four dose groups (0.056, 0.28, 1.4, and 7.0 mg total P/kg/month) with treatments of 2, 4, or 8 times/month.

There was a 50% bone loss of cancellous bone within one month after ovariectomy and increased bone turnover. Treated rats had greater increases in bone volume with 8 treatments/month as opposed to 2 treatments/month using the same total dose (the maximum was reached at 0.28 mg P/kg (8 doses) and 1.4 mg P/kg (2 doses)). The % of eroded surface in ovx vehicle was not different from non-ovx; there was a decrease in eroded surface at the 7 mg P/month (from 12% no dose to 3%); the osteoid surface decreased from 18% (no drug) to 0.5% at the highest dose.

OVARIECTOMIZED RATS (F-18) (journal article)

Three month-old rats were ovariectomized and drug treatment started 4 months later with s.c. drug 0, 0.28, 2.8 or 28 ug/kg twice weekly for 6 months.

L6: Only the medium (but not high) dose produced significant increases on ultimate load and stiffness vs the vehicle group. Trabecular bone fraction (bone volume) of L5 and ultimate load were highly correlated.

FEMORAL: There were no effects on

Midshaft: load to failure, yield load, or stiffness.

Neck: ultimate load or stiffness.

(Sponsor stated that "at least 17 rats/g (were needed) to detect a difference with a power of 95% between control and ovariectomized vehicle animals in ultimate load of femoral diaphysis" because could not show effect at high dose.)

TREATMENT STUDY**ONE YEAR STUDY IN OVARIECTOMIZED & OSTEOPENIC RATS (F-19&20)**

Seven-month old rats were ovariectomized and 6 months later, when rats had lost 40% of cancellous bone in tibia, were treated for one year with either 1.8 or 18 ug/kg s.c., twice a week.

There were four groups (10/s/g): sham-ovx/vehicle; ovx/vehicle; ovx + 1.8 ug/kg s.c. ALN and ovx + 18 ug/kg s.c. ALN (twice/week). Prior to treatment, ovx and non-ovx rats were killed to determine bone loss (t_0). At the end of the study, rats were labeled i.p. with oxytetracycline (25 mg/kg) and 10 days later, with calcein (20 mg/kg).

BONE STRENGTH AND HISTOMORPHOMETRY (See Appendix I)

L5: There was a significant increase in:

- 1) ash weight as a function of dose (vs ovx control),
- 2) load as a function of ash weight,
- 3) vertebral area fraction of bone.

L3: THERE WAS NO EFFECT ON STIFFNESS. There was a decrease in the percent of vertebral osteoid surface at both doses but no effect on vertebral mineral apposition rate.

L3 PARAMETER	NON-OVX	OVX-VEH	OVX + 1.8 ug/kg s.c	OVX + 18 ug/kg s.c.
Ultimate load (N)	230±67*	155±43	190±24	260±27*
Stiffness (N/mm)	750±120	670±110	690±140	770±140
Ash weight (mg)	52±3*	42±6	46±3*	55±4*

*p<0.05 vs OVX vehicle
mean± SD

(See p. 68 for definition of terms)

RAT L3 (significant effects at 1.8 and 18 ug/kg 2x/week)

PARAMETER	NON-OVX	OVX-VEH	1.8 ug/kg s.c.	18 ug/kg s.c.
Cn-Bv/TV (%)	40**	25	38**	30
OS/BS (%)	1.3	2.4	0.6**	0.1**
OcS/BS (%)	0.13	0.67*	0.3	0.23
MARc (um/d)	0.54	0.66	0.6	0.57
DL-MS/BS (%)	0.33	1.1*	0.13	0.19
Ct-BV/TV (%)	18	17	19**	21**
Vertebral Area Fraction (%)	0.35	0.30	0.36**	0.38**

* greater than non-ovx p<0.05

**greater than ovx-veh p<0.05

TIBIA (Metaphysis): Cancellous bone volume/tissue volume: The bone loss due to ovx was prevented in a dose-dependent manner.

FEMUR: THERE WERE NO EFFECTS ON ULTIMATE LOAD, ASH CONTENT, ENERGY TO FAILURE, or BENDING STIFFNESS AT EITHER DOSE. At the high dose (18 ug/kg) there was an increase in apparent density of cortical bone and an increase bone mineral density in the whole femur, midshaft, and distal femur (see Appendix).

1-YEAR STUDY IN OVARIECTOMIZED BABOONS (PREVENTION STUDY)

(Ref F-23 to F-27; see review of 3 1/93 and Appendix II)
 Three groups of sexually and skeletally mature female baboons, 7/g, were ovariectomized and treatment begun immediately with vehicle or 0.05 or 0.25 mg/kg, i.v. every two weeks for one year (i.v. used because food interferes with absorption). One group of unoperated baboons served as intact controls.

SIGNIFICANT CHANGES (see p.19 and APPENDIX II)

ALN reduced bone turnover as measured by reduced urinary lysylpyridinoline (osteoclast) and serum alkaline phosphatase (osteoblast) activity.

1-YEAR STUDY IN OVARECTOMIZED BABOONS (SEE ALSO APPENDIX II)
(0, 0.05, 0.25 mg/kg iv twice/month; tx immediately post-ovx)

ILIAC CREST (changes at 0.25 mg/kg i.v.):

Decreased: Osteoid surface, bone form. rate, actn. frequency

Increased: cancellous bone volume

(No effect on osteoid thickness at 0.05 or 0.25 mg/kg.)

L5

Cancellous bone volume increased at 0.05 and 0.25 mg/kg.

RADII

Cross sectional area of Haversian canal diameter increased in vehicle control vs 0.25 mg/kg.

CORTICAL BONE

formation rate decreased to non-ovx level.

BONE STRENGTH: L4 core strength increased at 0.25 mg/kg.

There was no effect on strength or stiffness in the femoral mid-shaft, femoral neck or L3.

1-YEAR I.V. BABOON STUDY (0, 0.05, 0.25 mg/kg every 2 weeks)

Table V. Bone Densitometry

	Non-OVX	OVX + VEH	OVX + ALN (0.05 mg/kg)	OVX + ALN (0.25 mg/kg)	ANOVA <i>P</i>
L1 BMD (g/cm ²)	1.17±0.19	1.03±0.10*	1.11±0.04	1.18±0.06	0.06
L2 BMD (g/cm ²)	1.16±0.18	1.01±0.06*	1.10±0.06	1.18±0.08	0.04
L3 BMD (g/cm ²)	1.13±0.13	1.02±0.07*	1.08±0.06	1.17±0.10	0.03
L4 BMD (g/cm ²)	1.14±0.12	1.01±0.08*	1.09±0.05	1.14±0.12	0.08
L2-L4 (g/cm ²)	1.14±0.14	1.01±0.06 [†]	1.09±0.05	1.16±0.10 [‡]	0.03
Femoral Neck BMD (g/cm ²)	0.69±0.06	0.73±0.04	0.69±0.07	0.77±0.05 [‡]	0.04
Radial BMD (g/cm ²)	0.49±0.05	0.52±0.05	0.52±0.04	0.53±0.06	NS
L4 Apparent Density (mg/cm ³)	436.8±83.2	365.2±57.1	427.8±111.6	592.1±204.4 [‡]	0.02

Data are mean±SD; *n* = 7 per group. * Significantly different from non-OVX and OVX + 0.25 mg/kg ALN; *P* < 0.05. † Significantly different from non-OVX; *P* < 0.05. ‡ Significantly different from OVX + VEH; *P* < 0.05. § Significantly different from OVX and OVX + 0.05 mg/kg ALN; *P* < 0.05. ¶ Significantly different from all other groups; *P* < 0.05.

Table VI. Mechanical Strength

	Non-OVX	OVX + VEH	OVX + ALN (0.05 mg/kg)	OVX + ALN (0.25 mg/kg)	ANOVA <i>P</i>
L4 strength (MPa)	11.4±2.77	9.24±1.36	13.0±4.02	18.3±6.96 [¶]	0.01
Femoral midshaft strength (N)	2,391.6±219.9	2,144.6±509.0	2,352.2±303.7	2,353.1±282.6	NS
Femoral neck strength (N)	135.6±35.9	186.6±110.2	173.4±78.0	166.8±62.8	NS
Femoral stiffness (N/mm)	1,531.7±150.2	1,374.0±254.4	1,429.5±185.7	1,388.4±170.3	NS

Data are mean±SD; *n* = 7 per group. ¶ Significantly different from all other groups; *P* < 0.05

SUBMITTED 3/31/95

27-WEEK RANGE-FINDING STUDY FOR OVX, ESTROGEN ± ALN

TT# 93-053-1. April 21, 1993. Merck.

TREATMENT: Four groups of Sprague-Dawley rats (7/g; 12 weeks-old) were fed a restricted diet of 17 g/day. Three groups were ovariectomized (ovx) and left untreated for 13 weeks to reduce bone mineral density. Two of the ovx groups were given 0.1 or 0.3 mkd ALN orally in study weeks 14 to 26; two groups received deionized water only.

RESULTS: Urinary pyridinoline levels were comparable to those in non-ovx controls, "This lack of effect cannot be explained." In addition, although BWs normally increase with ovx, in this study they decreased (stated that 2/7 failed to gain weight). All rats were discarded without necropsy DW 26 because "urinary pyridinoline levels did not support dose selection for study #93-053-0" (see below) (YET they did not do urinalyses in full study.)

COMBINED ESTROGEN AND ORAL ALN IN OSTEOPENIC RATS (vol 35)

TREATMENT STUDY (6 months treatment) Ref F-22

TT #93-053-0. April 22, 1993. Merck. Lot#: Y008

TREATMENT: Three-month old Sprague-Dawley CD rats were divided into groups of 12. One group was control (no ovx, deionized water), one group was sham-operated (d. water), and 6 groups were ovariectomized. Rats were on a restricted diet of 17 g of chow/day and were dosed "at least 2 hours prior to feeding" (the dosing in relation to feeding was in the protocol I requested but not in study report).

At nine months of age (study week 27; 6 months post-surgery), ovariectomized rats were dosed orally by gavage with once daily doses until study week 53 (TOTAL OF 26 WEEKS TREATMENT), as follows: d. water, estradiol (E), 0.2 mkd ALN, 1 mkd ALN, 0.2 mkd ALN + E. and 1 mkd ALN + E. 17-beta estradiol was administered as a 0.05 mg 60-day implant; groups not receiving E got placebo pellets. (The rats received 0.1 and 0.5 mkd for the first 4 weeks but "Subsequently, the clinical dose was increased to 0.2 mkd because of better efficacy at this dose..."; as a result, rat doses were doubled.

Urine samples were collected in study week 13 and saved frozen but were never analyzed. Blood for estradiol measurements was collected study week 31 (ovx + E) and study week 32 (sham ovx).

COMBINED ESTROGEN AND ORAL ALN IN OSTEOPENIC RATS**RESULTS**

"Statistical analyses of the mean body weight changes, serum phosphatase and ALKP levels were not conducted. Interpretation of changes in these parameters was based on a visual inspection of the data." (June 1, 1995; they were provided at my request on 7/6/95.)

MORTALITY: Two HD (one from "possible intubation accident" but no gross or histopath data obtained, not in protocol to do so) and one with polycystic renal disease that died before dosing started.

BODY WEIGHTS: Only estrogen (either alone or with MK-217) prevented the weight gain that occurred with ovx.

SERUM CHEMISTRY:

CALCIUM: No effects of any treatment

ALKP: ovx caused 2x increase which was prevented by E ($\pm$ MK-217). MK-217 (@1 mkd only) prevented the increase at week 49 but not at week 40.

	OVX + (mkd oral)					
	E	0.2	1.2	E+0.2	E+1 (week 40)	
PHOSPHORUS:	decreased	3	5	11	12	15% vs ovx alone

ESTRADIOL (pg/ml): 64 (sham-operated) vs 42 (ovx + estradiol)

URINALYSIS: not done; "It was felt that useful information would not be obtained from additional analyses of these samples."

BONE STUDIES IN OSTEOPENIC FEMALE RATS AFTER 6 MONTHS TX

TREATMENT	L6			
	ULTIMATE LOAD (N)	BMC (g/cm)	BMD (g/cm ²)	STIFFNESS (N/mm)
Sham/vehicle	460	0.055	0.178	730±95
Ovx/vehicle	330#	0.042	0.148#	640±58
Ovx + E	420	0.050	0.163*#	710±60
Ovx + 0.2 mkd	350#	0.048	0.156#	580±87
Ovx + 1 mkd	410	0.049	0.163*#	630±34
Ovx + 0.2 mkd + E	480*	0.053	0.166*#	900±58
Ovx + 1 mkd + E	440*	0.054	0.172*	800±120

Data represent mean±SEM (n=9-11/g)

*p<0.05 vs ovx/vehicle

#p<0.05 vs sham/vehicle tx group

TREATMENT	WHOLE FEMUR			
	ULTIMATE LOAD (N)	BMC (g/cm)	BMD (g/cm ²)	STIFFNESS (N/mm)
Sham	124	0.452	0.227	240±10
Ovx/vehicle	124	0.422	0.206	240±8
Ovx + E	127	0.433	0.216*	234±10
Ovx + 0.2 mkd	128	0.415	0.209	237±9
Ovx + 1 mkd	132	0.443	0.216**	247±8
Ovx + 0.2 mkd + E	130	0.431	0.216**	230±15
Ovx + 1 mkd + E	120	0.454	0.223*	240±13

DATA REPRESENT MEAN±SEM (n=10-12/g)

*p<0.05 vs ovx/vehicle

**p<0.05 vs sham/vehicle tx group

TREATMENT	PROXIMAL FEMUR	
	BMD (g/cm ²)	BMC (g/cm)
Sham	0.229	0.111
Ovx/vehicle	0.205#	0.096#
Ovx + E	0.220*	0.106*
Ovx + 0.2 mkd	0.207#	0.097#
Ovx + 1 mkd	0.218#*	0.103
Ovx + 0.2 mkd + E	0.216#*	0.103
Ovx + 1 mkd + E	0.224*	0.109

*p<0.05 vs ovx/vehicle

#p<0.05 vs sham/vehicle

TREATMENT	MID-FEMUR	
	BMD (g/cm ²)	BMC (g/cm)
Sham	0.213	0.050
Ovx/vehicle	0.206	0.050
Ovx + E	0.209	0.045
Ovx + 0.2 mkd	0.211	0.050
Ovx + 1 mkd	0.214	0.054
Ovx + 0.2 mkd + E	0.212	0.049
Ovx + 1 mkd + E	0.220	0.052

TIBIA: No effects on trabecular thickness, number or spacing in any groups (sham ovx had higher number and smaller spacing than rest). Cancellous Bone volume/tissue volume (%): Estradiol alone and 1 mg/kg ALN were significantly greater than the ovx/vehicle but not estradiol + 1 mg/kg alendronate (does not make sense). This was the only measure of bone volume.

DISTAL FEMUR OF RATS

TREATMENT	BMD (g/cm ²)	BMC (g/cm)
Sham	0.244	0.123
Ovx/vehicle	0.204#	0.111#
Ovx + E	0.224*	0.119
Ovx + 0.2 mkd	0.209#	0.111#
Ovx + 1 mkd	0.220#*	0.115#
Ovx + 0.2 mkd + E	0.225#*	0.117#
Ovx + 1 mkd + E	0.232*	0.126*

*p<0.05 vs ovx/vehicle

#p<0.05 vs sham/vehicle

THREE YEAR ORAL (GAVAGE) TOX. STUDY IN ADULT DOGS (vols 29/30)
 #89-034-0. Merck, PA. April 1989- April 1992. Lot: #8
 (see APPENDIX III)

TREATMENT: Four groups of adult beagle dogs (4/s/g; 20-21 months old) were given in deionized water, 0, 0.25, 0.5, or 1.0 mg/kg/day once daily for 3 years (-1, 1, and 3x the 10 mg human dose). "Beginning week 47, [after about 1 year of dosing] generally all dogs were fasted 2 hours prior to dosing and at least 2 hours after dosing to insure good absorption of the compound" (before then, not stated as to when fed but presumably dosed fed). Urine was collected DW 154 for "possible assay for urinary pyridinoline levels to determine the effect of MK-217 on bone remodeling." Dogs were labeled in vivo at study end with iv oxytetracycline and calcein. Tissues collected and fixed for future analysis: ilia, four ribs, rt tibia, L4 and L5. Both femurs, T11-13, and L1-L3 were cleaned of muscle and frozen at -20 for mechanical testing or drug analysis. Histology was done on controls and high dose only.

THREE YEAR ORAL (GAVAGE) TOX. STUDY IN ADULT DOGS (vols 29/30)
 0, 0.25, 0.5, or 1.0 mkd daily

RESULTS

MORTALITY: none drug-related (one at 0.5 mkd killed because of mast cell tumor DW 72)

CLINICAL SIGNS: "none drug-related"

But one at 0.5 mkd decreased activity/weakness, ataxia of hind limbs DW 111. x-rays showed initially progressive narrowing of the space between vertebrae T11-12, "compatible with partial intervertebral disk protrusion...seen frequently in beagles.." and two others showed this on radiography (see below).

BW/FC: no effects

OPHTHALMOLOGY: no drug effects

RADIOGRAPHY:

"None related to tx"

"UNRELATED":

Canine hip dysplasia (two at 0.25 and one at 0.5 mkd)

Narrowing intervert. disc space: one at 0.25, one at 0.5, and one at 1.0 mkd. No clinical signs except for one at 0.25 mkd. "not uncommon to beagles, no dose response". Since radiographs are not normally taken in dog studies, we have no way of knowing whether this differs from expected.

EKG: None drug-related

One A-V heart block Dws 78 and 104 (not 129 or 155 @0.25 mkd)

HEMATOLOGY

none drug-related

SERUM BIOCHEMISTRY

RELATED TO TX

Pi: decreased HD 11% Dws 4-78 "attributed to pharm action"
 decreased MD Dws 39

"UNRELATED TO TX" (but seen in essentially all dog studies):

Ca (total): decrease in HD wks 39, 64, 154; wks 8 (F)

Ca (ionized): decreased in HD (wks 39 and 64)

ALT: increased 2-3x during weeks 129-155 in:

one F @0.25 mkd, one M @0.5, and one M @1.0 mkd

URINALYSIS: KETONES present in 1 LD, 1 MD and 3 HD dogs

ORGAN WEIGHTS (%bw) N.S.

KIDNEY (f): 0.45; 0.44, 0.46, 0.49

HEART (f): 0.71; 0.72, 0.81, 0.80

HISTOPATHOLOGY IN 3-YR DOG STUDY (0; 0.25, 0.5, 1.0 MKD)

(CONTROL & HD only)

RIBS: "Tx-related, dose-dependent delay of bone remodeling in the ribs from all dogs...characterized microscopically by very slight to moderate retention of the primary spongiosa. ...reported in previous studies with MK-217, 87-101, 87-645, 88-115, 88-641."

"The no effect dose for the changes in the ribs was not determined." The NOEL is below the human dose both on a mg/kg and a surface area basis.

TIBIA: no changes

SPLEEN:	CONTROL	HD
HEMOSIDEROSIS:	2 F 1 M	3 f (all VS, S) 4
FOCAL SIDEROSIS:	0 F 1 M	1 F 2 M
LYMPHOID NODULAR HYPERPLASIA	1 MD F and 1 HD M (both moderate)	

A report from HM Saunders, V.M.D., on radiography (p. Q-776):
 "The cause of the calcified objects in the soft tissue adjacent to the stifles is unknown." (1 LD F; 1 LD M; 1 MD F) Also seen was possible rt stifle joint effusion (HD M)
 (The stifle is the joint of the hind leg analagous to the human knee.)

BONE STRENGTH AND HISTOMORPHOMETRY IN DOGS (VOL 30; p. Q-782)
 Examined were geometry, ash content, apparent density of mid-shaft femoral sections, ultimate load and stiffness of femora. Vertebral trabecular ash content, apparent density, compression tests (failure load, stiffness of L3 vert. cores).

No differences were seen between any groups (including controls) in either histomorphometric or biomechanical properties (all data in figures, no tables). "We question whether ALN in a non-osteopenic animal model would yield significant differences...". They note large group S.D. and small numbers of dogs examined.

HISTOMORPHOMETRIC ANALYSIS OF L5 IN 3-YEAR DOG STUDY

(vol 30; p. Q-813)

Continuation of above study (0, 0.25, 0.5, 1.0 mkd; 4/s/g)

Dogs were labeled iv with oxytetracycline and calcein 12 days apart. L5 dissected free of muscle, fixed, sectioned.

No significant effects on cancellous bone volume, cortical bone area, trabecular number, thickness, or spacing.

Osteoid thickness

4.4±0.8; 4.5±1.3; 4.1±0.7; 3.4±0.5 (females; NS)

5.3±0.5, 5.2±1.2; 3.3±0.4; 3.0±0.2 (males; NS)

BONE FORMATION RATE (L5) IN DOGS AFTER 3 YRS TX ($\mu\text{m}^3/\mu\text{m}^2/\text{yr}$)

DOSE- GENDER	CONTROL	ALN 0.25 mkd	ALN 0.5 mkd	ALN 1.0 mkd	p 2- tailed
MALES	70±4	17±2	19±10	6±3	0.0001
FEMALES	14±4	5±4	8±4	2±1	NS

MEAN APPPOSITION RATE (L5):

Significantly lower in treated dogs at all doses

Males p<0.002

Females p<0.037

Fx (femoral bending failure; N) and Stiffness (N/mm):

no effects (see Figs.)

**INDICES OF REMODELING AND MINERALIZATION IN L5
(OS/BS, %)**

DOSE- GENDER	CONTROL	ALN 0.25 mkd	ALN 0.5 mkd	ALN 1.0 mkd	p (2- tailed)
MALES	9.7±2	3.3±1	2±1	1±0.2	0.05
FEMALES	5±2	0.9±0.4	3±1	1±0.7	0.009

HISTOMORPHOMETRIC ANALYSIS OF L5 IN 3-YEAR DOG STUDY**ALN CONTENT OF T11 (no difference M/F)**

2 ug/g (0.25 mkd)
 6 ug/g (0.5 mkd)
 12 ug/g (1.0 mkd)

ALN EXCRETED IN URINE (24 H) DW 109

9, 19, 35 ug (L, M, HD)

ALN EXCRETED IN URINE (24 H) DW 153

13, 34, 19 ug (L, M, HD)

"Bone sections were devoid of multinucleated osteoclasts (only one cell identified out of 28 sections analyzed); the cancellous surface was not scalloped, indicating absence of current resorptive activity"

OVARECTOMIZED BABOONS (Effect of ovx on iliac crest; Ref. F-21)
 Three sexually and skeletally mature female baboons, 8 years old, were ovariectomized; three were left intact. Bone biopsies from the right iliac crest were obtained at baseline and after 6 months.

There was no effect on body weight; there was an increase in trabecular bone turnover as estimated by fractional osteoid and active forming surface, appositional rate, and radial closure rate. (lit ref)

EFFECTS OF ALN ON BONES AFTER LIFETIME EXPOSURE IN RATS (vol 29)

This is bone data from the rat carcinogenicity study (#89-089-0). Five-week old Sprague Dawley rats (75/s/g) were treated with ALN for 105 weeks by gavage at doses of 0, 1, 3.75, and 7.5/5 mg/kg/day. Rats had food available at all times. The high dose was lowered DW 9 (F) and DW 13 (M). At completion of the study, L3-L5 and right femora were analyzed:

NUMBERS OF RATS ANALYZED BY DOSE GROUP IN CA STUDY

DOSE	FEMALE	MALE
CONTROL	27	25
LD (1 mkd)	21	21
MD (3.75 mkd)	0	0
HD (5 mkd)	11	13

L4 VERTEBRAL COMPRESSION AND FEMORAL STRENGTH IN RATS AFTER LIFETIME EXPOSURE (carcinogenicity study): Summary data are provided in graph form and indicate a statistically significant increase as a function of dose in failure load (L4), femoral midshaft 3-point bending, and L3 vertebral area fraction of bone in both males and females after treatment from 5 to 110 weeks of age.

Merck mentioned data from a rat study in which rats that had been "in training" (exercising) up to 12 months in age achieved a higher peak trabecular bone volume at maturity compared to non-exercised controls. The rats that exercised retained the higher bone mass at 24 months (12 months after ceasing training).

Merck feels that the data after lifetime exposure (2-year carcinogenicity study, the only study where an increase in femoral bone strength was seen) was the result of 1) inhibition of bone resorption during bone growth resulting in an increased bone mass at maturity coupled with 2) "attenuation of BMU-based bone resorption" at maturity when bone loss would normally occur.

COMPARISON OF ALN AND FLUORIDE ON GROWING PIG BONE (F-42)

Three groups of female minipigs (12/g; 7-9 months old at start of study) were given orally 0 (vehicle), ALN (1 mkd), or NaF (2 mkd) for one year. At the termination of the study, fifteen pigs were labeled with oxytetracycline and calcein (both 20 mg/kg i.m.) with a 5-day interval between doses. L1-L5 and 12th thoracic vertebra, right tibia, both femora, 12 and 14th ribs, iliac crest and proximal tail were collected.

ALN decreased and NaF increased bone turnover in cancellous bone but neither changed bone volume. L4 core stiffness was increased by ALN. Fluoride had no effect on stiffness. There was no effect of either drug on failure load of femur, L2, or L4 (see APPENDIX IV attached).

HYPERCALCEMIA OF MALIGNANCY (Ref F-28)

LEYDIG CELL MODEL: Eighteen days after implantation with Leydig cell tumors, rats showed a rise in serum Ca of 2 mg/dl. The rise was prevented by daily s.c. injections of 0.4 or 4.0 mg/kg (but not 0.04 mg/kg ALN).

EFFECTS ON LOSS DUE TO IMMOBILIZATION (Refs. F-29 & -30)

The 12% bone loss in male rats (immobilized by tenotomy or sciatic neurectomy) could be reduced to 7% and 4% by two s.c. injections of 0.4 or 4 mg/kg, respectively, prior to immobilization. Measurement was made of bone ash. There was a decrease in eroded surfaces.

EFFECTS ON BONE LOSS DUE TO HYPERTHYROIDISM (Ref F-31 & -32)

Hypertthyroidism, induced by s.c. injection of L-thyroxin (T4) six times/week, produced increased bone turnover and cancellous bone loss in the tibia which was prevented by ALN 1.75 mg/kg p.o. two times/week (male rats).

A second 3-week study (250 ug/kg/day s.c. T4 or vehicle $\pm$ 0.5 mg/kg ALN, p.o. 2x/week or vehicle) again found bone loss in the tibia, but not in the vertebral body, "suggesting that histomorphometric observations obtained at one skeletal site can not be extrapolated to the entire skeleton." The reason is not known, although the authors speculate that there is greater redundancy of bone in the tibia, or, more likely, a higher basal turnover rate in tibia (parameters of bone remodeling 2- to 5-fold greater in tibia). In T4-treated rats, ALN maintained trabecular thickness and OS/BS at control values.

BONE ABLATION AND EFFECTS ON BONE IN RATS (Ref F-33, 34)

ALENDRONATE EFFECTS (Ref F-35): Male Sprague-Dawley rats had the marrow cavity of the tibia removed under anesthesia. Under these conditions, 35% of the volume of the marrow cavity fills with cancellous bone within 6-7 days before resorption and restoration of normal bone marrow 14 days later. After surgery, rats were treated with ALN s.c. for 6 days (0, 1, 2, 8, or 40 ug/kg/day) and sequentially killed at 0, 7, 10, 20, 30, and 60 days post-ablation. The hindlimbs were removed, the tibia fixed, sectioned, and stained. The resorption of bone was not affected at 1 and 2 ug/kg/day but was retarded dose-dependently at 8 and 40 ug/kg/day.

TOXICOLOGY STUDIES: GENTILI STUDIES (ITALY)**25-DAY IV TOXICITY IN RATS**

Treatment: Doses of 1 or 5 mkd

Results: BW and FC decreased

Urinary (5 mkd): urea nitrogen "marked increase"; Ca, Pi, K, protein, glc, leukocytes all increased

Plasma (5 mkd): Ca decreased

Histology: Urinary bladder hypertrophy

Severe renal alterations (hydropic change) in tubules

Bone trabeculae increased at 1 and 5 mkd

4-WEEK IV TOXICITY IN DOGS

Treatment: doses of 0.05, 0.25, 0.5 mkd; 5 days/week

Results: "increased bone tissue in tibial metaphysis and ossification of ribs"

JAPANESE STUDIES**3-MONTH IV TOXICITY STUDY IN RATS WITH 7 WEEK RECOVERY**

Treatment: Doses 0, 0.001, 0.01, 0.1, and 1 mkd

Results:

1 mkd: hypoplasia of incisor teeth, hyposthenuria

Anemia: 0.1 mkd (M) and 1 mkd (M/F)

Serum Ca: decreased 0.1&1 mkd

ALKP serum: decreased all doses (F) and ≥ 0.01 mkd (M)

CPK plasma: ≥ 0.1 mkd elevated (M/F)

HISTOPATHOLOGY: trabecular bone increase, hypoplasia incisor, basophilic change proximal convoluted renal tubular epithelium in rats at doses ≥ 0.01 mkd

RECOVERY: incisor, bone, hyposthenuria, anemia still observed

3-MONTH IV TOXICITY STUDY IN DOGS WITH 6-WEEK RECOVERY

Treatment: Doses 0, 0.0025, 0.05, 1 mkd

Results (Summary only):

CPK (plasma): increased HD

ALKP, Ca, Pi: decreased M and HD

Histopathology:

trabecular bone increased femur and tibia M and HD

Ca deposition with fibrosis in gastric mucosa (HD females)

RECOVERY: Histopathology findings still present

THREE DOSE IV NEPHROTOXICITY STUDY IN FEMALE DOGS (v.5)

TT# 88-045-0. Merck, West Point, PA. April '88-Aug '88

Treatment: Female dogs (6-months old; trained, conscious, with cannulated bladder for 3 hours daily sampling) were given 1 mkd by slow 90-110 minute infusion (n=2) or 1 mkd by one minute bolus (n=3) in sterile saline, pH 6, once daily for 3 doses. Blood samples were collected pretest and at 30 min intervals for 3 hours postdose.

RESULTS

Serum calcium and Pi decreased

Kidney wt: no change

Bladder histopathology:

Ulcer: 2 dogs

Hemorrhage: in 4 dogs; grade 1 and 2 "attributed to trauma induced by catheterization"

Kidney histopathology: focal renal tubular basophilia in one

URINALYSIS

Urine flow (ml/min) with:

Slow infusion: 0.4 to 0.7 ml/min (at baseline)
1.6 to 2.0 ml/min (60-150 min postdose)

Bolus: 0.4-0.7 ml/min (at baseline)
1.2 ml/min (60-180 min postdose)

0.5-0.4 ml/min (day 4 control values at 60 min)

Na excretion:

Slow infusion: 70 baseline to 210 uEq/min (90-120 min) day 1
110 " to 210 " " " day 2
100 " to 200 " (120-150 min) day 3

day 4 control: 100 and 132 (60 min)

Bolus: 70-80 uEq/min at baseline increased to 140-150 uEq/min between 90-180 min days (2&3) day 4 control: 90 and 50

K excretion: No effects

Plasma Na concentration (mEq/L): no effects

Plasma K concentration (mEq/L): no effects

Filtration fraction (%); hematocrit (%); pH: no effects

GENTILI STUDIES (SUMMARIES ONLY PROVIDED)

7-WEEK ORAL TOXICITY OF FREE ACID IN RATS

Treatment: Doses 0, 5, 10, 20 mkd for 5 days/week.

Results: GI hemorrhages in one HD female; most died of pneumonia.

9-WEEK ORAL TOXICITY IN RATS

Doses 0, 1.25, 2.5, 5 mkd in 5% gum arabic

Results:

Clinical signs: abnormal behavior (irritability, aggressive); Pi decreases in all females and HD males

Urinary: decreased creatinine all treated males and HD females; decreased Ca M and HD (M/F); decreased Pi M and HD (F)

Tibia: length reduced (all treated)

5-WEEK ORAL TOXICITY IN DOGS

Treatment: Doses of 10, 20, or 40 mkd (capsules)

Results: "GI changes (buccal mucosal ulceration & gastric hyperemia) M and HD; bone trabeculae increased all doses";

6-MONTH ORAL TOXICITY IN RATS WITH 2-MONTH RECOVERY

Treatment: Doses of 0.3, 0.9, 1.2 mkd by gavage in 5% gum arabic; 15/s/g killed at 6 months; 5/s/g had 2 month recovery period.

Results: "decrease in serum Pi and Ca (M and HD)"

1-YEAR ORAL TOXICITY IN DOGS WITH 3-MONTH RECOVERY

Treatment: Doses of 0, 15, 30, 60 mkd

Results: "increased bone trabeculae (1° spongy bone) all doses"

MERCK (ORAL STUDIES)**6-MONTH ORAL GAVAGE TOXICITY STUDY IN DOGS*** (vol 9)

TT #88-115-0. Merck, West Point, PA. Oct '88- April '89

TREATMENT: Four groups of beagles (4/s/g; 9 months old) were given by gavage in distilled water, 0, 0.5, 2, or 8 mg/kg/day. The relation of feeding to dosing was not stated. Tissues collected at necropsy for "possible future analysis": one rib, ilium, L1 vertebra, proximal third left femur fixed in 70% ethanol; rt femur, rt humerus and rt radius frozen at -20 as well as 50 g of liver of 3/s/g. Histopathology was done on control and high dose.

*(This study was submitted to IND 31,775 on 10/13/89 and reviewed 1/15/90.)

RESULTS:

Mortality: 2 dogs killed

One control M (DW 10): swelling left cervical area (anaerobic bacillus) and no serum chemistry findings

One HD Male (DW 16): necrotizing, suppurative bronchopneumonia "most likely an intubation accident"; however, findings included **increased** (p.2281):

Hgb, Hct, RBC, leukocytes, seg and non-seg neutrophils, A/G ratio, AST, ALT, Cholesterol and Triglycerides

decreased:

ALKP, calcium and ionized calcium, phosphorus
(histopathology: see below)

There were no drug effects on mortality, clinical signs, body weight, food consumption, ophthalmology, ECG, hematology, clinical chemistry, or organ weights.

Urinalysis (measured weeks 5,8,12,25; no baseline data and no statistics): "Ca excretion increased M and HD vs control" but final data are 13, 8, 11, 10 mg/dl and 26, 21, 21, 15 mg/18 hours (p.2163)

PATHOLOGY**GROSS**

Bone changes (Costochondral): ribs delay of bone remodeling as f(dose); medullary cavity near costochondral junction of sagittally sectioned ribs HD: dull gray

HISTOPATHOLOGY (6-MONTH DOG TOX; 0.5, 2, 8 mkd)

DOG THAT DIED (grades 1-5 in increasing severity)

Large intestine, Liver (cellular infiltration)
 Gallbladder (focal hemorrhage)
 Kidney (tubular degeneration, chronic nephritis, grade 2)
 Lungs (bronchopneumonia, grade 4)
 Lymph node (lymphoid hyperplasia, suppurative lymphadenitis)
 Thymus (involution)
 Rib and femur (spongiosa)

DOGS AT TERMINAL SACRIFICE

	FEMALES	MALES
Salivary glands (lymph infiltr)	0;0,0,1	0;0,0,1
Thyroid	0;0,0,0	0;0,0,1
lymphocytic thyroiditis	0;0,0,0	0;0,0,1
thyroglossal duct cyst		0;0,0,1
Testes (semin tubule degen)		0;0,0,1
Rib (1° spongiosa)	0;3,3,4	0;3,4,4
decreased osteoblasts	0;0,0,2	0;3,4,4
fibroplasia	0;3,4,4	0;3,4,4
retention		
Femur (1° spongiosa)	0;0,0,2	0;0,2,4
retention		

bone grades (rib & femur): 1-2 (L and MD);
 rib osteoblast and retention: 4 (HD)

1-YEAR ORAL TOXICITY STUDY IN DOGS

TT#88-641-0 Merck, US

Reviewed by C. Dutta/ Four groups of dogs (4/s/g) were given by gavage 0, 0.5, 2, or 8 mkd. A recovery group was treated for 13 weeks and taken off drug until necropsy week 53.

Serum Ca down HD; urinary Ca up, retention of primary spongiosa of ribs and femur from slight to severe in all treated dogs; still present in recovery group at week 53.

Chronic focal nephritis and mineralization of renal papilla in HD and recovery groups attributed to treatment.

REPRODUCTIVE TOXICITY

ORAL RANGE-FINDING IN NON-PREGNANT RABBITS (VOL 11)

TT #88-722-2

TREATMENT: Six groups of female rabbits were given for 13 days orally by gavage in 0.5% methylcellulose, 0, 1.5, 5, 15, 50, or 150 mkd.

RESULTS: There was mortality at 50 and 150 mkd. These groups were killed early; there were no findings in other groups.

ORAL RANGE-FINDING IN PREGNANT RABBITS (VOL 11)

TT #89-701-1. January 1989. Merck, West Point, PA

Lot: #008

TREATMENT: Four groups of New Zealand White rabbits (8 months old; 10/g) were given 0, 4, 10, or 25 mkd orally by gavage in deionized water, days 6 through 18 of gestation. Rabbits were ovulated with 25 USP units of HCG iv and artificially inseminated.

RESULTS

MORTALITY: none

BW/FC/PHYSICAL SIGNS/HEMATOLOGY/SERUM BIOCHEMISTRY: no effects

EMBRYO SURVIVAL/LIVE FETAL WT/EXTERNAL FETAL EXAM: no effects

ORAL RANGE-FINDING IN PREGNANT RABBITS (VOL 11)

TT #89-701-2. February 1989. Merck, West Point, PA

Lot: #008

TREATMENT: Four groups of New Zealand White rabbits (6 months old; 10/g) were given 0, 35, 50, or 75 mkd orally by gavage in deionized water, days 6 through 18 of gestation. Rabbits were ovulated with 25 USP units of HCG iv and artificially inseminated.

RESULTS

MORTALITY: 75 mkd group killed due to excessive wt loss

BW/FC: Wt loss MD (vs gain control)

PHYSICAL SIGNS: decreased water consumption M and HD

HEMATOLOGY: no effects

SERUM BIOCHEMISTRY (day 19 of gestation):

urea nitrogen: 13.5; 14.9, 17.3, [22 (day 16)]
 creatinine: 1.1; 1.2, 1.5, [1.7 (" ")]
 protein 5.0; 4.6*, 4.5*
 albumin, 3.7; 3/3*, 3.2* [2.6
 A/G: 2.9; 2.7, 2.5* [2.1
 calcium: 13.6; 12.9*, 12.7* [10.7
 phosphorus: 4.3; 3.9, 4.1 [3.8
 potassium: 4.0; 3.9, 3.4* [3.4

EMBRYO SURVIVAL: no effects

LIVE FETAL WT: decreased M and HD (13%; p<0.05)

EXTERNAL FETAL EXAM: one MD fetus had enlarged hemorrhagic eye
 "Maternotoxicity at all doses" p. c-229

EXPLORATORY URINE DRUG LEVEL IN PREGNANT RABBITS (day 8)

TT #89-701-3 February 1989. Merck, West Point, PA

Lot: #008

TREATMENT: Pregnant rabbits (4/g) were given doses of 0, 5, 35, and 75 mkg by gavage in deionized water on day 8 of gestation. A catheter was inserted into the bladder and urine collected 30 min prior to dosing and 0-3 and 3-6 hours after. No food or water were available, but 100 ml water was intubated 30 min before and 3 hours post dose. Samples were frozen; later thawed, acidified to pH 1, and analyzed.

EXCRETION (0-6 HOURS POSTDOSE)

DOSE (mg/kg)	ug (0-6 h)	PER CENT RECOVERY
5	30	0.2
35	300	0.2
75	800	0.3

ORAL DEVELOPMENTAL TOXICITY STUDY IN RABBITS

TT #89-701-0. April 1989. Merck, West Point, PA Lot: 008

TREATMENT: Four groups of 10 New Zealand White rabbits (6 months old; 18/g (ovulated with 25 USP units of HCG iv and artificially inseminated) were given 0, 3.5, 10, or 35 mkg orally by gavage in deionized water, days 6 through 13 of gestation. Rabbits were sacrificed day 28 of gestation. Thorax and viscera of dams examined in gross necropsy.

ORAL DEVELOPMENTAL TOXICITY STUDY IN RABBITS (0,3.5,10,35mkd)

RESULTS

MORTALITY: Two "treatment-related" at 35 mkd (one non-pregnant and one pregnant); both ate very little and lost weight

NECROPSY (rabbits that died):

#0327: LUNGS: Generalized congestion, edema, red discoloration
histology: diffuse congestion

#0334: STOMACH: edematous and hemorrhagic with surface erosions
"(erosive gastritis = COD)"

ABORTIONS: One (control) and 3 (3.5 mkd)

BODY WEIGHT/FOOD CONSUMPTION:

BW: wt gain decreased at 35 mkd (pregnant) with compensatory
gain postdose days 19-28

wt loss at 35 mkd (non-pregnant)

FC (day 19): 135; 140, 121, 121 g/day (other days similar)

LAPAROTOMY DATA	0	3.5	10	35 mkd
LIVE/PREGNANT:	14	15	15	10
LIVE/NOT PREGNANT:	3	0	3	6
DEAD NOT PREGNANT	0	0	0	1
DEAD PREGNANT	0	0	0	1
LIVE FETUSES:	98	95	106	66
IMPLANTS/PREGNANT FEMALE:	7.9	7.4	7.4	7.0
% PREIMPLANTATION LOSS:	15	32	25	25
LIVE FETUSES/PREGNANT FEMALE	7.0	6.3	7.1	6.6

NO EFFECTS ON: fetal wt

FETAL EXAM

EXTERNAL

1/15 litter with malformations (MD) 7% spina bifida

1/15 litter with variations (LD) 7% hematoma

VISCERAL: no drug-related effects

SKELETAL (per litter): 14;15,15,10 litters

Caudal vertebra malformation 1; 2, 0, 3 (7;13,0,30%)

Sternebral malformation 0; 0, 0, 1 (0; 0,0,10%)

Sternebral variation 0; 0, 0, 1 (0; 0,0,10%)

FETAL OSSIFICATION

Fetuses examined 98 95 106 66

% with incomplete oss. 32 31 36 35

ORAL RANGE-FINDING STUDY IN PREGNANT RATS

TT #89-702-1. January 1989. Merck, West Point, PA

Lot #: L-670,452-0057008

TREATMENT: Six groups of Sprague-Dawley CD rats (10 weeks old; 10/g) were given by gavage in deionized water, 0, 0.5, 1.5, 5.0, 10, and 25 mg/kg/day days 6 through 17 of gestation. Females were sacrificed on day 20 of gestation.

RESULTS

MORTALITY: none

ABORTION: none

PHYSICAL SIGNS: none treatment-related

BODY WEIGHT CHANGES (days 6-18):

18% gain (25 mkd) vs 29% (controls) (4/9 transient wt loss)

HEMATOLOGY: no drug effects

SERUM BIOCHEMISTRY (*p<0.05):

Phosphorous: 6.0; 6.0, 6.1, 6.5, 6.9*, 7.4* mg/dl

ALT: 48; 53, 54, 55, 54, 59* U/L

EMBRYO SURVIVAL (p<0.05)

implants/pregnant female: 17% decrease (25 mkd)

live fetuses/" " : 16% decrease (25 mkd)

LIVE FETAL WEIGHT: 7% decrease (not significant at 25 mkd)

3.3 g vs 3.5g for rest

EXTERNAL EXAM FETUSES: no drug effects

ORAL DEVELOPMENTAL TOXICITY IN PREGNANT RATS (VOL 12)

TT #89-702-0. March 1989. Merck, West Point, PA

Lot #: L-670,452-005Y008

TREATMENT: Six groups of Sprague-Dawley CD rats (12 weeks old; 25/g) were given by gavage in deionized water, 0, 5, 10, and 25 mg/kg/day days 6 through 17 of gestation. Females were sacrificed on day 20 of gestation. The 5 mkd group dosing solution was 55% of expected on the second sampling (week two). All fetuses were examined externally and skeletally; 1/3rd examined visceraally.

RESULTS

MORTALITY: none

ABORTION: none

PHYSICAL SIGNS: rales day 15 gestation (25 mkd)

BODY WEIGHT GAIN: decreased about 9% M and HD

FOOD CONSUMPTION: decreased M and HD (10 and 15%)

MATERNAL NECROPSY:

2 controls: lung mottled/red (pneumonia)
 1 control: lung autolyzed
 1 HD : lung mottled, edema
 1 HD : distended intestines "tx related"

LAPAROTOMY DATA (*p<0.05)

live fetal weight (g; males) 3.6; 3.5, 3.6, 3.4*
 (g; females) 3.4; 3.4, 3.5, 3.2

NOT SIGNIFICANT ACCORDING TO MERCK BUT CLEAR TREND:
 % preimplantation loss 5.7; 7.3, 7.8, 10.9

EXTERNAL EXAM 25; 24,24,25 litters
 litters with malformations 0; 0, 1, 1
 VISCERAL EXAM
 litters with malformations 0; 1, 0, 2
 SKELETAL EXAM

SUMMARY OF FETAL OSSIFICATION DATA (Litter)

	Control	5	10	25 mkd
# LITTERS EXAMINED	25	24	24	25
# WITH SITES OF INCOMPLETE OSSIFICATION				
	7	11 (p=0.175)	13 (p=0.032)	14 (p=0.016)

SITES OF INCOMPLETE OSSIFICATION

			p value
INCOMP. OSS. CERVICAL VERTEBRA			
0	2	1	11 not provided
INCOMP. OSS. THORACIC VERTEBRA			
1	1	6	9 " "
INCOMP. OSS. LUMBAR VERTEBRA			
0	1	0	5 " "
INCOMP. OSS. SKULL BONE			
1	4	1	9 " "
INCOMP. OSS. RIB			
0	3	2	3 " "
INCOMP. OSS. STERNEBRA			
7	10	21	37 p<0.05 trend
INCOMP. OSS. PELVIC BONE			
2	15	5	18 N.S. trend

EXPLORATORY FERTILITY STUDY IN PREGNANT RATS (VOL 13)

TT #89-708-2. May 1989. Merck, West Point, PA

Lot #: L-670,452-005Y008

TREATMENT: Two groups of pregnant Sprague-Dawley CD rats (14 weeks old) were given by gavage in deionized water, 0 (n=11) or 15 mg/kg/day (n=12) for 15 days prior to mating through gestation day 19 or 20.

RESULTS

MORTALITY: Five treated: two found dead on day 20 of gestation. Three were killed moribund on day 20 and one was "markedly lethargic on days 20 and 21.

PHYSICAL SIGNS: Tremors, ptosis, marked lethargy.

NECROPSY (p.C-755)

CONTROLS: no findings (n=11)

FOUND DEAD (n=2): small intestines moderately distended with gas

KILLED DAY 20 (n=8; findings in 5):

#894225, -227, -228: slight to marked distention of the small intestine

#894233: red-stained hair around nose and mouth

#894231: tan and grey patchy discoloration of the heart; slight area of necrosis in the heart

KILLED DAY 21 (n=2):

#894230: dark red discoloration of the left ventricle of heart and prominent architecture of the liver (histopath: marked myocardial necrosis but liver unremarkable)

BODY WEIGHT CHANGES: no effects

SERUM BIOCHEMISTRY (*p<0.05)

	Control	15 mkd
UREA	16.5	24.4*
CREAT	0.6	1.4*
AST	90	>303
ALT	32	180*
ALKPH	94	31*
Ca (total)	9.1	4.0* ¹
Ca (ion)	4.8	2.0*
TG	160	380*

URINALYSIS (*p<0.05)

Ca (total)	8.5	8.1 ¹
Creatinine	57	98
Ca/Creat	0.15	0.06*

1: estimated; values <4 below validated limits of instrument
(6/9 <4 in serum biochemistry)

ORAL FERTILITY STUDY IN PREGNANT RATS (VOL 12)

TT #89-708-0. March 1989. Merck, West Point, PA

Lot #: L-670,452-005Y008

TREATMENT: Four groups of Sprague-Dawley CD rats (10 weeks old; 20/g) were given by gavage in deionized water, 0, 5, 10, and 15 mg/kg/day beginning 15 days prior to mating, during mating, and through day 20 of gestation. The mating period was limited to 16 nights. Females were sacrificed on postpartum days 21-24.

RESULTS

MORTALITY (day 22 of gestation): 1 MD and 4 HD [one found dead @10 mkd; 3 killed moribund & 1 found dead @15 mkd]

ABORTIONS: none

PHYSICAL SIGNS (gestation day 22):

Labored breathing, lethargy, ptosis, dystocia (signs vanished after delivery completed): 3@10 mkd; 1@15 mkd

Tremors (in addition to above): 3@15 mkd

Gaseous distention of intestine: 3@15 mkd

NECROPSY (dams): p.C-631

STOMACH: ulcerative gastritis and gastric necrosis in two HD
dark focus in one @10 mkd

SMALL INTESTINE: distention one @10 mkd and 2 @15 mkd

KIDNEY: pelvis enlarged, dilation one @5 mkd

LUNG: pneumonia, red focus (two @ 5 mkd and one @15 mkd)

LARGE INTESTINE: distended (one control)

(stomach/small intestine: "similar lesions seen previously")

BODY WEIGHT CHANGES (dams): no treatment-related effects

FOOD CONSUMPTION (dams): no treatment-related effects

LIVE PUP WEIGHT: decreased 17-22% in dams with physical signs
(days 0-7)

One 5 mkd female failed to deliver (had 4 dead intrauterine pups on day 24 gestation sacrifice; "this was considered treatment-related".)

REPRODUCTIVE PERFORMANCE

Length of gestation: one MD delivered day 23
 Three HD did not deliver and were killed moribund days 21 or 22
 Females with live pups/preg. females (%): 100; 95, 95, 78

F1

Postimplantation survival (%): 94; 86, 85, 69*
 % Dead pups postnatal day 0: 0.35; 0.8, 5.3, 5.6
 Live pup weights: no effects

"Based on the female in the 5 mkd which had the 4 dead intrauterine pups at sacrifice on gestational day 24, there was no no-effect dose level in this study."

p.C-555

ORAL FERTILITY STUDY IN FEMALE RATS (vol 14)

TT #90-710-0. March 1990. Merck

TREATMENT: Four groups of Sprague-Dawley CD rats (40/g;) were given by oral gavage once daily in deionized water, 0, 1, 2, or 5 mg/kg/day fifteen days prior to cohabitation, throughout mating to gestational day 19 (C-section) or 20 postpartum (natural delivery).

RESULTS: FO

MORTALITY: two at 5 mkd on days 22 and 23 of gestation. Uteri contained dead, full-term pups "not unexpected based on association of MK-217 with hypocalcemia, dystocia, and late-pregnancy maternal deaths" no tissues examined microscopically

BW/FC: no drug effects

PHYSICAL SIGNS: none treatment-related

MATING PERFORMANCE AND FERTILITY:

Cesarean sectioned: 19; 19, 14, 17

Females with no live pups: 0; 0, 0, 2

Fo that littered:

% Postimplantation survival (litter mean): 93; 92, 94, 84*

GROSS NECROPSY: one at 2 mkd had pale, enlarged, kidneys with moderate chronic nephritis, "common"

RESULTS F₁ (0,1,2,5 mkd prior to mating thru gesta d.20)

EXTERNAL EXAM:

1 mkd: anal atresia and malformed tail (1 litter; 1 fetus)
 2 mkd: shortened torso (1 litter; 4 fetuses)
 open eyelid (1 litter; 1 fetus)
 5 mkd: exencephaly, cleft lip, cleft palate (1 litter; 3 fetuses)

VISCERAL EXAM: none drug related

SKELETAL EXAM (supernumary ribs as % of fetuses):

Significant treatment-related elevation (%): 13, 9, 21, 23*

DEVELOPMENTAL SIGNS F₁: no effects on surface righting, auditory startle, vaginal canalization, preputial separation, or testes descent

BODY WEIGHTS CHANGES (GRAMS; p<0.05):

F₁ FEMALES: no effects on BW

F₁ MALES : 411; 398, 393, 393* (weeks 1-8)
 111; 93*, 88*, 89* (weeks 9-13)

SWIM MAZE TESTING: mean trials to criterion

FEMALES (test 1): 5.6; 5.7, 5.9, 4.8
 (test 2): 5.6; 5.0, 5.9, 6.7*

MALES (test 1): 6.1; 5.9, 5.8, 6.2
 (test 2): 6.4; 6.7, 8.1, 7.3

F₁ MATING

MATERNAL BW: no effects

REPRODUCTIVE PERFORMANCE (n=16-19/g): no effects

STATUS F₂: no effects on numbers of live pups, pup weight, external, visceral, and skeletal exams

89-702-0: 5 mkd had been NOEL but here increase in supernumerary ribs at 5 mkd "may be related to the longer duration of treatment compared to the developmental tox study" p.C-1084

Decrease in BW in F₁ in #90-722-0 weeks 10-15; "considered tx related" p.C1085. "NOEL was 2 mkd" based on maternal toxicity

"A no-effect dose for developmental toxicity was not identified based on the decreased BW gain of F1 males postweaning at all treatment levels" C-1085 considered tx-related

ORAL FERTILITY STUDY IN MALE RATS (vol 16)

TT# 90-9813.

August 1990.

TREATMENT: Four groups of CD rats (25/g; 7 weeks old) were given daily by gavage in distilled water, 0, 1, 3, or 9 mg/kg/day for 71 days prior to mating and during cohabitation (maximum 14 days).

RESULTS

MORTALITY: one male at 9 mkd (cause unknown)

PHYSICAL SIGNS: abnormal breathing at 9 mkd (considered treatment related (seen 89-008-0 and 89-089-0)

BODY WEIGHT: no drug effects

TESTES WEIGHT: no data

GROSS EXAM: "no effects" (no data)

REPRODUCTIVE PERFORMANCE (males): no effects

REPRODUCTIVE STATUS (day 20 gestation): no effects

F1

EXTERNAL EXAM: one fetus cleft palate, micrognathia, anasarca (generalized massive edema) at 9 mkd

ORAL FERTILITY/PARTURITION STUDY IN PREGNANT RATS (VOL 12)

TT #89-708-1. May 1989. Merck, West Point, PA

Lot #: L-670,452-005Y008

TREATMENT: Four groups of Sprague-Dawley CD rats (10 weeks old; 23/g) were given by gavage in deionized water, 0, 0.5, 1.25, and 5 mg/kg/day days for two weeks prior to mating, during mating, and through day 20 of gestation. Females were sacrificed on postpartum days 3 to 5.

Purpose: to determine a NOEL for dystocia. 5 mkd (LD) was associated with dystocia in previous study.

RESULTS

MORTALITY: two at 5 mkd

PHYSICAL SIGNS: two @5 mkd: tremors, labored breathing day 21 (died)

**PROTRACTED PARTURITION: one @ 0.5 and one @5 mkd

ORAL FERTILITY/PARTURITION IN PREGNANT RATS (0,0.5,1.25,5 mkd)

NECROPSY (dams): no effects on viscera (p.C-722)

Lungs: reddening in one @ 1.25 and one @5 mkd

BODY WEIGHT CHANGES (dams): no treatment-related effects

REPRODUCTIVE PERFORMANCE

"Treatment related protracted parturition in one HD" (HD female with protracted parturition had 2 dead & 12 live pups)

Females with live pups	22	23	23	21
Females with no live pups	0	0	0	2

No other effects on day of mating, incidence of pregnancy, length of gestation, numbers of implants/female or numbers of F0 females with live pups.

F1

**Live pup weight (female)	6.3	6.1	5.9	5.9*
(male)	6.6	6.4	6.2	6.3

EXTERNAL EXAM: "no malformations" data?

**"p.c-650: pregnant rats need calcium; severe hypocalcemia 89-708-2 due to drug (inhibits Ca mobilization from bone NOEL 1.25 mkd")

ORAL LATE GESTATION AND LACTATION STUDY IN RATS (vol 15)

TT# 90-722-0. June 1990. Merck

TREATMENT: Four groups of Sprague-Dawley CD rats (20/g; 10 weeks old) were given daily by oral gavage in water, 0, 1, 2, or 5 mg/kg/day from gestation day 15 through lactation days 20.

RESULTS FO

MORTALITY: One female at 5 mkd day 22

ABORTIONS: none

PHYSICAL SIGNS: none drug related

BW/FC: no drug effects

REPRODUCTIVE PERFORMANCE:

One female at 5 mkd killed gestation day 24 (one intrauterine pup)

GROSS: no drug-related findings

ORAL LATE GESTATION AND LACTATION IN RATS (0,1,2,5 mkd) F1
 MORTALITY (pup deaths postnat days 4-21): 0; 0, 0, 4 (3 litters)

PHYSICAL SIGNS: none treatment related

PUP BW GAINS DURING LACTATION: no significant effects

EXAMS:

EXTERNAL: none

DEVELOPMENT: no effects on surface righting, auditory startle, vaginal canalization, preputial separation, descent of testes

MORTALITY/PHYSICAL SIGNS (POST WEANING): none

BODY WEIGHT CHANGE (wks 10-15): 108; 106, 99, 88* (males)

SWIM MAZE (mean trials to criterion in males)

test 1: 7.2; 7.2, 7.2, 7.7

test 2: 4.4; 4.8, 5.0, 5.1

F2

PARENTAL FEMALES: 16; 16, 15, 15

DEAD PUPS DAY 0: 2; 4, 3, 12

% LIVE PUPS 99; 99, 99, 93

"NOEL: 2 mkd"

ORAL POSTNATAL GROWTH STUDY IN RATS (vol 16)

TT #91-713-0. March 1991. Merck

TREATMENT: Four groups of female Sprague Dawley rats (25/g; 9 weeks old) were given daily orally by gavage in deionized water, 0, 0.1, 0.5, or 2.0 mkd from 15 days prior to cohabitation, during cohabitation, during gestation and through lactation day 20.

RESULTS

FO

MORTALITY/ABORTIONS/PHYSICAL SIGNS: no effects

BW: decrease of 13% HD during prepartum

REPRODUCTIVE PERFORMANCE:

** POSTIMPLANTATION SURVIVAL: 96; 90, 93, 84*% (p<0.05)

** Two at 0.1 mkd had no signs of parturition and 1 or 2 dead intra-uterine pups at sacrifice GD 24

F1

NO EFFECTS ON PHYSICAL SIGNS, FOOD CONSUMPTION, BODY WEIGHT, or EXTERNAL EXAMINATIONS.

MORTALITY: One F1 female at 2 mkd died postnatal day 78

REPRODUCTIVE PERFORMANCE: no effects STATUS AT PARTURITION:

CRITICAL PERIOD STUDY IN PREGNANT RATS (VOL 13)

TT #89-708-3. September 1989. Merck, West Point, PA

Lot #: L-670,452-005Y008

TREATMENT: Two groups of Sprague-Dawley CD rats (10 weeks old; 15-19/g) were given by gavage in deionized water, 0 or 15 mg/kg/day for varying periods of time (see below): p.C-788

GROUP NO.	n	TREATMENT	MORTALITY (maternal)	TX PERIOD
1	19	CONTROL	0 (0%)	14th day pre mating thru gestation day (GD) GD 20
2	15	ALENDRONA TE (15 mkd)	1 (7%)	6th day pre mating thru 1st day pre mating
3	15	ALN (15 mkd)	1 (7%)	GD 0 thru 6
4	15	ALN (15 mkd)	1 (7%)	GD 7 thru 13
5	15	ALN (15 mkd;	3 (20%)	GD 14 thru 20
6	19	ALN (15 mkd)	8 (42%)	14th day pre mating thru GD 20

MORTALITY: "No strictly critical period of treatment during gestation which caused the maternotoxicity and deaths in late gestation. The number of deaths were instead related to **duration** of treatment." "...treatment in late gestation may be more deleterious..." "...maternotoxicity was not reversed but was lessened by cessation of treatment." (p. C-794)

PHYSICAL SIGNS: sponsor stated that the lack of observations may be due to their having occurred at night and not been observed; in necropsy report, ptosis, tremors, and lethargy are listed

CRITICAL PERIOD STUDY IN PREGNANT RATS (0 or 15 mkd)

NECROPSY (dams; p.C-884):

GROSS: "some found dead were slightly cyanotic, had congested, reddened lungs; two gp 6 rats had mottled livers"

HISTOPATHOLOGY:

Lungs: congested with edema, alveolar accumulations of fibrin and histiocytosis

Livers: centrilobular congestion

Hearts (no gross lesions seen but hearts from three rats that died, one in group 5 & two in group 6, were examined):

Multifocal slight myocardial degeneration

** "A possible cause of death in these 3 rats may be congestive heart failure due to myocardial damage which appears to be treatment related. The cause of death for all other rats is undetermined at this time but may be related to treatment as well as time and duration of treatment."

BODY WEIGHT GAINS: no drug effects

SERUM CALCIUM (ION): no drug effects days 0,7,14,20

	gp1	gp2	gp3	gp4	gp5	gp6
PREGNANT FEMALES	16	13	13	13	14	16
NO. WITH LIVE PUPS	16	13	12	12	11	8
**LIVE PUP WT (F)	6.3	6.2	6.1*	6.2*	5.8*	6.2
(M)	6.7	6.6*	6.6*	6.6*	6.2*	6.6

EXPLORATORY STUDY OF HYPOCALCEMIA IN PREGNANT RATS (vol. 13)

TT #90-703-0. January 1990. Merck, West Point, PA

Lot#: L670,452-005Y008

TREATMENT: Two groups of pregnant Sprague-Dawley CD rats (11 weeks old; 20/g) were given by gavage in deionized water, 0 or 15 mg/kg/day days 1 through 21 of gestation.

RESULTS

MORTALITY/ABORTIONS: none but one female had muscle spasm and rigidity suggestive of tetany and was killed day 21 of gestation

BODY WEIGHT GAINS: no effects

**SERUM TOTAL CALCIUM
PREGNANT**

	DAMS		FETAL	
	CONTROL	TREATED	CONTROL	TREATED
DAY 21	9.8	7.3	9.4	9.6
DAY 22	9.6	7.7	7.8	7.4
DAY 23	no data	11.8	no data	8.7

NON-PREGNANT

11.4	12.0

EXPLORATORY CALCIUM SUPPLEMENTATION IN PREGNANT RATS (v.13)

TT #90-731-0. November 1990. Merck, West Point, PA

Lot#: L670,452-005Y008

TREATMENT: Four groups of Sprague-Dawley CD rats (9 weeks old; 19 treated and 20 controls/g) were given by gavage in deionized water 0 or 15 mg/kg/day for 14 days prior to cohabitation to day 21 of gestation. Group 1 were controls (water only), group 2 got 15 mkd; group 3 got 15 mkd + drinking water with 1% Calcium gluconate gestational days 15-21 (24-83 mg/rat/day); group 4 got 15 mkd + 0.22 mg calcium/rat/day as 1% infusion of Ca gluconate via s.c. pump (Alzet minipump) days 15-21.

RESULTS

MORTALITY/PHYSICAL SIGNS

Controls: no deaths or signs

15 mkd (no Ca): 1 had tremors and splayed limbs (killed day 21); 8 died (day 22); 1 died (postpartum day 0)

15 mkd (Ca in drinking water): 2 tremors and splayed limbs (killed day 21); 1 died (day 21); 9 died (day 22)

15 mkd (Ca from minipump): 1 tremors and splayed limbs (killed day 21); 1 died (day 21); 3 died (day 22); 2 died (postpartum day 0 or 1); one killed (postpartum day 0 due to poor condition from protracted labor)

Total deaths: 0/20; 10/19, 12/19, and 8/19

EXPLORATORY CALCIUM SUPPLEMENTATION IN PREGNANT RATS

BODY WEIGHT GAINS: No effects preparting, gestation (only difference is day 22 but n= 8, 8, 5, 2) or lactation to day 3.

Sponsor calculated days 0-20 of gestation:

gain 161; 146*, 153, 155 (statis. signif but not biol. sign.)
=62% increase controls vs 56% in treated

WATER CONSUMPTION: no drug effects

Ca CONSUMPTION: 24-83 mg/day

TOTAL SERUM CALCIUM
(mg/dl)

DRUG GROUP	DAY 15	DAY 21
Control	9.9	9.2
15 mkd	10.1	7.2*
15 mkd + Ca in water	10.0	7.2*
15 mkd + Ca in pump	9.9	6.5*

* p<0.0001 vs control (p.C-1001)

	mkd	mkd	15+Ca water	15+Ca pump
F1 PUPS	0	15		
% POSTIMPLANTATION SURVIVAL	95	82	85	77*
FEMALES WITH LIVE PUPS (day 0 postpartum)	20	9	6	10
LIVE PUPS/LITTER (day 0)	16	13	14	13
% LIVE PUPS (L.M.*; day 0)	99	86	100	84
DEAD PUPS/LITTER (days 0-3)	0.35	1.8	0.17	4.7
TOTAL DEAD PUPS (days 0-3)	7	16	1	47

a: L.M. = litter mean

p.C-954:

"Calcium supplementation did not ameliorate hypocalcemia and therefore did not reduce the numbers of affected females (maternal deaths, physical signs, neonatal deaths) typically observed in late gestation when pregnant rats are given MK-0217."

CALCIUM SUPPLEMENTATION (I.V.) IN PREGNANT RATS (Vol 13)
 TT #91-735-0. November 1991. Merck, West Point, PA
 Lot #: 11-670,452-005Y008

TREATMENT: Two groups of Sprague-Dawley CD rats with indwelling i.v. cannulas [4 control and 13 treated (15 mkd p.o. from 14 days prior to cohabitation through gestational day 20)]. Cannulas were inserted gestational days 11-16. At 2:00 pm gestational day 21, 10% Ca gluconate was infused via the catheters (9.3 mg Ca/rat).

RESULTS:

MORTALITY: 2 but "not treatment-related"

PHYSICAL SIGNS: 5 had rales and two had ptosis (treated)
 "rales may be treatment-related; a previous study had similar sign (snoring)"

GESTATION PERIOD: 22 days (control) and 22.3 days (treated)

Delivery was delayed from 6:00 pm to 8:40 pm (treated).

LITTERS: 4 control and 11 treated

Pup deaths (%) postnatal days 1-2: 0 and 4%

There were no deaths in 4 control litters (0/64 pups). There were deaths in 6/10 treated litters (6/155 pups). Merck used the % incidence of **pups** affected and historical control data to say no tx-related effects (Merck stated that the 50th percentile for litter mean % pup deaths was 1.0% and it was 4.0% here.)

Live pups/litter: 16 (control) 15.4 (treated)

Pups: no effects on external appearance or wts days 0 and 2

Maternotoxicity was reversed but not fetal toxicity.

RANGE-FINDING FOR MOUSE CARCINOGENICITY STUDY

14-WEEK ORAL GAVAGE RANGE-FINDING IN MOUSE

TT #89-034-0. August 1989. Merck, PA (vol 22)

Lot#:

TREATMENT: Four groups of CD-1 mice (5 weeks old; 15/s/g) were started with gavage doses of 0, 5, 10, 20, or 40 mg/kg/day in deionized water; the dose of 5 mkd was increased to 80 mkd (DW6) and the dose of 10 mkd was increased to 160 mkd during (DW 8).

DOSES AND TREATMENT SCHEDULE (RANGE-FINDING MICE)

DWs 1-6	DWs 7-8	DWs 9-14	Duration	# DOSES
mkd	mkd	mkd	higher dose	LOW/HIGH
5	80	80	8 weeks	38/53
10	10	160	6 weeks	50/41
20	20	20	14 weeks	91
40	40	40	14 weeks	91

RESULTS

MORTALITY (12 mice found dead; 12 sacrificed moribund):

0; 20, 40, 5/80, 10/160 mkd

"drug-related" 0; 0, 1, 0, 3 (M)

0; 0, 3, 1, 7 (F)

"9 probable intubation accidents" (data here to support this?)

p.126 of postmortem lists causes of death as:

6 intubation accidents; 2 trauma; 7 undetermined; 9 treatment related

Looks like 160 mkd is lethal in males

40 mkd " " " females

HD based on this data for males would be predicted to be 80 mkd and for females, 20 mkd assuming their assessment of which are drug-related are correct

CLINICAL SIGNS: (no data) p.1360

Abdominal distension at dosages ≥ 40 mkd beginning DW 11 (2-3/g at 40 and 80 mkd; 9/30 at 160 (denominator =30?))

Respiratory sounds "intermittently" at all dosages (frequency ranged from 2 mice at 20 mkd to all mice at 160 mkd)

Decreased activity, hunched posture, loss of skin turgor:
at ≥ 40 mkd

BODY WEIGHTS: decreased but sponsor did not calculate properly
Sponsor took grams change and compared treated to control instead of using total final body weight

	20, 40, 80, 160 mkd
% of final control wt:	89, 92, 89, 87% (F)
	97, 95, 90, 92% (M)

FOOD CONSUMPTION: "slight" decrease HD

ORAL (GAVAGE) RANGE-FINDING STUDY IN MICE
 HEMATOLOGY: no drug effects

CLINICAL CHEMISTRY: no drug effects

PLASMA DRUG LEVELS: not done

PATHOLOGY

ORGAN WEIGHTS: no effects

GROSS gaseous distention of the stomach, small intestine, and large intestine in: 0; 1, 5, 2, 12/30 (no data; no breakdown as to sex affected and no evidence of any effects histologically on large intestine)

HISTOPATHOLOGY (15/s/g unless specified; only stomach, small and large intestine, kidney, bone, gross changes examined in all)

	DOSE GROUPS (5) no. examined	FEMALES	MALES
SALIVARY GLAND		0; 20, 40, 5/80, 10/160 mkd	6; 1, 1, 1, 8 (15/s/g)
lymph. cell. infilt.		8; 1, 4, 2, 12	1; 0, 0, 0, 5
			0; 0, 0, 0, 0
STOMACH		FEMALES	MALES
glandular mucosa degen		0; 0, 1, 1, 6	0; 0, 1, 2, 6
glandular mucosa necrosis		0; 0, 3, 0, 0	0; 0, 2, 0, 0
non-gland. mucosa edema		0; 0, 0, 1, 2	0; 0, 0, 1, 1
non-gland. mucosa hyperker		0; 0, 1, 1, 4	0; 0, 2, 2, 5
SMALL INTESTINE			
mucosal degeneration		0; 0, 0, 0, 3	0; 0, 0, 0, 1
KIDNEY			
lymph. cell. infiltration		0; 1, 3, 1, 2	2; 1, 3, 4, 3
tubular necrosis		0; 0, 2, 0, 4	0; 1, 1, 0, 1
	no. examined	8; 1, 9, 3, 12	
UTERUS dilatation		0; 0, 5, 1, 2	
	no. examined	8; 1, 4, 2, 12	6; 1, 1, 1, 8
SPLEEN lymphoid atrophy		0; 0, 3; 0, 3	0; 0, 0, 0, 2

ORAL (GAVAGE) RANGE-FINDING STUDY IN MICE

	FEMALES		MALES	
DOSE GROUPS (5)	0;	20,	40,	5/80, 10/160 mkd
no. examined	8;	1,4,2,12	6;	1,1,1,8
THYMUS				
atrophy	1;	1,2,0,6	0;	1,1,0,2
necrosis	2;	0,2,0,5	0;	0,0,0,1
no. examined	8;	3,5,2,12	6;	1,1,1,8
LYMPH NODE				
atrophy	0;	0,2,0,1	0;	0,0,0,1
necrosis	1;	0,1,0,3	0;	0,1,0,2
BONE				
primary spongiosa	none	in controls;	all treated	affected
synovitis	1;	0,0,3,2	1;	0,1,1,1
LARGE INTESTINE	(no findings)			

92-WEEK ORAL GAVAGE CARCINOGENICITY STUDY IN MICE

TT #90-038-0. March 1990-December 1991. Merck, PA (vol 23)

Lot#:

TREATMENT: Groups of CD-1 mice (5 weeks old; 50/s/g) were dosed orally by gavage in deionized water. Males were given 0, 0; 1, 3, or 10 mg/kg/day; females were given 0, 0, 1, 2, and 5 mg/kg/day. Mice had free access to food and water.

RESULTS

MORTALITY: none drug-related

Survival: 54, 43; 38, 52, 52% males
 40, 52; 54, 46, 52% females

CLINICAL SIGNS: none drug-related (several had Staph and Streptococcus spp. infections)

BODY WEIGHTS (final):

 Females (g) 36.7, 34.9 (controls); 36.4, 35.7, 34.2 (L,M,HD)
 Males (g) 42.6, 45.9 (controls); 43.1, 42.1, 41.0 (L,M,HD)

FOOD CONSUMPTION (DWs 1-22): no effects

PATHOLOGY

GROSS: no data

92-WEEK ORAL GAVAGE CARCINOGENICITY STUDY IN MICE

HISTOPATHOLOGY (Neoplastic; trend test) (SEE APPENDIX V)

EYE (Harderian gland adenoma): 0,1; 1, 2, 6 females (p=0.003)

HISTOPATHOLOGY (Non-neoplastic): none drug-related

(see data sheets)

105-WEEK ORAL GAVAGE CARCINOGENICITY STUDY IN RATS (v.20/21)

TT #89-089-0. Sept. 1989-Sept. 1991. Merck, PA

Lot#: 1-670,452-005Y008

TREATMENT: Four groups of CD rats (5 weeks old; 75/s/g except for controls where there were 130/s/g) were given by gavage in deionized water, 0, 1.0, 3.75, or 7.5/5.0 mg/kg/day once daily for 105 weeks. The high dose was decreased from 7.5 to 5.0 mkd DW9 (for females) and DW13 (for males), but this was still too high and all surviving rats were killed DW 43 "due to excessive mortality". Food and water were available at all times.

RESULTS

MORTALITY: increased HD

3 HD females and 2 HD males died before dose lowered (Dws 9&13).

The HD group (7.5 to 5 mkd) was terminated DW 43 with 24/75 females and 20/75 males dead vs 3/130 females and 12/130 males dead in the control group. The L and MD survival rates were not different from controls. No tumor data was provided for the terminated group.

CLINICAL SIGNS (no data provided):

Dyspnea: HD (beginning DW 4)

Abdominal distension: HD (20-40%)

BODY WEIGHTS: "decreased HD"

FOOD CONSUMPTION: "decreased,HD (5-25%)"

OPHTHALMOLOGY: "no drug effects"; however "either uni- or bilateral posterior subcapsular cataracts were seen in 7 vs 17% for control and HD" (p.E716; no data).

HEMATOLOGY: "no drug effects" (no summary tables)

105-WEEK ORAL GAVAGE CARCINOGENICITY STUDY IN RATS (v.20/21)
PATHOLOGY

PLASMA DRUG LEVELS: not done

GROSS "none treatment-related except in HD" (no data)

CAUSE OF DEATH: unknown; rats died or were killed due to dyspnea (difficulty breathing) and gaseous abdominal distention "without any histologic change".

HISTOPATHOLOGY (NEOPLASTIC) (SEE APPENDIX V)

THYROID parafollicular cell adenomas trend increase (p=0.003)
(in males)

FEMALES			MALES		
15/130;	8/75	6/75	7/130;	7/75,	13/75
12%	;	11% 8%	5%	;	9% 17%

HISTOPATHOLOGY (NON-NEOPLASTIC)

BONE: "retention of primary spongiosa of long bones (femur/tibia)= primary bone change due to pharmacologic action" "prevents bone reabsorption; epiphyseal growth plate closure normally doesn't occur at sexual maturity as in other an./man

Retention of zone of partly ossified trabeculae beneath cartilagenous growth plate & extension into marrow seen in 100% females and 60 & 96% males at 1 and 3.75 mkd severity up in females; same long vs short treatment.

nasal cavity: retention of primary spongiosa in sphenoid bone in all HD rats at terminal sacrifice (similar to long bones)

nasal turbinates: (lack epiphyseal growth plate) slight thickening of bony component in HD rats killed at terminal sacrifice seen also in 1 year study at 2.5 and 5.0 mkd

LIVER AND SPLEEN: dose-related increase in extramedullary hematopoiesis in both males and females:

Sponsor stated that this was due to lack of marrow plus increased need for hematopoiesis (due to blood loss or inflammatory process); "seldom seen in adult humans where endochondral bone formation does not occur."

GENOTOXICITY STUDIES**AMES TEST** (TT# 88-8007. Merck) (D-1)

The test was negative $\pm$ S-9 up to 10,000 ug/plate in 4 strains of Salmonella and three strains of E.coli.

V-79 MAMMALIAN CELL MUTAGENESIS (TT# 88-8522; 88-8523; Merck)

The test was negative up to 1.5 mM (+S-9) and to 0.25 mM (-S-9).

IN VITRO ALKALINE ELUTION/RAT HEPATOCYTE ASSAY (D-3)

(TT#88-8496; 88-8858; Merck)

Cytotoxicity was absent up to 10 mM yet assay high dose was 0.3 mM due to precipitation in the L-15 medium as determined microscopically after 3 hours at 37°.

Observed visually, there was no ppt up to 4 mM (no incubation) and up to 1.4 mM (3 hours at 37°). Merck should have used 1.4 mM as the high dose; therefore, this is not a valid study.

CHROMOSOMAL ABERRATIONS IN CHO OVARY CELLS (D-4)

TT# 89-8618, -19, -29, -34, -35, 39.

The test was a significant increase in aberrations in the presence of S9 after 3 hours treatment and 17 or 20 hours incubation in three separate tests. Total aberrations and terminal deletions were increased.

STUDY NO.	Drug level	adjusted*		trend	
		(p value)		(p value)	
#89-8619	8 mM	0.002			
		<u>17 h</u>	<u>20 h</u>	<u>17 h</u>	<u>20 h</u>
#89-8629	5 mM		0.041	0.038	
	6 mM	0.049	0.037	0.004	0.005
	7 mM	0.049		0.007	
#89-8635	6 mM		0.011		0.002
#89-8635:	2, 5, and 6 mM but not 4 mM had increased aberrations.				

(*adjusted for multiple pairwise comparisons against control)

ABERRATIONS IN MOUSE BONE MARROW (D-5)

TT# 89-8638. Merck

Weanling female mice were given a single i.v. injection of 2.5, 8.3, or 25 mg/kg and killed at 6, 24, and 48 hours postdose. Mitomycin C controls were killed 24 hours postdose. Three hours before sacrifice, mice were given an i.p. injection of colchicine.

There were no clinical signs. There was no increase in cells with aberrations among ALN-treated mice; mitomycin C-treated were positive.

OTHER GENOTOXICITY STUDIES

Studies done in Japan and Italy were merely listed with doses used and results (usually a short paragraph).

SUMMARY AND EVALUATION

IND _____ was submitted by Merck on July 5, 1988 for the iv treatment of hypercalcemia of malignancy. The drug was originally developed by _____ from which Merck obtained the license. The first toxicity studies were done in Italy using the "free acid form" (it is not clear what this means since at least one of the phosphates should have been a salt if the solution administered were not to be too acidic). Merck had hoped to speed approval using subpart E but after consultation with the Division, changed their minds and dropped development of the iv indication entirely.

IND _____ was submitted by Merck for the oral treatment of Paget's disease and osteoporosis.

Presumably because of the original indication, most of the PK studies were done using i.v. dosing in male rats; no PK studies were done using oral dosing in females even though that is how the drug is to be used clinically.

Absorption orally was very low, on the order of 1-2% or less in male rats, dogs, and monkeys. Absorption was determined by measuring drug levels in the femur or tibia after simultaneous dosing with [3H]ALN i.v. and [14C]ALN p.o. followed by combustion

of bone to obtain the ratio of counts; [^{14}C]ALN was also measured in the urine as an index of absorption. The only study using oral doses and examining plasma levels was done in male rats at 5 mg/kg (levels were stated to be too low for detection; no higher doses were tried).

Excretion was mainly urinary; 0.1% of a single i.v. dose to rats was excreted in the bile.

Levels in tibia and femur were examined after oral and i.v. dosing and increased exponentially as dose increased, more so after oral dosing (see Fig.4). Levels in tibia and femur were 4-5x higher in fasted (vs fed) male rats. There were no differences between tibial levels in male and female rats after i.v. dosing. Young rats had 2- to 3-fold higher bone levels than adult rats.

Distribution of ALN was not homogeneous: joint regions (trabecular bone) had significantly higher concentrations than shaft (cortical) bone. This difference was hypothesized to be the result of surface/volume ratios, blood supply, and/or differences in bone turnover.

Drug levels in tibia and femur **decreased** in both hypocalcemic (-parathyroid) and hypercalcemic (+PTH) rats. Drug levels **increased** as a function of increasing renal failure and after aspirin- or indomethacin-induced peptic ulcers (thought to be due to gi mucosal erosion).

"ALN, like other members of the group, was widely distributed in calcified and noncalcified tissues." (p.G-91). They speculate that this distribution might be due to phagocytosis of large complexes of bisphosphonates with metal ions. Non-skeletal tissues with measurable ALN levels after single i.v. doses were kidney, liver, lung, muscle, and spleen. Only 1% of drug remained in these tissues 6 hours after a single 1 mg/kg i.v. dose whereas 30% remained 18 hours after a single 20 mg/kg i.v. dose (male rats).

The $t_{1/2}$ in femur and tibia was very long (>433 days in male rats.) Drug was protein-bound to varying extents: 90% rat, 70% man, 20-30% dogs and monkeys.

Although Merck says that ALN is not metabolized, they also state that "The isolation procedure alone precludes the presence of any chemical species other than very polar, very strong anions" and in a clinical study, they said that they could not rule out the presence of a metabolite in human urine.

The proposed mechanism of action involves an interaction with osteoclasts that prevents their extrusion of H^+ needed for resorbing bone. Bisphosphonates also have the ability to impair the crystallization and dissolution of calcium phosphate in hydroxyapatite. The K_d (dissociation constant) was 1 mM. The drug was buried in rat bone 6 days postdose and was on the cement line 7 weeks postdose.

PHARMACODYNAMICS

URINARY PYRIDINOLINE LEVELS are a product of bone collagen breakdown and thus a measure of bone resorption (osteoclast function). Although urine was collected, analyses were rarely done; an exception was the 2 year i.v. bone study in baboons where levels increased with ovx (vs sham controls and treated); there were no differences between the two doses (0.05 and 0.25 mg/kg).

ALKP levels are a measure of osteoblast function. In the 2 year i.v. bone study in baboons, levels increased with ovx (vs sham controls and treated) with no differences between the two doses, 0.05 and 0.25 mg/kg. In the 6-month rat study $\pm$ estrogen, ovx increased ALKP 2-fold; 1 mkd ALN (but not 0.2 mkd) prevented ALKP increase at week 49, but not week 40.

Bone strength and stiffness are the ultimate tests of drug function. However, it is important to measure both trabecular and cortical bone because "...histomorphometric observations obtained at one skeletal site can not be extrapolated to the entire skeleton". The higher basal turnover rate in trabecular bone means that most of the ALN will localize there. (p.F-31/32)

Increased vertebral strength was seen in ovariectomized rats and baboons; femur strength was not increased. What Merck says is that ALN "at multiples of the projected human dose **did not weaken the long bones**" (p. F-1375) and that the lack of significant differences in strength of femoral neck in rats after tx with ALN may involve preferential loss of cancellous bone after ovx and limited contribution of cancellous bone to strength of femoral neck. (p.F-1278) Femoral strength was increased only in the 2-year rat study where treatment started at a very young age (5 weeks).

3-YEAR DOG STUDY: No differences were seen between any groups (including controls) in either histomorphometric or biomechanical properties (all data in figures, no tables). "We question whether ALN in a non-osteopenic animal model would yield significant differences...". They note large group S.D. and small numbers of dogs examined.

Dr. Rober Neer (Massachusetts General Hospital, Boston, MA), a member of the Advisory Committee, is very concerned about the body's ability to repair microscopic cracks, an issue not yet addressed in any preclinical or clinical studies.

EXPOSURE TO DRUG

Animals had free access to chow in most toxicity and reproduction studies. In only a few studies, especially those designed to look at bone effects, were animals dosed fasted (rat study ALN + estrogen and the 1- and 3-year dog studies). The lack of control of food in relation to drug intake means that exposure in most studies is unknown and almost certainly lower than the mg/kg indicated (food decreases drug absorption up to 5-fold in rats). Merck stated in protocol amendment #2 for the ALN + estrogen study, "**Since feeding may affect the bioavailability of MK-217, all rats will be dosed at least two-hours prior to feeding.**"

TOXICITY**I.V. DOSING**

I.V. dosing caused kidney damage in dogs: "slight chronic nephritis with renal tubular degeneration characterized by multiple scattered foci of cellular infiltration, fibroblastic proliferation, and tubular epithelial necrosis" at a dose of 0.1 mkg for 4 weeks. (Pharm Rev 1/15/90)

I.V. dosing (rats and dogs; 0.1 & 1 mkg) caused hypertrophy of physis (cartilagenous growth plate), retention of primary spongiosa (woven bone, less osteoid and less cartilage resorption), and decreased numbers of osteoblasts in the primary spongiosa, consistent with lack of bone remodeling (extent and severity increased with dose).

Slight gastritis was seen in dogs after 1 month at 1 mkg (i.v.) Increases in urinary Ca and Pi were associated with decreases in plasma levels in dogs; only serum findings were present in rats.

ORAL DOSING**CALCIUM AND PHOSPHOROUS**

These tended to decrease in serum in dogs and rats, especially rats in late pregnancy. Urinary Pi and Pi/creatinine ratio increased transiently in dogs and rats at 5 mkg (1-year studies).

ORAL DOSING: KIDNEY

Oral dosing caused mineralization of the renal papilla and chronic focal nephritis in dogs treated for as little as 3 months (at 4 mg/kg). Merck argued that kidney damage occurred only in studies conducted on young dogs (7-8 months old), but it was seen in older dogs as well (21-months old). Tubular necrosis was present in female mice treated for 3 months at 40 mkg but not in mice treated for 92-weeks at 5 mkg. Treatment-related tubular necrosis were seen at 30 mkg in a 3-month study in rats but not in a 2-year study at 3.75 mkg, but again, absorption was not known in any study due to the continued presence of food.

BONE MARROW

Retention of primary spongiosa in rats reduced the marrow space causing extramedullary hematopoiesis.

NDA 20560

FOSAMAX

6 OF 7

LIVER AND SPLEEN

Rats had treatment-related extramedullary hematopoiesis in both liver and spleen (in males and females at 1 mkd after 2-years and at 2.5 mkd after 1-year) which was considered secondary to the bone change. A decrease in RBC in female rats was seen in the 1-year study at 2.5 mkd.

STOMACH

RATS: Degeneration of glandular mucosa, gastritis, mucous cell hyperplasia, and ulcers were seen in rats. MICE: Non-glandular hyperplasia; glandular mucosal necrosis were seen in mice at 40 mkd (3 months tx) and glandular mucosal degeneration was seen at a dose of 10 mkd increased to 160 mkd for 6 weeks in the same study. DOGS: In a 5-week study in dogs performed by Gentili (Italy), punctiform hemorrhages were seen in the gastric mucosa as well as gastritis and cellular necrosis in the intestinal villi after 5 weeks at 10 mkd.

PREGNANT RATS

PHYSICAL SIGNS: ptosis, tremors, lethargy, labored breathing, splayed limbs, protracted parturition

HEART: Some of the pregnant rats that died and were autopsied had multifocal myocardial degeneration: "A possible cause of death...may be congestive heart failure due to myocardial damage which appears to be treatment related" and "may be related to lower calcium levels due to drug administration".

PREGNANT RATS WHICH DIED DURING PREGNANCY:

LUNGS: congestion, edema, pneumonia, red focus

ABDOMEN: gaseous distention

LIVER: mottled, centrilobular congestion

POSTIMPLANTATION SURVIVAL: decreased at 2 mg/kg/day

PUP WT: decreased at 1 mg/kg/day

A major problem in pregnancy was the inability of dams to obtain the calcium needed for fetal bone growth and delivery of pups. Merck provided an explanation of maternal deaths: "ALN prevented bone remodeling and thus bone resorption denying calcium at a time of high demand." Calcium administered in the drinking water or by s.c. pump was ineffective in preventing maternal death; calcium administered i.v. late in pregnancy spared the dams but did not prevent fetal deaths.

SECRETION IN MILK: A translation of the summary of a Japanese paper (from the TEIJIN Institute for Bio-Medical Research) stated that ALN was transferred into milk in lactating rats after a single i.v. dose of [14C]-ALN (presumably 0.05 mg/kg). Radioactivity was detectable out to 24 hours postdose (the last point measured) even though plasma radioactivity was not detectable beyond 2 hours postdose. (This information came in response to my question: had they measured radioactivity in fetal bones; they had not.) (May 23, 1995 submission)

PRIMARY SPONGIOSA (FORMED DURING BONE GROWTH*)

Retention of primary spongiosa results from a block in the bone remodeling process. It was seen in both rats and dogs.

FIRST ARF SEQUENCE (replacing cartilage with woven bone)

The calcified cartilage septal matrix laid down by chondroblasts is partially resorbed by osteoclasts after which osteoblasts form a layer of woven bone on top. The trabeculae formed are called the *primary spongiosa* and is seen during growth of bones.

SECOND RF SEQUENCE (replacing woven bone with lamellar bone)

The woven bone and cartilaginous remnants are replaced with lamellar bone to produce the mature state of trabecular bone called the *secondary spongiosa*.

#Ref: R. Baron in "Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism", M.J.Favus, ed. Raven Press, NY, 1993. ARF= activation, resorption, formation.

In the nasal cavity of rats, there was retention of 1° spongiosa in the sphenoid bone and nasal turbinates. There was also retention in long bones (femur and tibia) with slightly greater severity in females vs males. These changes were seen in rats treated for 3 months or longer.

Retention of primary spongiosa was seen in ribs and femurs when 8 month-old dogs were treated for 1 year (at 0.5 mg/kg/day and above) and in 21 month-old dogs treated for 3 months and allowed a 9-month period to recover. The findings after 9 months recovery tended to be less severe than after 1-year of continuous treatment, suggesting "a trend toward restoration of bone remodelling..."

The effect in dog femurs was reported to be "histologically similar" but less severe than that seen in ribs. "Although cartilage was present in the zone corresponding to the physis, it did not show the structure of a normal growth plate...in any of the femurs examined." (p.B-2489) These abnormal findings in femurs were also present in 21-month old dogs treated for 3 months and allowed a 9-month recovery.

The effects on bones appeared at lower doses after longer exposures: retention of 1° spongiosa in femurs of female dogs was seen after 6 months at 8 mkd (but not 2 mkd), yet after 12-months tx, it was present at 0.5 mkd as well. Vertebrae were not examined histologically. Strength testing was not done in these studies where they saw these histomorphometric effects.

CARCINOGENICITY

There was a statistically significant increase ($p=0.003$) in parafollicular cell adenomas in high dose male rats (at 3.75 mkd or 3x the 10 mg human dose based on surface area, mg/m^2). The incidence may be underestimated where H&E staining is used, as done here; immunoperoxidase staining for calcitonin produced "considerably higher incidences" (Pathology of the Fisher Rat, p.531, Boorman, et al., eds, 1990).

Parafollicular cells are also called C-cells because they produce calcitonin which helps regulate serum calcium and phosphate levels. Calcitonin decreases serum Ca and Pi by inhibiting osteoclastic resorption of bone, blocking renal reabsorption, and decreasing renal activation of vit D.

Harderian gland adenomas were significantly increased ($p=0.003$) in high dose female mice at 5 mkg or 2x the 10 mg human dose based on surface area. There does not appear to be a written record of agreement on doses between Merck and FDA for the mouse carcinogenicity study as there was for the rat study. Given that the high dose could easily have been 20 mkd (4x higher than that actually used based on data from the range-finding study), a properly done mouse carcinogenicity study would presumably have yielded more findings than were seen here. In addition, it is important to remember that both carcinogenicity studies were done with rats and mice which had food available at all times; thus we do not know the true exposure which is surely less than that indicated by the mg/kg dose.

GENOTOXICITY: Chromosomal aberrations were increased significantly ($p < 0.05$) in CHO cells; the study was repeated twice and was positive each time. The Ames test, V-79 mammalian cell mutagenesis, and aberrations in mouse bone marrow tests were negative; an in vitro alkaline elution assay was done at doses too low to be valid.

RECOMMENDATION: Fosamax increased the strength of vertebral bones (in ovariectomized baboons and rats); stiffness was increased in young male (but not female) rats when treated throughout their lifetime. The fact that Fosamax did not decrease the strength of the long bones in any animal model including the ovariectomized and non-ovariectomized rat and non-ovariectomized dog and baboon models supports safety of clinical use.

I would recommend class labeling for the pregnancy section of bisphosphonates. Ciba-Geigy stated (Reproduction Toxicity Studies With Pamidronate, Drug Res. 42, p.654, 1992) "...in view of the effects of pamidronate on parturition and the fact that it crosses the placenta and binds to fetal bone, use of the drug in pregnancy should be avoided unless there is a life-saving medical need."

Pharmacology recommends approval of NDA 20-560
R Jordan
9/1/95

LIST OF ABBREVIATIONS
HISTOMORPHOMETRIC ANALYSES

AjAR	ADJUSTED APPPOSITION RATE (um/d)
OS/BS	OSTEOID SURFACE/BONE SURFACE (%)
BV/TV	BONE VOLUME/TOTAL VOLUME (%)
Cn-BV/TV	CANCELLOUS BONE VOLUME/TOTAL VOLUME (%)
Ct BV/TV	CORTICAL BONE/TOTAL VOLUME (%)
OcS/BS	OSTEOCLAST SURFACE/BONE SURFACE (%)
OTh	OSTEOID THICKNESS (um)
MAR	MINERAL APPPOSITION RATE (um/d)
MS/BS	MINERALIZING SURFACE/BONE SURFACE (%)
Mlt	MINERALIZING LAG TIME (days)
BFR/BS	BONE FORMATION RATE/BONE SURFACE (um ³ /um ² /year)
BMD	BONE MINERAL DENSITY (g/cm ²)
BMC	BONE MINERAL CONCENTRATION (g/cm)
TbTh	TRABECULAR THICKNESS (um)
TbN	TRABECULAR NUMBER (#/mm)
TbSp	TRABECULAR SEPARATION (um)

BIOMECHANICAL PARAMETERS

N	ULTIMATE OR FAILURE LOAD (measured in Newtons) Dependent on bone size
Pa	PASCAL (= 1 N/m ²) = unit of STRESS = Force/Area
N/mm	STIFFNESS (measure of intrinsic strength of bone)
STRESS	Force/Area = Newtons/m ²
STRAIN	Percentage change in length or relative deformation

ref: Turner and Burr, "Basic Biomechanical Measurements of Bone: A Tutorial", Bone, 14, 595-608, 1993.

MAR 3 1993

February 27, 1993

IND

Sponsor: Merck & Co., Inc., West Point, PA

Date Submitted: February 13, 1992

Date Received: February 18, 1992

REVIEW AND EVALUATION OF TOXICOLOGY DATA

Amendment Review

Drug: Aminohydroxybutane Bisphosphonate (AHButBP); Alendronate Sodium; MK-217 oral; Fosamax

Category: Bisphosphonate; Anti-resorptive agent

Proposed Clinical Indication: Treatment of postmenopausal osteoporosis.

MK-217: Thirty-Two-Week Bone Remodeling Study in Dogs. TT #90-064-0

The objective of this study was to determine the effect of MK-217 on fracture healing (transverse fracture of the cranial mid-diaphyseal surface of the right radius). Dogs (5/sex/group) were assigned to the following groups:

1. Control/Surgery/Control
2. MK-217 (2 mg/kg)/Surgery/Control
3. Control/Surgery/MK-217 (2 mg/kg)
4. MK-217/Surgery/Mk-217 (2 mg/kg)

In the relevant groups, MK-217 treatment was initiated 9 wks prior to surgical fracture of radii and resumed after surgery for 17 wks. Drug was administered orally and vehicle used was deionized water. Food was removed 2-hrs prior to and resumed 2-hrs post dosing.

Observed Effects

Lethargy dehydration, anorexia and pain on abdominal and cervical palpation were noted in one female in Group 4. These effects were attributed to "Beagle 'pain syndrome' (spontaneous panarteritis, necrotizing polyarteritis syndrome)".

Mortality

There were no deaths.

Body Weight and Food Consumption

No treatment related changes.

Radiographic Analysis

Such analysis was performed prior to, immediately following surgery and on wks 4, 8 and 16 post surgery. Sponsor noted that "Subjective evaluation of the 8-16 week

postsurgical radiographs indicated a trend toward larger callus size in treatment groups receiving MK-217 postsurgery, suggesting a mild delay in callus remodeling."

Gross Pathology

Only fractured radii were examined. Summary data on callus formation are presented below (Vol 1, pg 53):

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Group	No Callus		Small Callus		Moderate Callus		Large Callus	
	M	F	M	F	M	F	M	F
1	3/5		2/5	4/5		1/5		
2		2/5	5/5	3/5				
3		0	4/5	1/5		2/5	1/5	2/5
4	1/5		2/5		2/5	2/5		3/5

Histopathology

Groups given MK-217 prior to surgery had "complete bony union with no or small calluses and no retention of cartilage around the healing site". When MK-217 was administered following surgery, there was "cortical bony union but with a higher incidence of retained cartilage in larger calluses." In consideration of gross and histopathological findings, sponsor felt that "The daily administration of MK-217 for 16 wks after fracture of the right radius in adult dogs resulted in higher incidence of moderate to large calluses present at necropsy suggesting a delayed or slowed rate of bone remodeling at the repairing fracture site." (Vol 1, pg 56).

Histomorphometric Analysis

Calcein (10 mg/kg) was administered either day 4:14 or 7:17, prior to sacrifice. There were no significant differences between the mineral apposition rate (MAR: um/day) between control and treatment groups (fractured radii). These data are summarized below:

Group	Mean MAR	Max MAR	Min MAR
1	1.12+0.01	1.32	1.05
2	1.19+0.09	1.35	1.09
3	1.06+0.17	1.33	0.74
4	1.06+0.17	1.44	0.88

Note : Means are expressed + S.D.

Biomechanical Tests

Strength of the fractured radii was measured by a three-point bending test. There were no significant differences between the groups, in the ultimate strength and stiffness of the fractured radii and intact radii.

Effect of EHDP on Fracture Healing in Dogs

These data were provided as a publication. Additionally these EHDP data have already been reviewed for NDA 20-082 (Didronel, Proctor and Gamble Pharmaceutical Co.). Nevertheless, a brief summary is provided in this review.

In mature female beagle dogs, a surgical transverse fracture in the midshaft radius was made and then supported by an external splint. These dogs were given EHDP at s.c. doses of 0.1, 0.5 and 5 mg/kg (equivalent to 5, 10 and 100 mg/kg clinical oral doses) for 20 wks. At 0.5 mg/kg there was delayed healing of the fracture, as well as decreased bone strength. At 5.0 mg/kg there was no bony union at the fracture site and mineralization defects were noted.

Summary

The effect of MK-217 on fracture healing was examined in a 32-wk study in dogs. Only a 2 mg/kg oral dose given either before or after surgical fracture of the right radius was tested. Potential alterations in fracture healing were observed histologically when MK-217 was given post fracture. However, mineralization defects were not found. The 2 mg/kg dose is 5x the clinical MK-217 dose for treatment of osteoporosis (assuming there is no difference in % oral absorption between dogs and humans).

The sponsor also presented fracture healing data with another bisphosphonate, EHDP. With EHDP, problems with fracture healing have been found with doses equivalent to 10 and 100 mg/kg human oral doses. The therapeutic dose of EHDP for osteoporosis is 8 mg/kg. It should however be noted that the oral absorption of EHDP in dogs is 14% vs. 1% in humans and thus the multiples of the clinical doses associated with deleterious effects are not as low as they first appear.

Any concerns of altered fracture healing with MK-217 cannot be dismissed by comparison to EHDP data. Any effects of MK-217 on fracture healing will be indirectly addressed in the "treatment" bone quality study in monkeys. That is if MK-217 does inhibit fracture healing, then one would expect an increase in the number of spontaneous fractures in the treated monkeys.

Recommendation: NAI at this time.


Chhanda Dutta, Ph.D.

HFD-510/L Pierce/S Dutta/A Jordan/C Dutta

 3/3

(1) *Fuller*

MAR 1 1993

February 20, 1993

IND

Sponsor: Merck & Co., Inc., West Point, PA

Date Submitted: October 15, 1992

Date Received: October 19, 1992

REVIEW AND EVALUATION OF TOXICOLOGY DATA

Appendment Review

Drug: Aminohydroxybutane Bisphosphonate (AHButBP); Alendronate Sodium; MK-217 oral; Fosamax

Category: Bisphosphonate; Anti-resorptive agent

Proposed Clinical Indication: Treatment of Postmenopausal Osteoporosis.

The Effect of Two Year Treatment With the Aminobisphosphonate MK-217 on Bone Metabolism, Bone Histomorphometry, and Bone Strength in Ovariectomized Baboons.

Sexually mature female baboons (7/group) were ovariectomized (OVX) and treatment with MK-217 was initiated immediately following OVX. These baboons were also mature in terms of skeletal growth. The doses of MK-217 used were either 0.05 mg/kg or 0.25 mg/kg MK-217 i.v. every two weeks for two years. These doses were stated to be equivalent to 20 and 100 mg human oral doses, respectively, with the assumption of 1% absorption. Control groups included OVX and intact female baboons, that were given vehicle (saline).

Body Weight

Intact controls were found to have body wts 15% greater than both treated and control OVX baboons. The body wts of OVX females given MK-217 were not significantly different from OVX controls.

Clinical Chemistry

Although significant changes in serum Ca and P levels were noted in the MK-217 groups, they were sporadic. Additionally, serum chloride, sodium, potassium, glucose, creatinine and BUN were unchanged with treatment.

Data on SGPT activity were difficult to interpret. OVX controls were found to have significantly increased SGPT vs intact controls, at mo 15 only. Compared to the OVX+0.25 mg/kg group, intact controls were found to have significantly increased SGPT from mo 5 and thereafter. However, there was no significant difference in SGPT activity between OVX controls and MK-217 treated groups, throughout the study. SGOT activity was not different between the various control and treated groups.

At the end of the study range of serum E₂ levels in intact controls were 25-323 pg/ml (median 51 pg/ml); and in OVX animals were <10 -26 pg/ml (median 12 pg/ml).

There was no difference in serum PTH and Calcitonin (CT) levels between the study groups.

Hematology

Compared to intact controls, % segmented neutrophils was significantly decreased and % lymphocytes was significantly increased in the 0.05 mg/kg group. Other hematological parameters were unremarkable.

Urinalysis

No treatment related changes were noted.

Biochemical Markers of Bone Turnover

All markers were measured every three months.

Serum Tartrate-Resistant Acid Phosphatase (TRAP): (Marker of osteoclast activity). During the course of the study, TRAP levels were significantly higher in OVX controls (vs intact controls and both MK-217 groups). However, there was no dose related difference in TRAP levels with MK-217 treatment.

Urinary lysylpyridinoline/Creatinine: (Marker for bone resorption) The lysylpyridinoline/creatinine ratio was significantly greater in the OVX controls than in intact controls and in MK-217 treated baboons. There was no significant difference in lysylpyridinoline/creatinine ratio between 0.05 and 0.25 mg/kg doses.

Serum Alkaline Phosphatase (ALKP): Marker of osteoblast function. ALKP levels in OVX controls were significantly higher than intact controls and both dose groups of MK-217, throughout the study. Yet, MK-217 did not produce dose related changes in ALKP.

Serum Osteocalcin or Bone Gla-Protein (BGP): Marker of osteoblast function. BGP levels in OVX controls were significantly higher than intact controls and MK-217 treated groups, from mo 6 and thereafter. In the 0.05 mg/kg group, BGP levels were greater than intact controls from mo 9-24. On the other hand with 0.25 mg/kg, BGP levels were consistently lower than intact controls, throughout the study. There was no significant difference in BGP levels between the two doses.

Bone Mass/Density Measurements

These measurements were made by single photon absorptiometry (SPA). There were no significant differences in the radial bone mineral content (g/cm), density (g/cm²) and width (cm) between intact and OVX controls; as well as between OVX controls and MK-217 treated baboons.

There was no significant difference in the femoral neck bone density (g/cm²) between OVX and intact controls, throughout the study. Femoral neck density was significantly greater in the 0.25 mg/kg vs OVX controls on mos 3, 9 and 12 only; vs intact controls on mos 3, 6, 9, 15, 18, 21 and 24; and vs the 0.05 mg/kg group, from mo 3-24. Sponsor noted that measurement of femoral neck density had "... higher error than those of the radius and vertebrae".

Lumbar vertebral density (g/cm²) measurements were performed from L1-L4. There were no significant differences in any of the vertebral BMD values, between the two doses of MK-217.

-L1 BMD was significantly greater in intact controls vs OVX controls at mo 24. Compared to OVX controls, 0.25 mg/kg group had significantly increased L1 BMD at mos 21 and 24.

-L2 BMD was significantly greater in intact vs OVX controls at mo 24. On mos 9, 12, 18 and 24, L2 BMD in the 0.25 mg/kg group was significantly higher vs OVX controls.

-L3 BMD of intact controls was significantly greater than OVX controls, on mos 6, 12 and 18-24. From mo 6-24, the 0.25 mg/kg dose group has significantly higher L3 BMD than the OVX controls.

-L4 BMD of intact controls was significantly greater than OVX controls on mos 6, 9 and 24. L4 BMD in the 0.25 mg/kg group was significantly greater than OVX controls from mo 6-24.

-When L2-L4 BMD values were averaged, intact controls had significantly greater vertebral BMD on mo 6, 15 and 24. The average vertebral BMD in the 0.25 mg/kg group was significantly greater from mos 6-24.

Bone Histomorphometry

Such analysis was performed on iliac crest biopsies obtained at mos 0, 6, 12 and on iliac crest wedges and L5 vertebra bodies obtained at mo 24.

Iliac Crest Biopsy samples:

The cancellous bone volume (volume of bone vs bone marrow; data presented as bone volume per tissue volume or % BV/TV) was significantly smaller in OVX vs intact controls and MK-217 treated groups (mos 6 and 12). However, there was no significant difference in % BV/TV between the two doses.

Osteoid surface (content of unmineralized matrix in bone; %OS/BS), osteoid volume (total amount of unmineralized matrix) and # of osteoclasts per unit bone surface (N. Oc/mm) in OVX controls were significantly greater than that of all other groups (mos 6 and 12). However, there was no significant difference between these parameters with the two doses of MK-217.

Eroded surface (cumulative parameter of bone resorption, %ES/BS) in OVX controls was also significantly greater than that of all other groups.

Iliac Crest Wedge:

Bone volume was significantly greater in the 0.25 mg/kg group than both OVX and intact controls, intact controls and MK-217 treated baboons.

Osteoid surface in OVX controls was greater than in intact controls and MK-217 treated baboons. Moreover, osteoid surface in the 0.25 mg/kg group was significantly less than in intact controls. Osteoid thickness in OVX controls was significantly greater than that of all other groups. Osteoid thickness was not significantly different between the two dose groups.

Mineral apposition rate (rate of mineralization) in OVX controls was also statistically greater than that of other groups. Sponsor noted that the mineralization lag time was within 20 days in all groups and that lag time longer than 100 days is considered to indicate osteomalacia.

Wall thickness (amount of bone produced in one remodeling cycle) in the 0.05 mg/kg treated group was found to be significantly greater than both intact and OVX controls. However at the higher dose of MK-217, the wall thickness was significantly greater than OVX controls only.

The bone formation rate (BFR) and activation frequency (frequency of remodeling events; Ac F) in OVX controls was significantly greater than all other groups. Only the 0.25 mg/kg dose of MK-217 lowered BFR and Ac F significantly, compared to OVX controls.

Lumbar Vertebra L5:

Cancellous bone volume in OVX controls was not significantly lower than intact controls. However, in both doses of MK-217 there was a significant increase in the cancellous bone volume vs OVX controls. There was no significant difference between the two doses.

Cancellous bone architecture (consisting of trabecular thickness and number) was not significantly different between OVX and intact controls. With MK-217 treatment, trabecular number was unaffected, while the trabecular thickness was increased. The magnitude of change in trabecular thickness was not significantly different between the two doses.

Data on L5 osteoid surface was difficult to interpret. The osteoid surface in OVX controls was not significantly different than intact controls. Yet the osteoid surface in 0.25 mg/kg group was found to be significantly less than intact controls only.

Biomechanical Testing of Bone Strength

Biomechanics of both long bones (femora) and vertebral bodies (L4) were examined. Femoral neck and shaft strength were assessed by the three-point bending test. Vertebral body strength was measured in a core of L4 vertebra using the compression test.

Strength of the femoral neck and shaft was not significantly different between all the groups. On the other hand, ultimate strength of L4 vertebral body was found to be significantly greater in the 0.25 mg/kg group vs all other groups.

Summary

The current submission contained the final report of a bone quality study in ovariectomized baboon with MK-217. MK-217 was administered at i.v. doses of 0.05 and 0.25 mg/kg. Doses were given once every two weeks for a total period of two years. Sponsor stated that these i.v. doses were equivalent to clinical oral doses of 20 and 100 mg.

Biochemical and histomorphometric data indicated increased bone turnover in the OVX controls. Generally, MK-217 treatment resulted in slowing of bone turnover, indicated by significant decreases in biochemical markers of bone turnover (serum TRAP, ALKP, BGP and urinary lysylpyridinoline/creatinine) and by improvement in histomorphometric parameters from the iliac crest biopsy and iliac crest wedge (%OS/BS, %BV/TV and %ES/BS) vs. OVX controls. Moreover dynamic parameters of bone turnover such as MAR, BFR and AcF measured at the iliac crest wedge also improved with MK-217.

However, histomorphometric data from L5 vertebra were difficult to interpret. The %BV/TV and %OS/BS in OVX controls were not significantly different from intact controls, indicating that ovariectomy did not substantially affect trabecular bone turnover (or at least not at L5). Yet MK-217 increased %BV/TV and 0.25 mg/kg dose resulted in significantly decreased %OS/BS compared to intact controls. Analysis of bone architecture revealed that MK-217 increased trabecular thickness but had no effect on trabecular number. The difference in histomorphometric data from the iliac crest and lumbar vertebra stresses the point that changes observed at one site (whether with ovariectomy or treatment) cannot be assumed to reflect events at another site.

Densitometric data revealed no significant differences between radial bone and femoral neck densities of OVX and intact controls. Yet throughout the 24 mo treatment, 0.25 mg/kg dose significantly increased femoral neck density compared to 0.05 mg/kg group and intact controls. In contrast, ovariectomy resulted in decreased bone density in vertebral bodies L1-L4. The 0.25 mg/kg dose significantly increased BMD at each lumbar vertebral body as well as the average

BMD of L1-L4 from mos 6-24 of the study. In agreement with the densitometric data, the strength of femoral neck and shaft was not significantly different between all the groups, while the ultimate strength of L4 body in the 0.25 group was significantly greater than all other groups.

In conclusion, data from this study did not find any deleterious effects on bone quality with doses of MK-217 4x and 20 x the clinical dose. However, the following points should be kept in mind when referring to these data:

1. Results of this bone quality study in baboons are pertinent to the clinical indication of prevention of osteoporosis, since administration of MK-217 was initiated soon after ovariectomy. However, the current proposed clinical indication for MK-217 is for the treatment or the intervention of established osteoporosis.
2. The clinical therapeutic dose of MK-217 for osteoporosis is 5 mg/day or 0.1 mg/kg/day. Thus the doses used in this study were 4x and 20x the clinical dose. On the other hand, the difference in the treatment regimen should be kept in mind. That is, this study used i.v administration once every two weeks and clinically, MK-217 is intended to be administered as a daily oral dose.
3. Rationale for dose and bimonthly regimen selection was stated to be "(i) simultaneous ingestion of food reduces drug absorption and i.v administration provides best assurance for full dose delivery; (ii) human studies on hypercalcemia of malignancy have shown two to three weeks efficacy after a single i.v bolus, possibly corresponding to the duration of the resorption phase at a particular site; and (iii) previous dose-response studies in rats have indicated that the chosen dose levels should bracket the effective dose. (Vol 1, pg 12). Yet in the current baboon study, most of the effects of MK-217 on bone were not significantly different between the two doses, even though there was a 5-fold difference between the doses.

Recommendation: Since the sponsor has agreed to conduct a "treatment" study in ovariectomized monkeys with MK-217, NAI at this time.


Chhanda Dutta, Ph.D.

3/1/93

cc: HFD-510/L. Pierce/S Dutta/ A Jordan/ C. Dutta

AUG 21 1995

NDA 20-560

August 19, 1995

MEMO CONCERNING FOSAMAX LABELING

FDA held a teleconference with Merck on August 18, 1995 concerning revisions in the label for Fosamax. The Pharmacology revisions had been derived from the data base provided by Merck under the close supervision of the Pharmacology supervisor, Dr. Alex Jordan. Dr. Jordan analyzed the data in the NDA review in detail, especially that concerning reproductive toxicity.

Dr. Jordan's analysis of the data led him to wonder whether the Pregnancy Category C should not actually be the more restrictive Category D. However, a D category requires actual human data which we do not have. The least we could do, he felt, was to provide a concise but informative section for the use of physicians and patients.

Once all data was double-checked for accuracy (with Dr. Jordan) and format (with Dr. Troendle), it was FAXed to Merck in order that they might have it well in advance of the teleconference.

Mr. Randy Hedin spoke to the head of regulatory affairs, Dr. Edward Hemwall before the teleconference and was told that Merck basically accepted FDA revisions; their only concerns were the use of historical control data in reference to the carcinogenicity studies and some "wordsmithing". On the basis of this acceptance of our label, Dr. Jordan did not attend our meeting, nor did I feel it necessary to discuss the issues at the pre-meeting, since we had been told that our changes were acceptable.

However, Merck at the teleconference suddenly began to question the content of the pregnancy section: their main arguments appeared to be not with the findings themselves but to the listing of these at low multiples of the human dose. Merck began to bring up data from individual rats in individual reproduction studies (of which there were 17). I explained that the manner in which the studies were conducted would easily explain differences in findings:

- 1) Studies were of different durations and, as they themselves stated, the longer the studies, the lower the doses at which findings occurred and
- 2) Rats and rabbits in all reproductive toxicity studies were allowed access to food at all times.

Fosamax absorption is very sensitive to the presence of food: rats dosed fasted had 5 times the drug absorption of rats dosed fed. Since rats always had food present in these studies, there was no way to know what the actual drug exposure was. Because food was always present, it seems very likely that toxicity findings actually occurred at exposures ~~less~~ than the mg/kg doses would indicate and Merck's arguments that we should raise the levels at which findings occur is arguing for change in the wrong direction.

It is important that changes to the label not be made without the input from the the Supervisory Pharmacologist; Dr. Jordan left town thinking that the label to which he had agreed had been finalized and approved by Merck. Since they now proposes to make changes to the label substantively different from what Dr. Jordan had agreed to and because Dr. Jordan is out of town for one week, I think is important that no further changes be made to the preclinical section until he returns and has a chance to evaluate the data along with the primary reviewer.

Elizabeth Barbehenn, Ph.D.

cc: NDA Arch (20-560)

HFD-510

HFD-510/Jordan/Barbehenn/Dutta/Lutwak/Troendle

fosamax.mem

IND

March 23, 1992

Sponsor: Merck Sharp & Dohme Research Labs, West Point, PA

Submission Date: March 3, 1992

Date Received: March 5, 1992

REVIEW AND EVALUATION OF PHARMACOLOGY DATA

Amendment Review

Drug: Alendronate Sodium I.V.; AHButBP; MK-217; ONCLAST™

Category: Bisphosphonate; bone resorption inhibitor

Proposed Clinical Indication: Hypercalcemia of Malignancy

Comparison of MK-217 to Etidronate in Preclinical Studies

These data were presented in manuscript form and thus relevant points will be listed below. Quantities of MK-217 were expressed in mg P. To convert doses to mkd; 4 mg of MK-217 contains 1 mg P.

A. The effect of MK-217 and EHDP on Bone Formation Following Bone Marrow Injury in Rats

The basis of this model is that disruption of bone marrow activity results in active bone formation followed by rapid bone resorption. Then by day 20, the marrow cavity becomes filled. Hence anti-resorptive activity maintains trabecular bone in the marrow cavity and inhibition of mineralization will result in increased osteoid or non-mineralized bone.

Male SD rats were anesthetized and the marrow cavity of the left tibia was disrupted. The metaphysis of the tibia was kept intact. The marrow cavity was then flushed with saline several times and then filled with saline. MK-217 was administered at s.c. doses of 0.005, 0.025, 0.125 and 0.625 mg P/kg/day (equivalent to 0.02, 0.1, 0.5 and 2.5 mkd, respectively). EHDP was given s.c. at doses of 0.25, 1.25 and 6.25 mg P/kg/day. Duration of study was 10 days.

1. Vehicle treatment (assumed to be saline) resulted in 13% of the marrow cavity to be filled by bone. MK-217 treated rats (all doses) had bone volumes of 26-29%, with no dose relationship. Sponsor felt that max anti-resorptive effect was achieved at the LD.

2. Osteoid volume (extent of mineralization) was similar in controls and rats treated given 0.005-0.125 mg P/kg/day of MK-217. Inhibition of mineralization was found at HD.

3. The LD of EHDP resulted in bone volume similar to controls (hence no anti-resorptive effect). Although anti-resorptive effect was noted at the MD and HD, it was accompanied by inhibition of mineralization. Osteoid volume at the MD and HD were 48 and 82%, respectively.

B. Effect of MK-217 and EHDP on Bone Formation and Resorption in the Long Bones of Growing Rats

The Schenk model was used in this study. The model uses young growing rats which are treated with an anti-resorptive agent. Inhibition of normal resorption then results in increased bone volume, relative to controls. Inhibition of resorption is estimated by the amount of trabecular bone in the subepiphyseal region of long bones.

Male SD rats (6/group) were given daily s.c. injections of either MK-217 at 0.001, 0.01, 0.1 and 1.0 P mg/kg/day or EHDP at 0.01, 0.1, 1.0, 10 and 30 mg P/kg/day. Duration of treatment was 10 days. Parameters measured included ash weight of femora and amounts of secondary spongiosa, cancellous bone volume and osteoid thickness of tibia. Width of the epiphyseal plate of tibia was also measured.

1. Femoral ash weight was increased in a dose related manner with MK-217. Although increased femoral ash weight was increased by 0.01-1 mg P/kg/day of EHDP; doses of 10 and 30 mg P/kg/day resulted in decreased ash weight (inhibition of mineralization).

2. Dose related increase in cancellous bone volume occurred with MK-217. Increased cancellous bone volume was found only with 10 mg P/kg/day of EHDP.

3. Width of epiphyseal plate is an indicator of mineralization defects because widening of the growth plate occurs when mineralized cartilage is not replaced by new bone formation. Neither MK-217 nor EHDP treatment at doses of .001-1 mg P/kg/day produced changes in epiphyseal plate width. However, EHDP at 10 and 30 mg P/kg/day produced increased epiphyseal plate width.

4. Osteoid thickness was similar in control and MK-217 treated (all doses) rats. Dose related increased osteoid thickness was observed with 1-30 mg P/kg/day of EHDP.

C. Comparison of Effects of MK-217 and EHDP on Osteoclasts in Culture

Osteoclast-like cells were produced from a co-culture of mouse osteoblastic cells and mouse bone marrow. The osteoclast-like cells have been characterized to be multinucleated, to be rich in calcitonin receptors, to resorb bone in culture and to stain positively for tartrate-resistant acid phosphatase (TRAP).

Either MK-217 or EHDP were added to osteoblast-like cell cultures at concs of 3, 10, 30, 100 and 300 μ M. Both bisphosphonates reduced the number of TRAP positive cells, in a dose dependent manner. However, MK-217 at concs of 100 and 300 μ M completely suppressed TRAP positive cells.

D. Effects on NH_4^+ Permeability in Osteoclast-like Cells

Sponsor stated that some data suggests that the conc of MK-217 between bone and osteoclasts in the resorption space could change (increase) membrane permeability to Ca. This theory was tested by examining effect of MK-217 on membrane permeability to NH_4^+ . NH_4^+ permeability was assessed by intracellular pH changes (acidification) of osteoclasts upon exposure to NH_4^+ solution. MK-217 was tested at concs of 0.1-5 mM and EHDP was tested at 5 and 15 mM.

Dose related increased NH_4^+ permeability was observed in MK-217 treated osteoclasts. Increases in NH_4^+ permeability produced by 15 mM of EHDP were similar to that obtained with 0.1 mM of MK-217.

In general, this series of in vivo and in vitro studies showed that MK-217 is more potent in its anti-resorptive effect compared to EHDP. However, mineralization defects were often associated with the anti-resorptive doses of EHDP. The separation of anti-resorptive effect from osteomalacia appears to be the advantage of MK-217 over EHDP.

Recommendation: NAI at this time.


Chhanda Dutta, Ph.D.


9/17

CC: HFD-510/A Jordan/S Olmstead/C Dutta

JORDAN

IND

October 9, 1990

Sponsor: Merck Sharp & Dohme Research Lab, West Point, PA

Submission Date: October 1, 1990

Date Received: October 3, 1990

REVIEW AND EVALUATION OF TOXICOLOGY DATA

Amendment Review

Drug: Oral Alendronate; Aminohydroxybutane bisphosphonate;
AHButBP; MK-217; L-670-452

Proposed clinical indications: Hypercalcemia of malignancy;
Osteolytic neoplastic disease; Primary and secondary
hyperparathyroidism; Paget's disease; and Osteoporosis

Chronic Toxicity Studies

53 wk Study in Rats TT #88-641-0

Sprague-Dawley rats (30/sex/group) were given 0.5, 2.5 and 5.0 mg/kg/day of MK-217, by oral gavage. Control group received distilled water. An interim sacrifice at wk 27 was performed.

Mortality

Deaths occurred in all groups. One male each from the control and low dose groups were found dead on wk 20 and 44, respectively. Cause of death in the control animal was undetermined and a pituitary adenoma was noted in the low dose male. At the middle and high doses, deaths (6 animals/group) were mainly attributed to moderate granulomatous pneumonitis. These deaths were considered to be incidental.

Observed Effects

Snoring was noted in high dose males and females only, from wks 33 and 18, respectively. Frequency of this sign was 20% in males and 53% in females. Snoring was associated with dyspnea in approximately half of the affected females. The etiology of these conditions was not clearly established.

Body Weight and Food Consumption

The body weights of middle and high dose females were decreased from wk 12 of the study. At the end of the study, average body weights of middle and high dose females were 11% and 15% lower than control females, respectively. A statistically significant trend of decreased food consumption was found only in the high dose females. During the study, the mean body weight of high dose males was lower than other groups. At wk 52, the mean body weight was 8% lower than control males.

Hematology

RBC was significantly low (7%) in middle and high dose females on wks 39 and 51. This was accompanied by slight reductions in HGB and HCT in these groups. In treated males the RBC, HGB and HCT were consistently reduced, during the study. However statistical significance was obtained only for reduced RBC in high dose males on wks 14 and 25. Platelet count was significantly low (13%) in high dose animals, at wk 51. Lesser magnitude of reduced platelet count was also noted in middle dose animals. Sponsor felt that the changes in platelet count were incidental, since the values were within the range of control values.

Clinical Chemistry

A transient increase in cholesterol and triglyceride levels were found in treatment and control groups from wk 5 to 51. However these changes were not dose related. Calcium levels in high dose males were consistently reduced during the study. At wk 51, the 3% reduction in Ca levels was statistically significant. Dose related, significantly reduced serum P concentrations were noted throughout the study.

Urinalysis

Urinary phosphorus and the phosphorus/creatinine ratio values were increased in high dose animals, during the study. However, significant increases were found only in high dose males on wks 14 and 25. Changes in urinary phosphorus were attributed to treatment. Additionally, urinary Ca and calcium/creatinine values were consistently decreased in high dose animals. Since serum Ca changes were mainly observed in males, the sponsor was uncertain of a treatment effect on urinary Ca.

Organ Weights

Significantly increased relative pituitary weights were found in treated females, at the terminal sacrifice. Pituitary weights (absolute and relative) were unaffected in treated males. In high dose males, significantly increased relative prostatic weights were found at the interim sacrifice. However such changes were not evident at the terminal sacrifice.

Histopathology

Histological evidence for increased pituitary weights was not found. Benign adenomas and hyperplasia of the anterior lobe of the pituitary were noted in all groups, but a dose effect was absent. Additionally, histological changes were not found in the prostates of treated males.

Treatment induced changes included thickening of turbinate bones (nasal); extramedullary hematopoiesis in the spleen; and retention of the primary spongiosa in femurs. The incidence of increased thickness of the turbinates was dose related, but the condition was of slight severity even at the high dose. Sponsor did not find any correlation between these nasal changes and snoring.

Inhibition of bone resorption was indicated by the retention of primary spongiosa of femurs. This effect was more prominent in females at all doses. In the low dose group and middle dose males, the incidence and degree of inhibition of bone resorption was similar at 27 (interim sacrifice) and 53 wks. Other associated changes included smaller medullary cavity and decreased fat content in bone marrow. Extramedullary hematopoiesis in the spleen was noted in treated females and in high dose males. The incidence and severity of the condition were dose related. Bone marrow changes and extramedullary hematopoiesis in the spleen may have resulted from the decreased medullary cavity of bone.

53 wk Study in Dogs with Recovery Period TT #88-641-0

Beagle dogs (4/sex/group) were given 0.5, 2.0 and 8.0 mg/kg/day of MK-217, by oral gavage. The recovery group received 8.0 mg/kg/day from wks 1-13 and were then sacrificed at wk 53. Control group was given distilled water.

Mortality

One middle dose male and one high dose female were sacrificed as moribund on wks 48 and 50, respectively. Anorexia, vomiting, coughing and dyspnea were noted prior to sacrifice. These deaths were attributed to faulty intubation technique.

Body Weight

In high dose females and dogs in the recovery group, the body weights were consistently lower than other groups. At the end of the study, the average body weights of these groups were 7-10% lower than that of controls. However, it should be noted that the average body weight of dogs in the recovery group were lower than controls at the start of the study.

Clinical Chemistry

Significant hypocalcemic effect was seen in the recovery group, on wks 5-13. Decreased serum Ca levels were also noted in the high dose group during this time, but the magnitude of change was not statistically significant. On wks 5 and 8, serum P levels were significantly decreased at all doses. Serum P levels were also decreased on wk 13 at all doses, but statistical significance was obtained only in the high dose and recovery groups. Serum Ca and P levels in treated animals were similar to controls, for the duration of the study.

Urinalysis

Urinary Ca and calcium/creatinine ratios were increased in treated animals, on wks 8 and 13. These parameters were slightly increased during the remainder of the study.

Histopathology

Retention of primary spongiosa of ribs and femur were noted in treated animals. Severity of the condition in the ribs ranged from very slight at the low dose to severe at the high dose. Accompanying changes included a prominent mesenchymal layer

(osteogenic) in the periosteum; and a decreased number of osteoblasts per unit of surface. Eventhough treatment ceased on wk 13; at wk 53 moderate to marked retention of primary spongiosa was present in ribs of the recovery group. However, the primary spongiosa was less dense than that found in dogs treated with 8 mg/kg/day for 53 wks.

Slight to marked retention of primary spongiosa was also noted in the femurs of treated dogs. Cartilaginous changes at the growth plate included zones of resting cartilage; hypertrophic and ossifying cartilage. In the recovery group, these changes were present at a lesser degree.

Chronic focal nephritis and mineralization of renal papilla were noted in one dog each of the high dose and recovery groups. These renal changes were attributed to treatment.

Summary: Limited toxic effects of MK-217 were observed in the 53 wk studies in rats and dogs. Treatment related deaths did not occur in either of the studies. Decreased body weights were found in rats at 5.0 mg/kg/day (5x HD) and in dogs at 8.0 mg/kg/day (8x HD). Hypocalcemia and hypophosphatemia were also noted in both studies. In rats, decreased serum Ca and P at 5 mg/kg/day (5x HD) were accompanied by increases in urinary calcium and phosphate. In the dog study, hypocalcemia and hypophosphatemia were observed at 8 mg/kg/day (8x HD), only during wks 5-13. Thereafter serum Ca and P levels in these animals were similar to controls. It is unclear why the period of hypocalcemia and hypophosphatemia were similar in high dose and recovery groups. The high dose group received 8 mg/kg/day of MK-217 for 53 wks, whereas the recovery group was given 8 mg/kg/day for only 13 wks.

Hematological effects were found only in the rat study. Decreased RBC, HGB and HCT were observed with 2.5 and 5.0 mg/kg/day (2.5x and 5x HD). Decreased platelet counts were also noted at these doses, however the values were within the range of control values.

Renal toxicity was noted only in the dog study. Chronic focal nephritis and mineralization of renal papilla were noted at 8 mg/kg/day. One dog each, of the high dose and recovery groups displayed these conditions.

Inhibition of bone resorption by MK-217 was indicated by histological evidence. In rats, increased thickness of turbinates (nasal bones) and retention of primary spongiosa of the femur were noted with 0.5-5.0 mg/kg/day (0.5-5.0x HD). Effects on the femur were more prominent in females. Other changes included a reduction in the size of the medullary cavity and decreased fat content in bone marrow. Moreover, the decreased medullary cavity led to extramedullary hematopoiesis in the spleen. The incidence and severity of these changes were dose related.

Retention of the primary spongiosa of ribs and femur were noted in dogs with 0.5-8 mg/kg/day (0.5-8x HD). The severity of this effect in ribs was dose related. Furthermore a decrease in the number of osteoblasts in the ribs was noted. In femurs, cartilaginous changes (resting cartilage, hypertrophy and ossification of cartilage) were noted at the growth plates. These changes were also present in the recovery group (8 mg/kg/day for 13 wks), but at a lesser degree.

In the review of the previous submission, it was noted that 14 wk studies in rats found minimal toxic effects of MK-217 at 5.0 mg/kg/day. In the current study, 53 wks of treatment of rats with 5.0 mg/kg/day also resulted in limited toxicity. On the other hand, high mortality of rats occurred with 5-7.5 mg/kg/day, in an ongoing 2 yr carcinogenicity study. This drastic difference in toxicity is puzzling.

Recommendation: Following comment is to be included in the letter to the sponsor. Toxicity of 5.0 mg/kg/day of MK-217 in rats has ranged from minimal (53 wks) to high mortality (ongoing carcinogenicity study). If the data is available, it would be of interest to compare the drug levels obtained in these rat studies. Other possible explanations of this variable toxicity are invited.


Chhanda Dutta, Ph.D.

CC: IND, HFD-510, HFD-345
HFD-510/A Jordan/C Dutta


10/16/90

IND

July 25, 1990

Sponsor: Merck Sharp & Dohme Research Labs, West Point, PA

Submission Date: October 18, 1989 (Serial No. 016)

REVIEW AND EVALUATION OF TOXICOLOGY DATA

Amendment ReviewDrug: Oral Alendronate; Aminoxybutane bisphosphonate;
(AHButBP); MK-217; L-670-452

Category: Bisphosphonates, bone resorption inhibitors

Proposed Clinical Indications: Hypercalcemia of malignancy, osteolytic neoplastic disease, primary and secondary hyperparathyroidism and Paget's disease.

14 wks Study in Rats TT #89-008-0

Groups of 15 M and 15 F CRL:CD (SD), albino rats were given MK-217 by oral gavage. Doses used were 10.0, 30.0, 90.0 and 150 mg/kg/day. Controls received vehicle (0.5% methylcellulose).

Mortality

Animals in the 150 and 90 mg/kg/day groups were sacrificed (Wks 2 and 8, respectively), due to drug toxicity. Other animals in these groups had been sacrificed as moribund, at an earlier time.

Observed effects

The animals sacrificed early had difficulty in breathing, lethargy and distended abdomens. These effects were dose related. Upon necropsy, these animals were found to have gastritis, ulcers and marked gastrointestinal distension. An increased incidence of labored breathing was noted in surviving rats, as the study proceeded.

Body weight and Food consumption

Decreased gain in body weight was noted at all doses. This effect was dose related. At 150 mg/kg/day, male and female rats had 87% and 111% reductions, respectively. With the 90 mg/kg/day dose, the decrease was 40% in males and 58% in females. Dose related decrease in food consumption was also observed. Change in food consumption was slight for the low dose group and it was observed near the end of the study.

Hematology

Dose related increases in RBC, HGB and HCT were noted. These increases most often occurred in moribund rats and were thought to be secondary to dehydration. Additionally, females

were affected more than males. Test drug related decrease in lymphocyte count was found in the high dose group. At 150 mg/kg/day, the decrease was 32% in males and 17% in females. This effect was thought to be secondary to treatment related stress. A 7-8% increase in MCV was also found in the high dose animals. Dose dependent increase in neutrophils was also found.

Clinical Chemistry

Animals receiving 30-150 mg/kg/day of MK-217 had elevated BUN concentration. More pronounced effect was seen at the high dose. Decreased serum creatinine was also seen in some of these animals. Serum ALB and TP were decreased in a dose dependent manner. Dose relationship of increased SGOT and SGPT levels was also noted. Serum CA and P were decreased in a dose related manner. Such decreases are reflective of the pharmacological actions of MK-217, rather than toxicity. Decreased ALKP levels in treated animals could reflect inhibition of osteoblast activity.

Organ Weights

Since the high dose groups were sacrificed early in the study, concurrent controls were not available for comparison. Animals in the 30 mg/kg/day group had decreased weights of liver, thymus, kidney, adrenals and spleen. Uterine weight was reduced in females and slight decreases in testes and prostate weights were noted in males.

Gross Pathology

Various degrees of distension of the stomach, small and large intestines were observed in treated animals. These pathologies were not evident in controls and thus were considered to be drug induced.

Histopathology

Several treatment related lesions were noted in the stomach. Such lesions included degeneration of the glandular mucosa, acute gastritis and mucous cell hyperplasia. The incidences of the degenerative and hyperplastic conditions did not differ with the dosage. Acute gastritis was predominantly found at dosages of 30 mg/kg/day and higher. Varying degrees of gastritis were found in both the glandular and non-glandular regions of the stomach. Ulcers or erosions were found along with the gastritis. Some animals in the 30 and 90 mg/kg/day groups were found to have renal tubular necrosis.

Necrosis of the spleen, thymus and lymph nodes was noted in high dose animals, which were sacrificed early. Thymic atrophy was found at all doses used. Decreased number of lymphoid cells in the spleen and lymph nodes was found at doses of 30 mg/kg/day and higher. The sponsor felt that although these effects were test drug related, they were more likely resultant from stress.

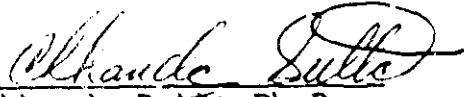
At all doses, the number of osteoblasts lining spicules in the long bones was decreased. This would indicate inhibition of bone formation. Retention of primary spongiosa was noted in all treated animals. The degree of retention was not related to dosage, but rather to the length of exposure to the test drug. An increase in the number of osteoclasts was found in the high dose groups. However animals from other groups sacrificed after Day 37 of the study did not show this effect. Thus the sponsor concluded that the increased number of osteoclasts seen soon after treatment, is a phenomenon associated with high doses of MK-217.

Summary

MK-217 at doses of 90 and 150 mg/kg/day resulted in high mortality. Dose dependent decrease in serum ALB and increases in SGOT and SGPT levels indicated hepatotoxicity. Renal toxicity was noted at doses of 30 mg/kg/day and higher. This dose range was also associated with acute gastritis and ulcers. Inhibition of bone formation by MK-217 was indicated by the decreased level of ALKP and the lower number of osteoblasts in the spicules of long bones. Additionally, inhibition of bone resorption was indicated by the retention of the primary spongiosa. Minimal toxicity was found with 10 mg/kg/day (10x human dose) of MK-217.

The results of this study are consistent with the findings of an earlier 14 wk toxicity study in rats. In that study, minimal toxicity was seen with 1.25-5.0 mg/kg/day of MK-217. A 53 wk toxicity study in rats is currently pending submission. Doses used in this study are 0.5, 2.5 and 5.0 mg/kg/day. Minimal toxicity was noted in the wk 27 interim report. In an ongoing 2 yr carcinogenicity study in rats, high mortality rates were seen with 5.0-7.5 mg/kg/day. Yet minimal toxicity has been noted at these doses in previous studies. This discrepancy remains to be resolved.

Recommendation: NAI at this time.


Chhanda Dutta Ph.D.

CC: IND, HFD-510, HFD-345
HFD-502/Weissinger
HFD-510/A Jordan/C Dutta


7/31/90

INL
Merk Sharp & Dohme Research Laboratories
West Point, PE
8/25, 89

11/8/89

NOV 9 1989

Review and Evaluation of Pharmacology and Toxicology Data
Amendment of 8/24/89

Drug: MK-217 I.V. (AHButBP, Aminohydroxybutane Bisphosphonate)

Category: Agent for treating hypercalcemia

This submission contains the report for a toxicity study.

14-Week Oral Toxicity in Crl:CD(SD BR rats, 89: The purpose of this study was to determine the potential toxicity of the test agent and to assist in the selection of doses for an upcoming carcinogenicity study.

Rats (15/s/group) received 0, 10, 30, 90 and 150 mg/kg/day.

Results: Due to overt compound-induced toxicity including deaths, the animals in the 150 and 90 mg/kg/day groups were killed during weeks 2 and 8, respectively. There were also drug-related deaths in the 30 mg/kg/day group. The table below summarizes the number of animals dying or killed before scheduled termination in all dosage levels.

Control	0/30
MK-0217	
10 mg/kg/day	1/30
30 mg/kg/day	16/30
90 mg/kg/day	17/30
150 mg/kg/day	6/30

Most of these animals had one or more of the following clinical signs and/or gross lesions: labored breathing, distended abdomen and gaseous distension of the G.I. tract. Many also had histologic evidence of gastritis and gastric erosions or ulcers.

Treatment-related decrease in rate of body weight gains were noted at all dosage levels. The table below summarizes the % decrease in body weight gain as compared to control.

Body Weight Gain as Percent of Control

	Male	Female
MK-0217		
10 mg/kg/day	-8	-13
30 mg/kg/day	-27	-16
90 mg/kg/day	-40	-58*
150 mg/kg/day	-87	-111**

* last weight in DW 7

**last weight in DW 2

Treatment-related microscopic lesions were found in numerous animals in the 30, 90 and 150 mg/kg/day. These consisted of degeneration, acute gastritis, erosion and mucous cell hyperplasia of the gastric glandular mucosa. Microscopic gastric changes were generally not seen in the 10 mg/kg/day group, although gaseous distension was seen in 4 animals in this group. There was, however, one animal in this group with gastric erosion and acute gastritis. Since similar changes were seen at higher doses, this one occurrence is also likely to be drug-related.

Treatment-related microscopic changes were also seen in the kidneys of animals in the 30 and 90 mg/kg/day groups. These were characterized by renal tubular necrosis and occasional regenerative changes. These changes were not seen in animals in the 150 mg/kg/day group because of early termination of this dose group.

In addition to the above-mentioned primary drug-related changes, there were many secondary changes in other organs related to stress in the 30, 90 and 150 mg/kg/day groups. These included lymphoid cell necrosis, lymphoid cell depletion or atrophy in the spleens, lymph nodes and thymuses.

The sponsor indicated that due to inflammatory and /or degeneration changes in the stomach and kidneys and due to high rate of mortality, doses of 30 mg/kg/day or higher are not appropriate for long-term studies. At 10 mg/kg/day, there were drug-related decreases in the rate of body weight gains compared to controls and there were drug-related GI tract lesions. Thus this dose is also not considered appropriate for a 2-year carcinogenicity study. In a previous 3-month oral toxicity study in rats at 5 mg/kg/day, there were no drug related effects on body weights or on any organs. Therefore a high dose of 7.5 mg/kg/day (4xMHD of 100 mg/day) is proposed for the upcoming 2-year carcinogenicity study. A low dose of 1 mg/kg/day (0.5xMHD) is proposed for the 2-year carcinogenicity study. The proposed middle-dosage level is 3.75mg/kg/day (2xMHD).

Comments: Hypercalcemia is a life threatening disease. The drug is 10 times more effective than EHDP. Nephrotoxic is a common adverse effect of this class of drug. According to M.O. (Dr. S Dutta) the average life expectancy span of these tumor bearing patients is 3 months. The duration of treatment with the drug is only 5-6 days. Since the proposed dosage of the drug for the 2-year carcinogenicity study is at such low dose (0.5-4xMHD) Pharmacology feels that for this indication, carcinogenicity study can be waived. However if the sponsor intends to use this drug for treating Paget's disease carcinogenicity studies in rats and mice need to be performed.

Recommendation: For treating Paget's disease carcinogenicity studies need to be performed.

I. Huang
I. Huang, Ph. D.

CC: Orig IND, HFD-345, HFD-510, HFD-510/AJordan, HFD-510/IHuang,
HFD-502/JWeissinger

A Jordan
11/9/89

3 wk dog
4 wk dog
dog III rat

JUN 1 1989

IND 5/8/89
Merk, Sharp & Dohme Research Laboratories
West Point, PE
2/6/89

Review and Evaluation of Pharmacology and Toxicology Data
Amendment of 2/2/89

Drug: AHButBP (MK-217 Oral, oral aminohydroxybutane bisphosphonate)

Category: Treatment of Paget's disease.

This submission contains the reports of four toxicity studies. All studies were conducted by

I. Study of Subchronic Toxicity of AHButBP Administered Orally in Beagle Dogs for Five Weeks, 87

Dogs (3/group) received 0 (1F), 10 (2M, 1F), 20 (1F, 2M) and 40 mg/kg/day (2F, 1M)

Results:

1. Clinical Signs, Body Weight, Food Consumption: With the exception of the male dog in the 40 mg/kg group all treated dogs showed exophthalmus. Dogs in the high dose group exhibited hyperexcitability and restlessness when being handled.

2. Hematology: Unremarkable.

3. Urinalysis: Unremarkable.

4. Autopsy: In two animals treated with 40 mg/kg and in one animal treated with 20 mg/kg and in two animals treated with 10 mg/kg were noted areas of punctiform hemorrhages in the gastric mucosa. In one dog in the high dose group was also noted catarrhal enteritis.

5. Organ Weights: Unremarkable.

6. Histological Examination: In some treated dogs has been noted a slight superficial damage of the mucosa: superficial gastritis with lymphocitis infiltration or cellular necrosis of the columnar epithelial layer of the intestinal villi (in the case of catarrhal enteritis).

The other finding noted in all treated animals concerns the bone (rib) where it's evident a considerable increase of the compact tissue as compared to the spongy tissue. For this evaluation from the rib was removed a part comprising the costo-chondral junction and two fragments, connected to this part of the costal cartilage and of the body of the rib. The increase of bony tissue is best seen in this last fragment. This increase is more or less of the same degree in all of the animals treated with the drug except in one male in the 40 mg/kg group and two males in the 10 mg/kg group where the increase is of a slightly lesser degree, but always clearly evident.

II. Four Week Oral Study in Beagle Dogs, 87: Dogs received 0 (1F), 15 (1M, 1F), 30 (2F, 1M), 60 (2F, 1M) mg/kg/day.

Results:

1. Body Weight, Food Consumption: One female dog in the 60 mg/kg group had reduced food consumption starting from the 22nd day of treatment.
2. Clinical Signs: High dose dogs showed emesis, diarrhea, vomiting, excitability, tremors, buccal ulcers, bleeding buccal ulcers at the labial commissure, ulceration at the nasal septum.
3. Hematology and Clinical Chemistry: Treated dogs showed decrease in HB. High dose dogs showed creatinemia, decrease in erythrocytes and serum calcium, increase in leukocytes.
4. Urinalysis: In one female dog in the 60 mg/kg group was observed an increase of the urinary pH and the presence of leukocytes, proteins, glucose and blood. The urinary sediment presented numerous leukocytes, cell of renal origin, and other epithelial cells of the lower urinary tract. In the sediment of two other dogs (one male in the 15 mg/kg group and 1 male in the 30 mg/kg group) were also observed cells of renal origin.
5. Macroscopic Examination:

15 mg/kg group:

M: Hemorrhagic spots in the gastric mucosa
F: Numerous hemorrhagic spots in the basal region of the bladder's mucosa and an evident hyperemia of the organ. In the gall-bladder's mucosa was observed a hyperemic and hemorrhagic area.

30 mg/kg group:

F: The gastric mucosa in the cardiac region presented a few punctiform hemorrhages and erosion of the same mucosa in three or four areas.
M: Presence of numerous punctiform hemorrhages in the basal region of the vesical mucosa. The gastric mucosa presented necrotic areas in the cardiac region.

60 mg/kg group:

M: In the gastric mucosa was noted an ulcer, 1 mm in diameter. In the bile of the gall-bladder were noted numerous clots of blackist material.

F:
No. 1. Hyperemia of the vesical mucosa. Spleen reduced in volume. The gastric mucosa of the cardiac region presented numerous hemorrhagic areas.

No. 2

Stomach: Presence of abundant liquid, of the mucous appearance and brown-blackish in color, due to blood derived from the ulcerations present in the mucosa of the cardias.

Gall-Bladder: Bile of brilliant-green color, instead of greenish-brown, with abundant clots of blackish material.

Liver: On the parietal surface of the left lateral lobe, was observed an area 1.5 cm in diameter, of lighter color, while the caudate lobe appeared ischemic.

Intestine: Catarrhal enteritis with greenish mucous

Kidney: At cutting, the organs had lesser consistency than normal, and presented hematic stasis.

Lymph nodes of the neck origin: They appeared hyperemic and hypertrophic.

6. Organ Weight:

Thyroid: Slight, dose dependent increase of the relative weight.

Adrenals: Increase of both values in the female dog in the high dose group.

Kidney: Increase of both values in one male dog in the 15 mg/kg group and in a female dog in the 60 mg/kg group.

Thymus: In three animals treated with the high dose was noted a reduction of both values, such reduction, even if of lesser degree is present in one male in the 15 mg/kg group and in one male in the 30 mg/kg group

7. Histologic Examination:

15 mg/kg

F: Presence of areas of superficial erosions in the stratified squamous epithelium.

M: In the lungs were noted various bronchioles filled with decaying cells, of probable granulocytic origin. In the kidney was noted a glomerulus in fatty change.

30 mg/kg

M: Hypertrophy of the vesical mucosa was observed.

60 mg/kg;

M: The lungs presented hematic stasis in the large vessels. In the esophagus were noted extensive degeneration of the epithelium, with reasonable granulocytic infiltration. The mucosa of the gall-bladder was reduced in thickness with flaking areas. In the kidneys some glomeruli presented periglomerular lymphocytic infiltration.

F No 1: The thymus seemed composed of adipose tissue (fatty change). In the esophageal mucosa were noted areas of superficial erosion, with reduction of the thickness of the epithelium. In the liver were noted hepatocytes in cytoplasmatic sufferance and dilated of blood-filled sinusoids (hyperemia). The gall-bladder's mucosa was reduced in thickness with flaking of lining epithelium. In the kidney were observed alterations of the proximal and distal tubules, which appeared dilated and filled with amorphous eosinophilic colloid along with hematic stasis of the medulla.

F. No. 2: Partial fatty change in the thymus. The esophageal mucosa presented areas of superficial erosion reduction in thickness of the epithelium with considerable granulocytic infiltration and areas of hyperplasia. The gall-bladder was partially lacking in lining epithelium.

III. First Teratogenic Study in Sprague-Dawley Rats, 85: Rats (10/group) received 0, 20 or 40 mg/kg/day from the 7th to the 17th day of pregnancy.

Results:

1. Bodyweight of Pregnant Females: An average increase in bodyweight of about 35 % was observed in the control group, the increase is on the contrast 33 % in the 20 mg/kg and 39 % in the 40 mg/kg group.

2. Fertility: Control group had a fertility index of 91%. At the 20 mg/kg dosage the fertility index was 82 % while at the 40 mg/kg dosage was 70 %.

3. Mortality: No death occurred in the control group; in the 20 mg/kg group 3 deceases occurred, on the 11th (one), and on the 15th day (2); other two animals were killed on the 14th and on the 15th day, just before dying.

In the 40 mg/kg 5 deceases occurred between the 10th and the 11th day of pregnancy. Death was caused by severe G.I. damage which caused thinning and dyspnoea by pulmonary disorder.

4. Number of the embryofetal Implantations, of the Living and Dead Fetuses and of the Resorptions: Unremarkable.

5. average Weight of the Living Fetuses: In the groups dosed with the drug the average value of the living fetuses is lower than in the control group, expecially in the high dose group.

6. Fetal Anomalies: Unremarkable.

IV. Second Teratogenic Study in Sprague-Dawley Rats, 87:

Rats (10/group) received 0, 5 or 10 mg/kg/day from the 7th to the 17th day of pregnancy.

Results:

1. Body Weights of the Pregnant Mothers: In the control group there's a gradual increase in the mean body weight of about 57 % whereas in th groups treated with the drug there was an increase of 44 % and 37 % respectively at the doses of 5 and 10 mg/kg.

2. Mortality; Two deaths in the 10 mg/kg group. These deaths lies in possible errors committed during the oral administration of the drug or probably due to premature birth.

3. Number of Embryofetal Implants: A slight decrease of the absolute and average values was observed in treated groups. The differences are not statistically significant, but are dose-dependent.

4. Number of living Fetuses: A slight and almost equal decrease was observed in both treated groups.

5. Number of Resorbed Fetuses: Unremarkable.

6. Average Weights of the Living Fetuses: At the 10 mg/kg dose a slight but significant decrease was observed.

7. Somatic, Visceral And Skeletal Alterations: Unremarkable.

Comments: The current clinical doses are 10, 20 and 50 mg/day for one week.

The submission of the reports of the five week oral study in dogs and the second teratology study in rats was requested by Pharmacology. Summaries of these two studies were submitted in the original submission.

All studies submitted in this amendment were conducted by Gentili Institute S.P.A., Pisa, Italy. For all studies the acid form of the drug was used and no GLP statements were enclosed. For clinical trials the sodium salt form of the drug will be used.

The two dog studies were poorly performed. In the control group only one dog was used. For treated groups only three dogs were used per group. Because of the small number of animals per group no statistical evaluations were performed. Each animal was evaluated individually. The urine samples were obtained through a bladder catheter. The 24 hour urine was not collected. The sponsor indicated that the collection system on the metabolic cages does not allow a good separation of urine and feces.

A 14-week oral toxicity in dogs was reported in the original submission. The drug was tested at 0, 2, 4 and 8 mg/kg/day. Besides the pharmacologically-induced alterations in calcium and phosphorus homeostasis and bone changes the adverse effects of the drug observed were slight renal change (tubular degeneration) and the presence of oxalate crystals in urine samples at 4 mg/kg.

The five week oral study in dogs (10, 20 and 40 mg/kg/day) revealed that the drug at 10 mg/kg caused gastric erosions/gastritis and exophthalmos. The sponsor indicated in the original submission that in this dog study the free acid

form of the drug was used (in the 14 week oral study the sodium salt of the drug was used). The solubility of the salt of the drug exceeds the free acid. Therefore following oral administration of the drug it appears that gastric erosions in dogs were related to local irritation of poorly soluble of the free acid.

The submitted four week oral study at doses (15, 30, 60 mg/kg/day) higher than those used in the five week oral dog study revealed that the drug caused adverse effects on clinical signs, changes in hematological, clinical chemistry and urinalysis parameters. Furthermore the drug also caused changes in some organ weights and lesions of gastric mucosa, bladder, gallbladder, vesical mucosa, kidney, lung, thymus, liver, intestine, and lymph nodes. It appears that these adverse effects of the drug could not be explained as merely the local effect of the free acid form of the drug on G.I. tract due to low solubility.

As previously indicated that for these two dog studies no GLP statements were enclosed and the form of the drug used was different from that intended for clinical studies. Neverthness no action will be taken by Pharmacology as in the original summary Pharmacology already indicated for further chronic studies higher doses of the drug in salt form to be used in order to identify all potential toxicities of the drug.

The two teratology studies revealed that the drug is not teratogenic. However it did have some effect on the mothers and their fetuses. In these two studies the drug was given from 7th to the 17th day of pregnancy. According to FDA Guidelines the drug needs to be given from the 6th to 15th of pregnancy. for these two studies the acid form of the drug was used and no GLP statments were enclosed. Pharmacology requests the sponsor to repeat the teratology study using the salt form and according to FDA Guidelines.

Recommendation: To repeat the teratology study (using the salt form and according to FDA Guidelines).

I. Huang
I. Huang, Ph. D.

CC: Orig IND, HFD-345, HFD-510/HFD-510/AJordan, HFD-510/IHuang,
HFD-502/JWeissinger

I spoke with David Blois (6/1/89) about the teratology studies & he said that Merck is doing the study in the U.S. & that the Italian studies were submitted as full disclosure & not to support drug safety. So no need to send letter to Merck.

11 11

Jordan

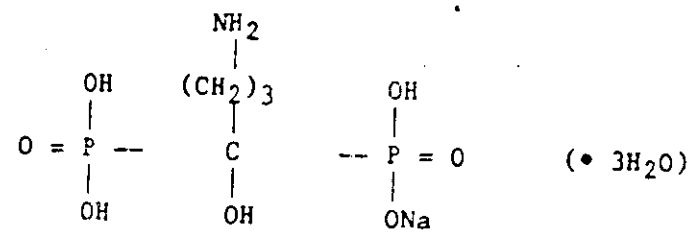
IND
Merk sharp & Dohme Research Laboratories
West Point, PE
8/30/88

10/31/86

NOV 3 1988

Review and Evaluation of Pharmacology and Toxicology Data
Original Summary

Drug: Oral aminohydroxybutane bisphosphonate (AHButBP, MK-217)



AHButBP

Formulation:

MK-217 CAPSULES

COMPOSITION	MG/CAPSULE		
	5.0 mg	25.0 mg	50.0 mg
MK-217 Sodium Trihydrate*	6.55	32.75	65.5

*Equivalent to the corresponding amount of MK-217.

Category: Treatment of Paget's disease

Proposed Clinical Investigation:

Objective: To obtain data on the safety and tolerability of the drug, especially related to G.I. tolerability and to dose range for biochemical evidence of efficacy in suitable target populations.

Clinical Protocol: 6-8 patients with Paget's disease. The drug will be given at 5, 10, 25, 50 and 75 mg p.o. once.

Preclinical Animal Studies:

Pharmacology:

I. In Vitro Pharmacology: In order to assess the potential cytotoxic effects of bisphosphonates on osteoclasts, several model systems have been

investigated. These models are discussed below in which the cytotoxic effects of AHBuBP appeared to be less than that of other bisphosphonates currently under investigation (AHPPrBP).

A. Effect of Bisphosphonates on Rat Osteoclasts in Vitro: Utilizing the formation of resorption pits in femoral slices as an assay of osteoclast activity, dose-dependent inhibition was observed with AHBuBP. The lowest concentration of AHBuBP found to be inhibitory was $10^{-7}M$. However, cytotoxic effects of AHBuBP on cultured rat osteoclasts were not detectable until $10^{-3}M$. Osteoclast cell viability was assessed by microscopic appearance and determination of cell motility.

In comparison, the lowest concentration of AHPPrBP (APD, aminohydroxypropylidene bisphosphonate) and EHDP (etidronate hydroxyethylidene bisphosphonate) which inhibited the formation of resorption pits was $10^{-6}M$, whereas cytotoxicity was evident at $10^{-4}M$ EHDP and $10^{-5}M$ AHPPrBP.

B. Effects of Bisphosphonates on Macrophage: Utilizing mouse peritoneal macrophage, bisphosphonate-induced cytotoxicity (KC_{50} =molar concentration producing 50 % killing) and migration inhibition (MIC_{50} =molar concentration producing 50 % inhibition of migration) was investigated.

BISPHOSPHONATE ³	KC_{50} (mM)	MIC_{50} (mM)
AHPPrBP	0.6 ± 0.1	0.3 ± 0.1
Cl ₂ MBP	1.5 ± 0.5	0.5 ± 0.6
EHDP	3.8 ± 0.5	1.9 ± 0.8
AHBuBP	7.3 ± 0.5	4.5 ± 0.9
AHHexBP	5.1 ± 0.4	1.0 ± 0.1

(Values are mean $\pm$ SE)

- ³ AHBuBP = Aminohydroxybutylidene bisphosphonate (MK-217)
 AHPPrBP = APD = aminohydroxypropylidene bisphosphonate
 AHHexBP = Aminohydroxyhexylidene bisphosphonate
 Cl₂MDP = Clodronate = dichloromethylenebisphosphonate
 EHDP = Etidronate = hydroxyethylidene bisphosphonate - HEBP

In another study, mouse bone marrow-derived macrophages were cultured in the presence of bisphosphonate to assess the effects of these compounds on cell viability. At a concentration of $2.5 \times 10^{-5}M$ the relative activity of these compounds to reduce cell viability appeared to be AHPPrBP > AHBuBP = Cl₂MBP.

II. Preclinical Pharmacology (in Vivo): The relative potency of bisphosphonates to inhibit bone resorption as assessed by their ability to increase tibial metaphyseal density in growing rats was studied. Each bisphosphonate was administered s.c. daily for seven days. The resulting potency sequence was AHBuBP > AHPrBP = AHHexBP > Cl₂MBP (AHBuBP:AHPrBP=5 to 10 and AHBuBP:Cl₂MBP=100, ED₅₀ for AHBuBP=0.005 mg P/kg/day. For AHBuBP, inhibition of bone formation was only observed at doses ten times higher than that producing the maximum inhibition of bone resorption.

The activity of AHBuBP to inhibit bone resorption based on widening of the tibial metaphysis and an increase in subepiphyseal trabecular bone volume were studied. A maximum effect was observed at 0.01 mg P/kg/day (s.c. 10 days) A 1000 times higher dose of EHDP (10 mg P/kg/day) was ineffective in inhibiting bone resorption and actually reduced bone volume relative to vehicle-treated animals. There was no evidence of osteomalacia in the AHBuBP-treated animals even at doses up to 1 mg P/kg/day. The dose of EHDP which was ineffective in inhibiting bone resorption in this model (10 mg P/kg/day) produced significant evidence of osteomalacia based on widening of the epiphyseal width.

B. Model of Immobilization-Induced Osteopenia: AHBuBP was also effective in preventing bone loss due to immobilization. Unilateral hind limb immobilization was produced in the rat by sciatic neurectomy. Bone loss was assessed 20 days postsurgery by ashed femoral weight. Animals were treated with AHBuBP (1-0.01 mg P/kg/day) or vehicle for two days prior to neurectomy.

AHBuBP (0.1 mg P/kg) was effective in reducing bone loss due to immobilization-induced bone resorption.

In a separate group of animals treated in the same fashion and assessed 20 days after hind limb immobilization, control animals manifested a 12 % loss on bone mass while AHBuBP-treated rats (0.1 mg P/kg/day) lost only 6.5%. Histologic analysis of the tibia from these animals revealed significant increases in subepiphyseal trabecular bone volume in all AHBuBP-treated animals. This evidence for decreased bone resorption was demonstrated in both the immobilized leg and the normal leg in comparison to vehicle-treated rats.

C. Rat Model of Secondary Hyperparathyroidism: Secondary hyperparathyroidism was induced in rats by feeding a low-calcium diet for 28 days. A study was conducted to assess the ability of varying doses and dosing regimens of AHBuBP to inhibit bone resorption in this model. Five treatment schedules of three doses of AHBuBP were studied: total doses of 2.8, 0.28, 0.028 mgP/kg were administered s.c. over the 28 days of the experiment and divided into five separate dosing regimens-daily, every other day, twice weekly, once weekly and as a single 24-hour infusion over the first day of the experiment. Ashed weights of femors were compared to assess the extent of bone loss. The vehicle-treated animals fed the low-calcium diet manifested a 44 % reduction in bone mass compared to rats fed normal diets. Essentially all dose of the drug were effective to varying degrees in increasing bone mass compared to controls although the lowest dose was partially effective only when administered daily.

D. Inhibition of Retinoid-Induced Hypercalcemia: Three days of treating thyroparathyroidectomized rats with the retinoid Ro 13-6298 raises plasma Ca due to stimulation of bone resorption. A single s.c. treatment with AHBuBP (0.1 mg P/kg) on the first day of treatment with the retinoid completely blocked this effect with one tenth the dose being 40 % as effective. For example, the change in plasma calcium concentration by day 3 in the retinoid-treated animals was +0.79 mM compared to -0.09 mM for untreated controls, -0.37 mM in the AHBuBP-treated controls and -0.43 mM in the retinoid-treated animals who also received AHBuBP on day 0 (0.01 mgP/kg) . A single 0.1 mg P/kg s.c. dose of AHBuBP was effective even if administered up to 20 days prior to retinoid treatment. The potency of AHBuBP was 100 times that of Cl_2MDP in this model.

E. Animal Models of Hypercalcemia of Malignancy: Rat carrying hypercalcemia-inducing Walker carcinosarcoma cells was treated with a single s.c. injection of AHBuBP. Doses as low as 0.01 mg P/kg prevented hypercalciuria for up to nine days and reduced, though did not totally prevent hypercalcemia. In a separate study, daily s.c. injections of this dose effectively prevented hypercalcemia for at least seven days in this model. At day 7 Ca in controls = 1.84 mM, tumor containing animals Ca =2.36 mM and tumor+AHBuBP=1.92 mM; urinary calcium (mmol/mmol Cr) controls = 0.17, tumor=0.62, tumor+AHBuBP 0.12.

A rat model of humoral hypercalcemia of malignancy by implanting rat Leydig tumor cells. Animals were treated with bisphosphonates s.c. for 3 days, 10 to 18 days post implantation of the tumor.

Doses as low as 0.1 to 1 mg P/kg/day (0.4 to 4 mg AHBuBP P/kg/day) appeared effective in preventing hypercalcemia as early as day 2 of treatment. AHBuBP at 0.1 mg P/kg normalized serum calcium concentration in this model by day 3 and at 1 mg P/kg/day Ca was normal at days 2 and 3.

III. Ancillary Pharmacology:

Administration of 1 mg/kg (i.v. bolus unless noted otherwise) to dogs produced no abnormal findings in the standard ancillary pharmacology evaluation: cardiovascular, hemodynamics (HR and BP); interactions with drugs acting on the autonomic nervous system; renal (1 mg/kg infused i.v. over 90 to 110 minutes) GFR, RPF, urine volume, electrolyte excretion; respiratory, respiratory frequency, compliance, spirometry, and G.I. 10 mg/kg via gastric fistula did not directly stimulate basal or inhibit gastrin-stimulated gastric acid secretion.

The compound was also devoid of CNS effects in mice in the pharmacometric screen at 100 mg/kg i.p.

Pharmacokinetics:

I. Physiologic Disposition and Metabolism of AHBuBP: The sponsor stated that based on results obtained with other bisphosphonates in animals or humans it is likely that 1) following initial i.v. administration a significant percentage (30-50 %) of the compound will distribute to bone and the remainder will be cleared relatively quickly from the circulation and 2) the oral bioavailability will be poor (on the order of 1 to 5 %). The available data suggest that once distributed to bone such compounds are removed from that compartment relatively slowly with residence times of several months to years depending on the turnover rates of the skeleton. The P-C-P moiety does not appear to be metabolized in man. Whether AHBuBP behaves similarly remains to be defined in appropriately designed studies.

As estimate of oral bioavailability in the rat can be derived from a comparison of the effect of oral vs i.v. AHBuBP on bone histomorphology. When AHBuBP was given orally to rats at dose levels of 0, 1.25, 2.5 and 5 mg/kg/day for 14 weeks, a dose-dependent increase in trabecular bone area was observed (15 % in controls, 40 % at 2.5 mg/kg, 70 % at 5 mg/kg). A dose of 0.05 mg/kg/day i.v. also produced a 70 % increase in trabecular bone area after five weeks. This suggests an oral bioavailability, based on this bioassay, on the order of 1%.

II. Pharmacokinetic Studies with ¹⁴C-AHBuBP in Rats: The following data assume that all radioactivity was unchanged drug. This assumption is currently being evaluated.

A. 24-Hour Plasma and Urine Kinetics and Tissue Distribution: In this initial range finding study, four rats were dosed i.v. at 1 mg/kg and plasma and urine were sampled through 24 hours. The bulk of urinary recovery was during the first 6 hours, during which plasma levels had declined through three orders of magnitude but showing the beginning of a much longer phase by 24-hours. Incremental renal clearances were quite constant for the two sampling periods, averaging 4.9 for 0-6 hours and 4.2 for 6-24 hours, which for rats is approximately equal to GFR. Since urine is the only quantitatively significant component of elimination, plasma clearance should be equal to renal clearance. Plasma clearance based upon AUC is three-fold higher at 15 ml/min/kg; i.e. AUC through this interval is only one-third AUC to infinity, demanding a very long terminal $t_{1/2}$.

Except for RBCs, all tissues examined had positive gradients for C-14 relative to plasma, those for liver and kidney being especially high at ca 60:1 and 300:1. The aggregate total, however of the contents of all non-skeletal tissues calculated from observed concentrations and standard values for their individual masses was no more than one percent of the dose. The total C-14 content of whole tibia and especially of femur were remarkably constant and total skeleton contents were 50 and 49.6 percent of dose. These are probably under-estimates, since the surface:mass ratios of these long bones are lower than for the skeleton as a whole. Indeed, estimates from material balance at 120 hours, taking into account urinary excretion, biliary excretion and the contents of all other tissues, would require that 63 % of the dose is sequestered in hard tissue.

B. Five-Day Bone Uptake, Urinary Recovery and Half-life Estimates. Following i.v. bolus of 1 mg/kg groups of 3 rats each were sacrificed daily for determination of C-14 in bone, while urine was collected daily from all surviving animals.

The purpose of this study was two fold: 1) to determine the time required for bone uptake to achieve a plateau value and thus provide a basis for absorption estimates uncomplicated by rate and 2). to determine the interval to such time as urinary excretion rate becomes monoexponential and provide a basis from which to subsequently calculate terminal half-life. On the basis of the data in hand only a preliminary estimates of the latter can be made.

Concentrations of C-14 equivalents in tibia and femur through 120 hours approach maximal levels by 24 hours. The consistently higher concentrations in tibia suggest that uptake is a function of surface:mass, further implying that estimates of whole skeleton content based upon counting of large bones are minimal.

Urinary excretion rates through five days declined dramatically, having reached an accumulative recovery of only 36 percent of dose, i.e. total body burden was still 64 percent and declining thereafter at a rate too small to allow calculation of terminal half-life by conventional means unless samplings were over very extended intervals. As an expedient a minimal estimate for half-life can be made from a knowledge of total body pool and the fraction thereof being eliminated per unit time. Assuming urine to be the sole mode of elimination and daily excretion to be 0.1 percent per day an elimination rate of 0.0016 per day can be estimated from the equation for monoexponential decay. From which $t_{1/2}$ is estimated to be 433 days.

C. Oral Absorption Estimate: Parallel groups of rats (n=3) were dosed i.v. at 0.2, 1 and 5 mg/kg and orally at 1, 5 and 25 mg/kg and femurs and tibias harvested at 24 hours. The concentration vs dose relationships are plotted. In both bones concentrations were remarkably reproducible after i.v. dosing and linear over the 25-fold range employed. After oral dosing, variability was significant. Whether based upon best-fit lines or upon the respective i.v. and oral doses providing comparable bone levels (i.e. 0.2 and 25) the estimate for oral absorption is 0.8 percent.

D. Biliary Excretion: Incremental recoveries of C-14 in each of two rats receiving 1 mg/kg i.v. of C-14 labeled drug were studied. Average accumulative recovery through six hours was 0.13 percent of dose or 1/200 of the quantity excreted in urine over the same interval. In light of this finding fecal recoveries have not been measured.

E. Metabolism: To examine whether biotransformation of drug occur, each of two 24-hour urines were worked up for HPLC by a procedure previously devised to partially isolate the parent compound for quantitative analysis. The results of the isolation procedure alone preclude the presence of any chemical species

other than very polar, very strong anions. The radiochromatogram shows a single peak with the same retention time and the same considerable tailing as the starting material, a phenomenon characteristic of polyvalent acids on ion-exchange packing. There is thus no indication of other than unchanged drug in the only quantitatively significant excretory matrix.

Toxicity Studies:

I. Acute Toxicity Studies in Mouse and Rat: A summary table was enclosed in the submission. No details were given.

	P.O.		I.V.	
	MALE	FEMALE	MALE	FEMALE
Mouse	1280 (1024 to 1726) [†]	966 (796 to 1207)	48.4 (40.8 to 59)	51.1 (45.8 to 57)
Rat	626 (419 to 779)	552 (35 to 727)	42.1 (38.5 to 46)	40.2 (34.5 to 47)

[†] Ninety-five percent C.I.

II. Acute Oral and I.V. Study in Rabbits, 87:

The doses studies have been of:

mg/kg 1000-500-250 orally

mg/kg 50-25-12.5 i.v.

For each dose and administration route eight animals (four males and four females) have been used.

Results: The dose of 250 mg/kg p.o. was perfectly tolerated. At other doses some animals died between the second and seventh day of treatment, after evident weight loss (food consumption practically absent). At the autptic examination in all the animals were noted severe alterations of the gastric mucosa with extensive hemorrhage areas and ulcerations especially in the area of the gastric fundus. The intestine was free of solid content and the colon presented hemorrhagic areas.

With the higher dose of 50 mg/kg i.v. all the animals immediately following the administration, manifested violent convulsions of short duration, followed by loss of body tone, dyspnea and death in complete muscular atonicity.

With the intermediate dose of 25 mg/kg i.v. all animals manifested vocalization during the injection, immediately followed by convulsions of short duration, loss of body tone, dyspnea, reduction of the respiratory rate. After a few minutes the animals regained body tone and returned to normal conditions. In the following days, the animals greatly reduced their food consumption and a general and variable reduction in weight is observed.

Six animals died between the third and seventh day treatment. The autoptic examination has shown serious gastric alteration. In which the gastric mucosa presents numerous punctiform hemorrhages and ulcerations especially in the gastric fundus. In a few animals it has been observed the presence of purulent secretion in the nasal cavities and in the trachea. The intestine appeared completely empty of solid material.

Two animals survived and were sacrificed on the 15th day. An evident state of malnutrition was noted in both animals, whose intestines were free of solid content but dilated with gas. The gastric mucosa presented areas with punctiform hemorrhages. The kidneys appeared light-colored but normal in shape and volume.

With the lower dose of 12.5 mg/kg i.v. the animals presented restlessness both at the end of the injection and seconds following it, but without convulsions or dyspnea. In the days following the treatment no behavioral alterations were noted and food consumption was regular. The increase in body weight, evaluated on the 15th day was reasonable (40 %). The autoptic examination has not revealed alterations of the various organs and apparatuses.

	Maximum tolerated dose	Minimum lethal dose
Orally	500 mg/kg	1000 mg/kg
Intravenously	12.5 mg/kg	25 mg/kg

III. Fourteen-Week Oral Toxicity Study in Crl:CD(SD)BR Rats , 88: Rats (15/s/group) received 0, 1.25, 2.5 and 5 mg/kg/day.

Results:

A. Physical Signs: Unremarkable

B. Mortality: There were no treatment-related deaths associated with the administration of the drug.

C. Food Consumption: A tendency towards slightly decreased food consumption was observed in the treated female rats receiving the drug. This effect was greatest in the high-dose animals (approximately 20 percent below control, drug week 7). No such change was noted in male rats treated with this agent.

D. Body Weight: A significant decrease below the control mean value (17 percent) in body weight gain was observed in female rats treated with the high dose of the drug. The magnitude of this treatment-related effect appeared to correlate with the decrease in food consumption noted for this same treatment group (10-20 percent below control).

E. Ophthalmic Examination: Unremarkable

F. Hematology: Unremarkable

G. Clinical Chemistry: Oral administration of the drug to rats produced slight to moderate dose-related decreases in mean values for serum phosphorus, total calcium and alkaline phosphatase in animals of either sex. The maximal decreases in these parameters were approximately 4 percent below the control mean for total calcium, 25 % below the control mean for phosphorus and 30 percent below the control mean for alkaline phosphatase. Such changes were anticipated based upon the known pharmacology of this class of agents and were supported in this study by bone changes observed in treated animals.

H. Urinalysis: Unremarkable

I. Organ Weights: Many organs weights of the treated female rats were decreased (kidney, liver, thymus, ovaries). These changes are considered reflections of decreased body weight of treated females and are not directly attributed to the administration of the drug but, rather, are a reflection of decreased body weight gain.

J. Gross Necropsy: Unremarkable

K. Microscopic Examination: The only treatment-related change seen was in the bones of both sexes from all treated groups and consisted of retention of the primary spongiosa characterized by elongation of the cartilaginous cores with decreased osteoid deposition and decreased resorption of cartilage. This was due to lack of remodeling and is an expected pharmacologic effect. The change was more prominent in females than in males with an average degree of prominence in females from the low, middle and high dose level groups, respectively, of slight, moderate, and marked while the corresponding average values of males were very slight and moderate.

IV. 14-Week Oral Toxicity Study in Beagle Dogs, 87-88: Dogs (4/s/group) received 0, 2, 4, and 8 mg/kg/day.

Results:

A. Mortality: There were no deaths.

B. Physical Examination: There were no treatment-related changes.

C. Body Weights, Food Consumption: Unremarkable

D. Ophthalmologic Examination, Electrocardiographic Examination: Unremarkable.

E. Hematology, Clinical Chemistry: No treatment-related hematologic changes were observed. All the treatment-related changes observed reflected the pharmacological activity of the compound. In drug weeks 4 and 8, a significant

decrease in serum calcium values was observed in treated dogs from the high-dose group. In drug week 12, these values were no longer significantly decreased. In fact a recovery (possibly a hormonal feed-back effect) was noted. Only one animal still had a serum total calcium value below the 95 % confidence limits (10.3 mg /100 ml). Therefore a treatment-related effect was still observed in this dog at drug week 12. In drug weeks 4 and 8 all the individual values, except one in drug week 8 were below the 95 % confidence limits.

During this study, some individual values below the 95 % confidence limits were also noted in the other three groups. The number of affected dogs was greater in the low and mid-dose groups than in the control group where only 3 individual values in drug week 4 were below the 95 % confidence limits. A decrease in serum calcium is an expected pharmacologic changes due to this class of compounds. Therefore although there were no statistically significant decreases in mean values from the low and mid dose groups, these individual changes were considered related to treatment.

In drug weeks 4 and 8, a significant decrease in serum phosphorus values was observed in dogs from all treatment groups. In drug week 12 a recovery in mean serum phosphorus value was noted in the high-dose group (most likely due to hormonal feedback effect). In the low and mid dose groups, the decreases in mean values were still observed (-25.0% and -20.5 % , respectively). One individual in each treatment group still had a serum phosphorus value which remained below the 95 % confidence limits. A decrease in serum phosphorus values is expected with an agent in this class. Therefore, even if there was no longer a statistically significant decrease in the mean value from the high dose group, the changes still observed in the low and mid dose groups in drug week 12 were considered treatment-related as well as the low individual value (3.2 mg/100 ml) in one male from the high dose group.

F. Urinalysis: In drug weeks 8 and 12 in the urine from the three treated groups, there was an increase in total calcium and in the ratio total calcium/creatinine when compared to the control values. However, there was no dose-dependent relationship, the increases observed in the high dose group being the lowest because of one or two low values.

In drug week 12 in the urine from the high dose group, there was a decrease in phosphorus and in the ratio phosphorus/creatinine mean values -22 % and -24 %, respectively when compared to the control mean values. One male had very low individual values (5.4 mg/16 hrs and 0.04 mg/mg respectively). However without any control historical data and pretest values and because great variations were observed in the individual values from this group, the relationship of these decreases to treatment is uncertain.

In drug weeks 8 and 12, calcium oxalate crystals were more frequently observed in the urines of dogs from the three treated groups with a dose-related relationship in drug week 12. These crystals were only sporadically observed in pretest and control urines. Consequently the changes observed in drug weeks 8 and 12 were considered treatment-related.

G. Organ Weights: Unremarkable

H. Gross Examination: Unremarkable

I. Histopathology: Very slight to slight focal renal tubular degeneration was found in three treated animals (one in 8 mg/kg and two in 4 mg/kg group).

In the three above mentioned animals plus in an additional dog of the 3 mg/kg group there was very slight to slight renal cortical mineralization. The mineral deposits were all most always positive for von Kossa staining, strongly suggesting that a large proportion of their composition was calcium.

Examination of the ribs revealed a slight to marked retention of the primary spongiosa in all treated animals. The change appeared more pronounced in the group treated with 8 mg/kg/day.

Retention of primary spongiosa was often, but not always paralleled by very slight thickening of cortical bone, hypertrophy of the physis and/or decreased number of osteoblasts. These changes were more frequent in the 8 mg/kg group. The bone changes reflect a lack of bone remodeling and are considered to be related to the pharmacologic action of the drug.

V. Five-week I.V. Study in Crl:CD(SD) BR Rats, 87: Rats (15/s/group) received 0, 0.05, 0.25 and 1 mg/kg/day.

Results:

A. Physical Signs, Mortality, Food Consumption, Body Weight, Ophthalmologic Examination: Unremarkable

B. Hematology, Clinical Chemistry: Decreases in mean serum calcium and phosphorus compared to controls occurred in all drug-treated groups in week 4. The decreases in average serum calcium values compared to controls were greater with increased dose in male and female rats. Serum phosphorus values although markedly decreased in drug-treated rats compared to controls were only slightly greater with increased dose in males and no dose-related response was seen in females in the range of doses used in this study

Slightly higher average SGPT activity values compared to controls were seen in male and female rats given 1 mg/kg/day and in males given 0.25 mg/kg/day. The difference from controls was only statistically significant at the high dosage level. Although the individual values of these animals showed considerable individual variations and since the number of animals showing higher values were more prevalent at the high dose for males and females and also at the middle dose in males, these changes may be due to treatment.

Average serum alkaline phosphatase activities compared to controls were slightly less in all female (21 to 28 percent) and male (12 to 16 percent) drug-treated groups. These differences were statistically significant in the female drug-treated groups, but not in the male drug-treated groups. Only 1

drug-treated male and female had values slightly below the historical 95 % spread of values and the relationship of this change to treatment is not known.

C. Urinalysis: Unremarkable

D. Organ Weights; Unremarkable

E. Gross and Microscopic Changes: All rats from the low, mid and high dosage groups had treatment-related, dose-dependent bone changes. Bone changes observed in all treatment groups included 1) hypertrophy of the physis (cartilaginous growth plate), 2) retention of the primary spongiosa (early bone spicules) and 3) decreased number of osteoblasts in the primary spongiosa. Hypertrophy of the physis was characterized by a thickened cartilaginous growth plate, an increased number of cartilage cells in the zone of cell maturation, and by irregular arrangement of the cartilage columns. Retention of the primary spongiosa was used to describe elongation of the cartilage cores. More specifically, the cartilage cores had less osteoid deposition and less cartilage resorption. Finally, many of the new trabeculae in the primary spongiosa had a decreased number of osteoblasts. These histomorphologic changes are consistent with a lack of bone remodeling and are expected findings with this compound. The bone changes were most severe in the 1 mg/kg/day treatment group, both sexes were affected equally.

All rats in the low, mid and high-dosage groups appeared to have an increased number of osteoclasts lining the spicules within the primary spongiosa. The pathogenesis of this finding is unknown and its relationship to treatment is indefinite.

VI. Five-Week I.V. Toxicity Study in Beagle Dogs, 87: Dogs (4/s/group) received 0, 0.1 and 1 mg/kg/day (infused over 2 hr).

Results

A. Physical Signs, Mortality, Body Weight, Food Consumption, Ophthalmic Examination: Unremarkable

B. Hematology, Clinical Chemistry: The i. v. administration of the drug at doses of 0.1 and 1 mg/kg/day resulted in decrease in serum alkaline phosphatase, calcium (total and ionized) and phosphorus level.

After 4 weeks of treatment, there was approximately a 33 % decrease in alkaline phosphatase in both male and female dogs at the low dosage level. At the higher dosage decrements of 43 % and 35 % in alkaline phosphatase were observed for males and females, respectively.

Accompanying the decreased serum alkaline phosphatase activity there was a dose-related decrease in serum total calcium. In male dogs, serum calcium levels were reduced approximately 7 % and 10 % of their pretest values by the low and high doses of the drug, respectively. Similar decrements in serum calcium were observed in female dogs (-4 % low dose and -10.6 % high dose). In addition, dose-related decreases were evident in the serum ionized calcium content with the greatest change equivalent to approximately a 5 % decrease from pretest values in both male and female dogs at 1 mg/kg/day.

Finally, a marked decrease in serum phosphorus levels was produced by both dosage levels of the drug in male and female dogs on the study. In this case there was no apparent dose-relationship at the two dosages employed since both dosages produced approximately a 40 % and 50 % decrease in serum phosphorus levels in female and male dogs, respectively

C. Urinalysis: Notable increases in urine calcium and slight increases in urine phosphorus were apparent in both male and female dogs treated with 1 mg/kg/day of the drug while lesser increases were seen at 0.1 mg/kg/day. All values were normalized to urine creatinine concentration. Since these increases in urine phosphorus and calcium paralleled the decreases in serum phosphorus and calcium which were associated with the anticipated pharmacological action of the drug, they are considered treatment-related.

In the 1 mg/kg/day group 2 out of 4 male dogs had urinary erythrocyte readings of 6-10 (400X). This change was not observed in pretest males or in the control male dogs. Furthermore, the appearance of urinary occult blood in the same 2 high dose male dogs supports the observed increases in erythrocyte values in these same 2 animals. Histopathology results relative to the kidneys of these 2 animals revealed an inflammatory response believed to be associated with treatment. This type of response could result in the observed urinalysis changes described here. Thus these changes are also thought to be treatment-related.

D. Electrocardiogram: Unremarkable.

E. Organ Weights: Unremarkable

F. Gross Changes: The costo-chondral junctions of the ribs of some dogs in both treated groups were noted to be swollen. This corresponded to the bone changes seen microscopically in these animals.

G. Microscopic Changes: Treatment-related changes were seen in the kidneys, urinary bladder, bone and bone marrow and stomach.

Very slight to moderate focal tubular degeneration was seen in 6 of 8 dogs in the 0.1 mg/kg/day group and 8 of 8 dogs in the 1 mg/kg/day group. Nearly all of these same animals had an associated very slight or slight chronic focal nephritis. These changes were characterized by the presence of scattered tubules primarily in the cortex with proteinaceous casts and occasional necrotic cells, and which had epithelium with increased basophilia, vacuolation, cytoplasmic droplets. The chronic nephritis was often associated with these degenerating tubules.

Three of the 8 dogs in the 1 mg/kg/day group and 1 of 8 dogs in the 0.1 mg/kg/day group also had very slight or slight pyelitis with this inflammatory infiltrate most likely associated with the cortical changes described above.

Very slight or slight focal hemorrhage cystitis was seen in 2 of 8 dogs in the 1 mg/kg/day group only and is most likely related to the renal changes seen in the dogs in this group.

Treatment-related bone changes (primarily in the rib, but also in the distal femur) most likely related to the pharmacologic activity of the compound were seen in all dogs in both treated groups with some differences in severity noted between these two groups. These changes consisted primarily of physis hypertrophy and retention of the primary spongiosa.

Hypertrophy or enlargement of the physis or cartilagenous growth plate was seen in all dogs in the 1 mg/kg/day group to a slight or moderate degree of severity. This change was characterized by an increase in the number and size of the chondrocytes forming the various zones of the physis. Very slight or slight hypertrophy of the physis was seen in 5 of 8 of the dogs in the 0.1 mg/kg/day group.

Although all dogs in both treated groups had retention or persistence of the zone of primary spongiosa, 5 of 8 dogs in the 1 mg/kg/day group had this change present to a marked degree of severity, while only 1 of 8 dogs in the 0.1 mg/kg/day group had this change present to this degree of severity (the change was present at a moderate degree of severity in remaining dogs in these groups).

Other changes consisted of a decreased number of osteoblasts in the primary spongiosa just below the cartilagenous growth plate and focal mineralization of the bone marrow. The former change was seen in all dogs in the 1 mg/kg/day group (slight to moderate) compared to only 4 of 8 dogs in the 0.1 mg/kg/day group (very slight or slight).

The focal mineralization of the bone marrow, primarily in the rib section was seen in all male dogs in both treatment groups. Only 1 female dog in the 1 mg/kg/day had slight mineralization in the bone marrow.

All the above bone and bone marrow changes may be due to a lack of remodeling of the rapidly growing bone and are interpreted to be related to the pharmacologic activity (inhibition of bone resorptions).

Very slight or slight diffuse gastritis was seen in 3 of 8 dogs in the 1 mg/kg/day group only. Scattered necrotic gastric glands usually deep in the fundic mucosa were seen in these animals. A mild inflammatory component was present in these animals. The cause of this change is not known.

VII. Oral Subchronic Toxicity Test in Beagle Dogs: A summary was submitted.

Oral treatment with the drug in beagle dog for five weeks at dosages of 10, 20 and 40 mg/kg (three animals for each dose) has been sufficiently tolerated. Normal food intake and normal change of body weight have been observed.

Normal hematological and urinary parameters are resulted at each observation during and at the end of treatment. Nevertheless all dogs treated with the drug (except one dog of the high dose) have shown exophthalmos beginning from the 4th weeks. In one animal conjunctivitis was observed too.

In all dogs of the high dose group hyperemia of buccal mucosa and labial ulcerations are occurred. At necropsy, focal injuries in the glandular stomach (erosion or diffuse gastritis but no ulcers) were observed in five animals (two high dose, one mid dose, two low dose).

Teratogenic Activity in Rats, 87: A summary was reported:

Doses: 0-5-10 mg/kg

20/group

Results:

Oral administration of the drug at 5-10 mg/kg doses did not prove to be teratogenic in rats. However at both doses changes in the experimental animals and progeny were observed.

Decrease in body weight of dams, dose dependent.

Slight decrease in the average number of live fetuses per rat.

Slight decrease of the average body weight of the live fetuses (significant at 10 mg/kg dose)

Slight percentage increase in embryofetal resorption

Neither somatic nor visceral and skeletal alterations were observed in live fetuses.

Mutagenesis Studies

A. Ames test: The mutagenic activity of the drug has been evaluated at doses of 0.5-5-10 mM in five strains of *Salmonella typhimurium* in presence and absence of liver homogenate of rats induced with phenobarbital and B-naphthoflavon: whether in presence or absence of the metabolic activation system, the compound did not present any mutagenic activity.

A. Mutagenic Evaluation of the Drug by Means of the 5 Loci Mutation Test in *Schizosaccharomices Pombe*: The mutagenic activity of the drug has been evaluated in the *S. pombe* yeast (forward mutation in the doses of 50-15-30- mM in absence and presence of S 9 mix). In both tests the compound has not presented any mutagenic activity.

C. Analysis of the Stimulation of Un-Scheduled DNA Synthesis on Human Cells By Means of the Drug: The compound has been analysed at different concentrations (0-10 mM) compatible with the survival of the cells in presence as well as in absence of metabolic activation.

D.: Micronucleus Test in the Bone Marrow of Swiss Mice: The results demonstrate that the drug does not induce the formation of micronuclei in bone marrow cells of Swiss mice.

Comments: The geminal bisphosphonates (previously referred to as biphosphonates) are derivatives of inorganic pyrophosphate, a naturally occurring inhibitor of both calcium phosphate crystallization and dissolution in vitro. The bisphosphonates have been demonstrated to be potent inhibitors of bone resorption both in vitro and in vivo in animals and in man. The principal cell type responsible for bone resorption is the osteoclast and bisphosphonates appear to be able to markedly impair the activity of these cells.

Bisphosphonates have been applied to the management of a broad range of skeletal disorders characterized by increased bone turnover including: hypercalcemia of malignancy, osteolytic neoplastic disease, primary and secondary hyperparathyroidism and Paget's disease of bone. An additional potential therapeutic opportunity for this class of compounds may be the prevention or reversal of bone loss in patients with osteoporosis (e.g. immobilization-induced, drug-induced, postmenopausal, and aging-related bone loss).

The bisphosphonates are targeted to bone by the high avidity of the P-C-P moiety for calcium. At this site these compounds inhibit osteoclast-mediated bone resorption by a mechanism which is not yet fully defined. While in vitro bisphosphonates may induce biochemical changes in osteoclasts, they do not appear to be grossly cytotoxic in vivo. One postulated mechanism of action is that bisphosphonates act to reduce the recruitment and/or activation of osteoclasts at sites of bone turnover.

While the bisphosphonates do not appear to be directly tumorolytic, in experimental models they have been shown to impede the invasion of bone by skeletal tumor implants. This could obviously impact on its therapeutic utility in patients with neoplastic disease.

MK-217, AHBuBP is a recent addition to the bisphosphonate class of compounds. It has been licensed by Merck & Co., Inc. from Institute Gentili (Pisa, Italy) for world wide development. Available evidence indicates that it is the most potent bisphosphonate currently in clinical investigation. In addition, preliminary evidence indicates that the aminobisphosphonates, including Mk-217 may not impair bone mineralization and thus should not be associated with osteomalacia as may be seen with a currently used bisphosphonate (etidronate disodium).

A 14 week oral toxicity study was conducted in rats (1.25, 2.5 and 5 mg/kg=1.5xMHD of 75 mg). The drug caused decreases in body weight gain and food consumption at 2.5 mg/kg/day. At dosages of 1.25 and 2.5 mg/kg/day other treatment-related changes noted were related to the pharmacologic activity of the compound and consisted of a dose-dependent decrease of serum total calcium, phosphorus and alkaline phosphatase activity. Associated with the serum biochemical changes there were treatment-related bone changes characterized by retention of the primary spongiosa with elongation of the cartilaginous cores, decreased osteoid deposition and decreased resorption of cartilage.

A 14-week oral toxicity was performed in dogs (0, 2, 4 and 8 mg/kg/day=5xMHD). Pharmacologically-induced alterations in calcium and phosphorus homeostasis were observed at all dosages. However in the 8 mg/kg/day dosage group the mean values of serum calcium and phosphorus returned to basal levels near termination of the study which was most likely due to a hormonal feedback effect. Histologic changes consistent with a lack of bone remodeling, similar to that observed in treated rats. Very slight to slight renal changes were also seen at dosages of 4 and 8 mg/kg/day but no evidence of renal toxicity was noted in animals receiving 2 mg/kg/day. Furthermore oxalate crystals were frequently observed in urines of treated dogs. No treatment-related gastric lesions were noted in in this study.

In a study completed by Institute Gentilli gastric erosions/gastritis and exophthamos were noted in Beagle dogs receiving oral dosages as low as 10 mg/kg/day (5xMHD) for five weeks. In that study dogs were administered the free acid of aminohydroxybutane bisphosphonate. In the 14 week oral dog study a salt of of aminohydroxybutane bisphosphonate was used and the solubility of the salt of the drug greatly exceeds the free acid. Therefore following oral administration of the drug it appears that gastric erosions in dogs were related to local irritation of the poorly soluble character of the free acid.

A five week i.v. study was conducted in rats at 0, 0.05, 0.25 and 1 mg/kg/day. The estimate for oral absorption of the drug in rats is 0.8 percent. 1 mg/kg/day given i.v. will be approximately equal to 125 mg/kg/day given p.o. . The only non-pharmacological related adverse effect observed in this study was increases in SGPT seen in males and females given 1 mg/kg/day and in males given 0.25 mg/kg/day (30 mg/kg/day p.o.).

Four mutagenicity studies have been conducted with the drug. The results were negative.

Conclusion: The submitted toxicity studies support the safety of the intended clinical doses.

Recommendation: To allow to proceed.

The submitted oral toxicity studies in rats and dogs were conducted at only 1-5xMHD. The additional longer-term toxicity studies should be conducted at higher doses in order to identify all potential toxicities of the drug. Also, subchronic range-finding studies should be performed to establish a maximum tolerated dose for the carcinogenicity studies. Similar range-finding studies are necessary to establish a MID in mice.

Because of the poor bioavailability of the drug, it is recommended that the protocol for the carcinogenicity studies and the rationale for dose selection be submitted for Agency review prior to initiation of these studies.

Based on the submitted data, drug bioavailability in rats seems to be fairly linear up to 5 mg/kg. Information on the degree of bioavailability with higher doses in rats, mice and dogs would be particularly useful.

When available, please submit the data on the bioavailability of the drug in humans.

Please submit full reports on the five week oral toxicity study in dogs and the teratology study in rats.

I. Huang
I. Huang, Ph. D.

CC: Orig IND, HFD-345, HFD-510, HFD-510/A. Jordan, HFD-510/IHuang,
HFD-502/JWeissinger

A. Jordan
11/3/88

NOV 11 1988

AUG 31 1995

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA # 20-560 CHEM. REVIEW #: 2 REVIEW DATE: 8-31-95

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	3-31-95	3-31-95	4-4-95
Amendment	8-21-95	8-22-95	8-22-95
	8-29-95	8-30-95	8-30-95
	8-30-95		

NAME & ADDRESS OF APPLICANT: Merck Research Laboratories
P.O. Box 4, BLA-3 Office Plaza
West Point, PA 19486-0004

DRUG PRODUCT NAME:
Proprietary: Fosamax
Non-proprietary/USAN: Alendronate sodium tablet
Code Name/Number: L-670,452; MK-217
Chem. Type/Ther. Class: 1 P

DNA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL. CATEGORY/INDICATION: 1. Treatment of osteoporosis in postmenopausal women; 2. treatment of Paget's disease of bone.

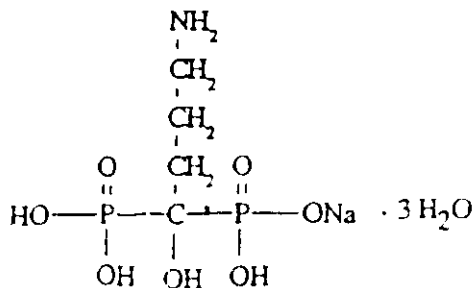
DOSAGE FORM: Tablets

STRENGTHS: 10 mg/tablet and 40 mg/tablet

ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT.:

(4-Amino-1-hydroxybutylidene)bisphosphonic acid monosodium salt trihydrate



Molecular Formula: $\text{C}_4\text{H}_{12}\text{NNaO}_7\text{P}_2 \cdot 3\text{H}_2\text{O}$
Molecular Weight: 325.12

NDA# 20-560

Merck & Co

Fosamax

SUPPORTING DOCUMENTS: IND (Fosamax, Merck, Sharp, and Dohme)

RELATED DOCUMENTS:

CONSULTS: Environmental assessment (EA) was sent for review on April 25, 1995.

REMARKS/COMMENTS:

1. The 8/21/95 amendment is in response to chemistry deficiencies communicated to the sponsor by fax on August 9, 1995.
2. The 8/29/95 amendment responded to requests after preliminary review of the 8/21/95 amendment.
3. The 8/30/95 amendment provided additional information on the dissolution specification for Fosamax tablets (10 mg and 40 mg).

CONCLUSIONS & RECOMMENDATIONS:

The sponsor's response to chemistry deficiencies is satisfactory. Moreover, the established cGMP of facilities located in is acceptable to the Office of Compliance. Because there are no more pending CMC issues, this application is approvable from chemistry viewpoint. However, the sponsor should be reminded: (1). the test methods are under validation. If any problems or questions arise, their cooperation in finalizing the procedure is required. (2). Lot number and expiration date should be included on the carton label for blister packages.

cc:

Orig. NDA #20-560

HFD-510/Division File

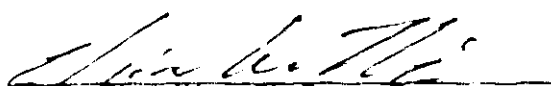
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HFD-510/CHedin

HFD-510/YYChiu

R/D init. by: *Chiu*

8/30/95



Chfen-Hua Niu, Ph.D.

Review Chemist

filename: Disc #2/NDA/NDA20560.002

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-560

FOSAMAX Tablets

(alendronate sodium)

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 new drug application for FOSAMAX Tablets, Merck Research Laboratories has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (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 treatment of diseases involving excessive bone resorption. The drug substance will be manufactured by Merck Sharp & Dohme, County Tipperary, Ireland. The drug product will be manufactured 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 the 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 promelas*), 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.

8/14/95 Nancy B. Sager
DATE PREPARED BY
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

8/15/95 Robert A. Jerussi
DATE CONCURRED
Robert A. Jerussi, Ph.D.
Associate Director for Chemistry
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Control

NDA # 20-560 CHEM. REVIEW #: 1 REVIEW DATE: 8-8-95

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	3-31-95	3-31-95	4-1-95
Amendment	5-1-95	5-3-95	5-4-95
	8-1-95	8/7/95	8/8/95
	8/3/95	8/4/95	8/8/95
	8/7/95		

NAME & ADDRESS OF APPLICANT: Merck Research Laboratories
P.O. Box 4, BLA-3 Office Plaza
West Point, PA 19486-0004

DRUG PRODUCT NAME:
Proprietary: Fosamax
Non-proprietary/USAN: Alendronate sodium tablet
Code Name/Number: L-670,452; MK-217
Chem. Type/Ther. Class: 1 P

DNA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL. CATEGORY/INDICATION: 1. Treatment of osteoporosis in postmenopausal women; 2. treatment of Paget's disease of bone.

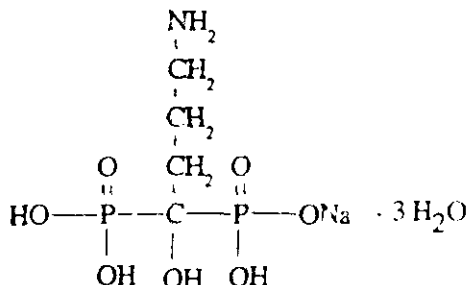
DOSAGE FORM: Tablets

STRENGTHS: 10 mg/tablet and 40 mg/tablet

ROUTE OF ADMINISTRATION: Oral
DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:

(4-Amino-1-hydroxybutylidene)bisphosphonic acid monosodium salt trihydrate



Molecular Formula: C₄H₁₂NNaO₇P₂·3H₂O
Molecular Weight: 325.12

NDA# 20-560

Merck & Co

Fosamax

SUPPORTING DOCUMENTS: IND (Fosamax, Merck, Sharp, and Dohme)

RELATED DOCUMENTS:

CONSULTS: Environmental assessment (EA) was sent for review on April 25, 1995.

REMARKS/COMMENTS:

1. Alendronate is a germinal aminobisphosphonate which is a potent specific inhibitor of osteoclast-mediated bone resorption. This germinal bisphosphonates are synthetic, structural analogs of inorganic pyrophosphate, an endogenous regulator of calcium metabolism that inhibits both calcium phosphate dissolution and crystallization in vitro. However, pyrophosphate is rapidly metabolized by a variety of phosphatases. In contrast, the P-C-P backbone of bisphosphonates is resistant to enzymatic breakdown in vivo and does not appear to be metabolized by any vertebrate species.

2. The 5/1/95 amendment provided clarification on manufacturing sites for Fosamax.

*3. The 8/1/95 amendment provided clarification on the reprocessing and rework

*4. The 8/3/95 ^{and 8/7/95} amendments provided additional information on the reprocessing.

5. The trade name, Fosamax, was reviewed and found to be acceptable by the Labeling and Nomenclature Committee (see the attached).

CONCLUSIONS & RECOMMENDATIONS:

Sufficient information on chemistry and manufacturing controls of the drug substance and the drug product has been submitted for the NDA. Therefore, the drug product is approvable from chemistry viewpoint provided that (1) the ~~one~~ ^{one} facilities ~~are~~ found to be in compliance with cGMP regulations, and (2) the deficiencies listed in the draft letter are properly answered.

cc:

Orig. NDA #20-560

HFD-510/Division File

HFD-51C/CHNiu/7/3/95

HFD-510/CHedin

HFD-510/YYChiu

R/D init. by: *CHNiu*

8/7/95

Chien-Hua Niu
Chien-Hua Niu, Ph.D.

Review Chemist

filename: Disc #2/NDA/NDA20560.001

SENSITIVE

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-560

FOSAMAX™

(Alendronate Sodium)

DIVISION OF METABOLISM AND ENDOCRINE
DRUG PRODUCTS (HFD-510)

CENTER FOR DRUG EVALUATION AND RESEARCH

DATE COMPLETED: August 14, 1995

ENVIRONMENTAL ASSESSMENT

1. **Date:**

EA dated: August 15, 1994

Consult #1
to HFD-004: April 28, 1995

Amendments: July 6, 1995*
August 1, 1995*

*Information reviewed

CSO: Randy Hedin

2. **Name of Applicant/Petitioner:**

Merck Research Laboratories
Merck and Co., Inc.

3. **Address:**

West Point, PA, 19485

RESPONSE TO DEFICIENCY LETTER DATED JULY 10, 1995, AMENDMENT DATE
AUGUST 1, 1995.

1. **General Issues:**

a. A signed statement of compliance with applicable
emission requirements should be provided from the
identified contract packaging facilities.

RESPONSE: The certifications are provided. **ADEQUATE**

b. A revised non-confidential EA should be provided.

RESPONSE: The revised non-confidential EA is provided and is
acceptable. **ADEQUATE**

2. Regarding Section 3, address: the complete street address
of the applicant should be provided.

RESPONSE: The address is provided. **ADEQUATE**

3. Regarding Section 4, description of the proposed action:

- a. The complete addresses of the drug substance manufacturing location and all facilities associated with the finished dosage form should be provided.

RESPONSE: The addresses are provided. **ADEQUATE**

- b. Concerning the disposal locations, identification, including the complete addresses, of the current off-site incineration facility and off-site landfill should be provided.

RESPONSE: The current disposal facilities for the West Point facility is provided. Additional information is also provided for the Irish facility. **ADEQUATE**

4. Regarding Section 5, the identification of the chemical substances that are subject to the proposed action: impurities found in the drug substance at quantities that are significant with respect to the environment should be identified in the EA or clearly referenced in a confidential appendix. Also, any additives used in the drug substance should be identified.

RESPONSE: There are no impurities that are at environmentally significant levels nor are there any additives. The potential impurities are included as confidential business information. **ADEQUATE**

5. Regarding Section 6, the introduction of substances into the environment: for the site(s) of production:

- a. A complete reporting of the concentrations of the drug substance expected to be released as a result of drug product manufacture should be provided.

RESPONSE: The expected environmental concentrations at the off-site POTW is estimated as 2.4 ppb for the Puerto Rico facility and 1.8 ppb in Wilson, NC. The concentration at the receiving stream in Wilson, NC is 1.7 ppb. The MEEC for the Irish facility was already reported as 32 ppb and for use the MEEC is 0.15 ppb. The worst case toxicity value has been reported for green algae at an NOEL of 500 ppb, with a minimum inhibitory concentration as > 500 ppb. There is a 100 fold or greater difference between MEEC's and the lowest toxicity value except for the Irish manufacturing facility. There is a 15 fold difference between the expected environmental concentration entering the Suir river (point of

entry) and the toxic level to green algae. Based on typical environmental process it is expected that significant dilution will occur in the river.
ADEQUATE

- b. Either the existing permit expiration dates or updated information, if the Integrated Pollution Control License has been granted, should be provided for the Irish facility. Identification of the off-site solid waste management system should be provided (including permit number and expiration date).

RESPONSE: The license is still under review with final approval expected in October or November 1995. The off-site disposal information has been provided. **ADEQUATE**

- c. Controls in place at the Wilson, North Carolina, facility to prevent air emissions should be discussed in detail.

RESPONSE: Additional information is provided indicating adequate emission controls. **ADEQUATE**

- d. Concerning the controls on releases at the Arecibo, Puerto Rico, facility, detailed descriptions of the dust collection system should be provided. Controls on particulate emissions generated by vacuuming equipment prior to water washing should be described. The solid waste incinerator used should be identified, including the permit number and expiration date.

RESPONSE: Additional information is provided indicating adequate emission controls. **ADEQUATE**

- e. Regarding West Point, PA, the off-site incineration facility and the facility receiving the ash from the on-site incinerator should be identified. All applicable permit numbers and permit expiration dates should be provided for both on-site and off-site operations. If no permit or permit expiration date is required, this should be clearly stated.

RESPONSE: The off-site incineration and landfill facilities are adequately identified. **ADEQUATE**

6. Additional information on how the octanol/water partition coefficient was determined (e.g., concentration) should be provided. Please refer to FDA or EPA test methodology for reporting requirements.

RESPONSE: The octanol/water partition coefficient was determined using HPLC. The test methodology appears acceptable.

ADEQUATE

7. Regarding Section 8, the environmental effects of released substances: the unit of measure for the concentration of drug substance in receiving waters is estimated to be 0.032 mg/. [sic] (Page F-55). The complete unit of measure should be provided.

RESPONSE: The correction has been made. It is mg/L. **ADEQUATE**

RESPONSE TO INFORMAL COMMUNICATION OF JUNE 23, 1995, AMENDMENT DATED JULY, 6, 1995 (These deficiencies were noted during the refuse to file review and were only suppose to be communicated if the application was RTF'd. The deficiencies were communicated to the company. The EA was sufficient for application filing)

1. Complete addresses: Answered as part of 2 and 3a. above. **ADEQUATE**
2. Impurities: Answered as part of 4 above. **ADEQUATE**
3. Synthesis Flow Chart: A synthesis flow diagram is provided. **ADEQUATE**
4. A citation of and statement of compliance with applicable emission requirements: A statement of compliance is provided on page 31. Additional wording has been included in section 6. **ADEQUATE**
5. The firm should do an MEEC and EEC calculation: This was answered in 5a above. **ADEQUATE**

SUMMARY

The information provided is sufficient to write a FONSI. The worst case toxicity value has been reported for green algae at a NOEL of 500 ppb, with a minimum inhibitory concentration of > 500 ppb. There is a 100 fold or greater difference between MEEC's and the lowest toxicity value except for the Irish manufacturing facility. There is a 15 fold difference between the expected environmental concentration entering the Suir river (point of entry) and the toxic level to green algae. Based on typical environmental process it is expected that significant dilution will occur in the river. As the environmental concentrations are all expected to be below effects levels, adverse environmental impacts are not expected.

ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT
FOR

FOSAMAX™

(alendronate sodium)

TABLETS

NDA 20-560

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

FOSAMAX Tablets

(alendronate sodium)

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 new drug application for **FOSAMAX Tablets**, **Merck research Laboratories** has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (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 treatment of diseases involving excessive bone resorption. The drug substance will be manufactured by Merck Sharp & Dohme, County Tipperary, Ireland. The drug product will be manufactured 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 the 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 promelas*), 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.

8/14/95 Nancy B. Sager
DATE PREPARED BY
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

8/15/95 Robert A. Jerussi
DATE CONCURRED
Robert A. Jerussi, Ph.D.
Associate Director for Chemistry
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

**NDA 20-560: FOSAMAX™ (Alendronate Sodium)
ENVIRONMENTAL ASSESSMENT
Responses to FDA July 10, 1995 Information Request**

**REDACTIONS MADE
BY APPLICANT**

Attachment #2
Non-confidential Environmental Assessment

PROACTIVE MADE
F-1

Alendronate Sodium
Chemical and Pharmaceutical Manufacturing and
Control Documentation
I. Summary
F. Environmental Assessment

1. Date

August 15, 1994

2. Name of Applicant

Merck Research Laboratories
Merck and 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 and Co., Inc. has filed a New Drug Application for Tablets FOSAMAX® (alendronate sodium MSD). Alendronate sodium is a potent inhibitor of bone resorption and is intended for the treatment of diseases involving excessive bone resorption such as osteoporosis, Paget's disease, neoplastic invasion of bone and resorptive hypercalcemia. Chemically, alendronate sodium is a bisphosphonate and is structurally related to pyrophosphate, an endogenous regulator of calcium metabolism

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REDACTIONS MADE
BY APPLICANT

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 will be 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 will also be marketed for the treatment of Paget's disease. Less than 1% of the bulk drug will be formulated as the 40 mg tablet. The total quantity to be manufactured in the 5th year of production to support the U. S. market is estimated to be less than

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 and packaged at Merck Manufacturing Division facilities at Wilson, North Carolina, and Arecibo, Puerto Rico. The drug product may also be packaged at

Returned and outdated drug-related materials will be disposed of at the Merck West Point, Pennsylvania, facility.

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REDACTIONS MADE
BY APPLICANT

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.

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CORRECTIONS MADE
BY APPLICANT

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.

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ALL INFORMATION MADE
BY APPLICANT

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.

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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°C. 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 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.

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REDACTIONS MADE
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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 north.

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.

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10/17/94

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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 July 24, 1991 (Franchise No. FP-197-91)

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REDACTIONS MADE
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from the Department of Natural Resources which allows the extraction of 100,000 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 June 30, 1994.

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.

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REDUCTIONS MADE
BY [unclear]

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. The De Diego Expressway (PR-2) is located to the north of the site. 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 regional geology (Barceloneta Quadrangle) is composed of sedimentary rocks, of Tertiary or Quaternary age. These sedimentary rocks are overlain by Quaternary deposits composed of alluvial, beach, swamps, landslide and lagoonal deposits with artificial fill.

In general, the sedimentary rocks consist of limestone, chalk and marl. At many localities, the bedrock is concealed by the surficial deposits, the result of mass movement and/or chemical weathering. Most of the unconsolidated deposits comprise gravel, sand, clay, and silt, also some peat and peaty muck and artificial fill deposits may be present at the flood plains.

The nearby site geology is underlain by sedimentary rocks. These geologic formations are known as Camuy, Aymamon and Aguada Limestones, respectively.

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REDACTIONS MADE

The outcropping geologic formation at the site comprises blanket deposits which rest on the valleys between the limestone hills over the older formations previously mentioned. In general, these deposits contain: clayey quartz sand and sandy clay, locally cemented by iron oxides. Commonly such deposits are reddish to light brown in color.

Varied karst features evolved as the different limestones weathered in the tropical climate. Collapse sinkholes and related depressions are one of the dominant karst features where the Aymamon Limestone is overlain by unconsolidated sediments termed blanket deposits. The site has sinkholes beneath it. Two "inactive" sinkholes beneath the main building; and two active ones, beneath the parking lot and the drainage pit. 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. Consumption will be on an in-patient and out-patient basis. A total of less than kg annually (5th year average) will be required for the U. S. market. The maximum expected environmental concentration (MEEC) as a result of patient use is thus anticipated to be extremely low (< mcg/L, which is equivalent to mcg/l of the free acid).

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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.

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BY APPLICANT

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 Resources (PA DER) 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 DER 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 North Wales Water Authority operates as many as three public wells within a half-mile of the plant property. 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.

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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 Wissahickon 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 Wissahickon Creek.

The location of the discharge from the UGTA is downstream from the West Point site. Pennsylvania DER 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.

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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. These are discussed further in Section 7. 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

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Ballydine, Kilsheelan, Ireland facility to supply the U S. market (less than kg annually). Estimated maximum concentrations of the alendronate sodium equivalent leaving the on-site wastewater treatment plant will be approximately mg/l. As a result of subsequent dilution, maximum receiving water concentrations of drug substance will be approximately mg/l. The reasonability of recovering drug substance by recycling aqueous liquors from the purification step back into the process has been demonstrated to retain product quality. This serves to reduce concentrations of the drug substance in the plant discharge.

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. Estimated releases are less than 0.1% of production output. 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.

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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 is estimated to be less than mcg/liter (equivalent to mcg/L of the free acid form), based on the projected fifth year average production level for the U. S. market. This assumes that 74% of the total drug administered will be discharged in domestic sewage (reflects the fraction of the U. S. population which discharge sanitary waste to Publicly Owned Treatment Works), a uniform distribution throughout the U.S. population, a per capita water usage of 150 gallons per day, and excretion of 100% of the drug activity. Lifetime exposure to this concentration would result in ingestion of less than a single mg daily dose. 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 return product. On-site incineration facilities will handle the majority of this waste with resulting releases of the constituents listed in Appendix III limited to less than 0.1% of throughput. 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.

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BY [illegible]

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 Regulations of the Ireland Department of the Environment under the Air Pollution Act, 1987. Permit number ENV/A.P/2/91, issued by the Tipperary County Council, governs the sources of atmospheric emissions from the process scrubber, dust emissions from the dry processing equipment and from other sources not directly related to this process such as the waste solvent incinerator and steam boilers.

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.

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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 permitted by the county council of Tipperary County, Ireland.

Aqueous waste streams are subject to and in compliance with Ireland's Department of the Environment, Local Government (Water Pollution) Regulations of 1978. The wastewater treatment plant operation is permitted by the county council of Tipperary County, Ireland (Permit Number ENV/W/36/80, which also governs the effluent discharge to the River Suir).

The list of substances which may be discharged in the form of aqueous emissions is detailed in Appendix III.

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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. Currently, non-hazardous waste is disposed of at a local authority landfill at Carrick-on Siur Co. Tipperary. Since it is operated by the local authority (Tipperary S.R. County Council) no environmental licenses are required.

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. Currently, hazardous waste is disposed off-site by incineration at Rechem facilities in Southampton, England and Pontypool, Wales - license AG8047 and AG7946 respectively. Both of the facilities have IPC (Integrated Pollution Control) licenses issued by the United Kingdom's HMIP (Her Majesty's Inspectorate of Pollution). There are no expiration dates on these licenses.

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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 Formulation

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.

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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 Formulation

The plant wastewater is collected for metering and sampling prior to discharge to the City of Wilson collection system for processing in the Public Works Treatment Facility. 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

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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 Formulation

All unused market packages will be sent to West Point for incineration at permitted disposal facilities. Any solid waste resulting from formulation 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

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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 collector 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.

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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 also regulated by a discharge agreement with PRASA (dated February 27, 1991). This current agreement limits the site average daily wastewater discharge to a biological oxygen demand (BOD5) of 250 mg/l, total suspended solids (TSS) of 250 mg/l, and pH of 7.5 to 8.5.

Approval of the proposed action will not impact the facility's ability to comply with the conditions of the wastewater agreement.

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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.

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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 permit #46-301-191B (expiration: August 8, 1998) and permit #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 Resources (PA DER), Chapters 121-141. Approval of the proposed

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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 pretreatment along with other sanitary waste. This wastewater is discharged for further treatment to the UGTA. The treated effluent is discharged from the UGTA under NPDES Permit Number PA 0023256. This permit is administered by PA DER.

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 (Subcategory A for fermentation products). 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 1.255 million gal/day; BOD = 250 mg/L (daily maximum); TSS = 300 mg/L; and pH between 5.5 - 9.0. These limits are subject to and in compliance with UGTA's wastewater discharge limits. Approval of the proposed action will not impact the

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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 4/6/00) 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 300437, 400459 (expiration: June 16, 2005), and 300501 (expiration: January 1, 1997) issued by PA DER and Permit PAD002387926 issued by both EPA and PA DER. 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 Resources, 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

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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 3/31/09. 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.

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d. 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.

e. Expected Maximum Annual Production

It is expected that the maximum annual production of alendronate sodium (5th year) will be on the order of kilograms per year with less than kg/yr required to support the U. S. market. As such, this represents only a small fraction of the total annual production capacity of Merck's Ballydine, Ireland; Wilson, North Carolina; and Arecibo, Puerto Rico facilities. Pollution prevention, solvent recovery and recycle will be implemented to the extent practical to minimize the release of chemicals into the environment. In addition, control equipment, as indicated in 6b above, are employed to further reduce chemical emissions. Incremental environmental effects as a result of product use and disposal are minimal.

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7. Fate of Emitted Substances to the Environment

Environmentally relevant physical-chemical and ecotoxicological properties of alendronate sodium have been evaluated by standard and widely accepted laboratory procedures. Except where noted, all studies were conducted by the Merck Research Laboratories (MRL), Rahway, New Jersey and West Point, Pennsylvania. Results and studies presented in the technical sections of the NDA document or appendices are only summarized here. Copies of the environmental fate and effect study reports are provided in Appendix V.

a. Physical-Chemical Properties

1) Aqueous Solubility

Alendronate sodium is freely soluble in water (40 g/L) at ambient temperature (~25°C). At 18 and 40°C, the solubility of the non-hydrated form of the drug substance is 33.0 and 46 g/L, respectively. The aqueous solubility of the free acid is about 8 g/L.

2) Partition Coefficient

The partition coefficient (K_p = concentration in organic phase/concentration in aqueous phase) has been determined for alendronate sodium in an octanol - water (phosphate buffer, pH 7) system. The resulting drug substance concentrations in the different

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phases were determined by HPLC analyses. The results show a K_p of 0.0025, which corresponds to a log P value of negative (-) 2.6.

The experimental procedure for determination of the octanol/water partition coefficient involved the HPLC analysis of the alendronate sodium content (analyzed as Fmoc derivative) of an aqueous phosphate buffer (pH 7) solution before and after equilibration with *n*-octanol. A precisely weighed quantity (74.937 mg) of alendronate sodium (lot no. L-670,452-005Y024) was dissolved in 25.0 mL of pH 7 aqueous phosphate buffer, which had been pre-equilibrated with *n*-octanol (Solution A). An aliquot (3.0 mL) of Solution A was diluted to 25.0 mL with pH 7 aqueous phosphate buffer (Solution B). Duplicate aliquots (2.0 mL) of each solution were mixed with 25.0 mL of *n*-octanol for about one hour. The resulting mixtures were centrifuged and the layers were separated. The following dilutions with aqueous sodium citrate solution were made: 25 times for Solution A and corresponding aqueous phases, and 10 times for Solution B and corresponding aqueous phases. Reference solutions were prepared of lot no. L-670,452-005Y024 (1.564 mg in 10.0 mL sodium citrate solution, followed by 10x and 100x dilutions). The above sample and reference solutions were derivatized with 9-fluorenylmethyl chloroformate (Fmoc) as described in the HPLC method and analyzed by HPLC.

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3) Solution pH

The pH of an aqueous solution of alendronate sodium (1 % solution) is approximately 4.4. For aqueous solutions of the corresponding bisphosphonic acid (8 mg/mL) and disodium salt (50 mg/mL), the pH values are 2.2 and 8.7 respectively.

4) Dissociation Constant (pKa)

The pKa value for alendronate sodium is 6.9, determined by the potentiometric titration of alendronate sodium in tetramethylammonium chloride solutions (I=0.5) with tetramethylammonium hydroxide and hydrochloric acid.

The pKa values for the parent bisphosphonic acid (protonated ammonium species), obtained by potentiometric titration in water with ~0.1 M potassium hydroxide, are: pKa₁ < 2 (first phosphate hydrogen); pKa₂ < 2 (second phosphonate hydrogen); pKa₃ = 6.2; pKa₄ = 9.9 (ammonium hydrogen); pKa₅ = 10.2 (amine hydrogen). Titration experiments performed by Gentili on aqueous tetramethylammonium chloride solutions (I = 0.5) of the bisphosphonic acid, using tetramethylammonium hydroxide and hydrochloric acid as titrants, resulted in pKa values of 0.81 ± 0.22 , 2.24 ± 0.03 , 6.29 ± 0.03 , 10.84 ± 0.06 , and 12.21 ± 0.11 .

5) Chirality and Specific Rotation

Alendronate sodium is achiral and, thus, is not optically active.

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6) Thermal Behavior

The thermal behavior of alendronate sodium has been investigated by differential scanning calorimetry (DSC) in an inert atmosphere. The DSC curve for alendronate sodium (Figure F-1), obtained via open cup DSC under nitrogen at a heating rate of 20°C/min, is characterized by an endotherm having a peak temperature of ~135°C, an extrapolated onset temperature of 124°C and an endothermal heat content of ~403 joules/gram. Also, a combined endotherm and exotherm was observed in the 250-280°C temperature range.

Visually, the sample remained unchanged following the 135°C endotherm indicating that the endotherm corresponds to the loss of hydrated water. In the 250-280°C temperature range there is visible evidence of sample decomposition to which the combined endotherm-exotherm observed in that region of the DSC can be attributed.

When subjected to thermogravimetric analysis (TGA) under nitrogen, a stepwise weight loss of ~16.6% occurs in approximately the same temperature region as the endotherm attributed to hydrate water loss during DSC analysis.

An additional study was conducted in both an inert and oxidizing atmosphere over the temperature range of 25-600°C. Figure F-2 shows the weight-normalized heat flow curves obtained under nitrogen and oxygen atmospheres. Both the DSC (Figure F-2a) and TG (Figure F-2b)

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response signals differ only above 300°C with an unresolved endothermic-exothermic sequence in the 250-300°C region. Essentially three major processes occur: dehydration, pyrolysis, and char formation following pyrolysis or oxidation to the tar stage.

Dehydration proceeds in two endothermic stages with a total weight loss close to theoretical (16.6%). A 1.79 and 14.66% weight loss was obtained in the temperature ranges of 30-80 and 80-150°C, respectively, under nitrogen at a heating rate of 1°C/min. From the endothermic data, the dehydration enthalpy was calculated to be 155.1 kJ/mol (37 Kcal/mol).

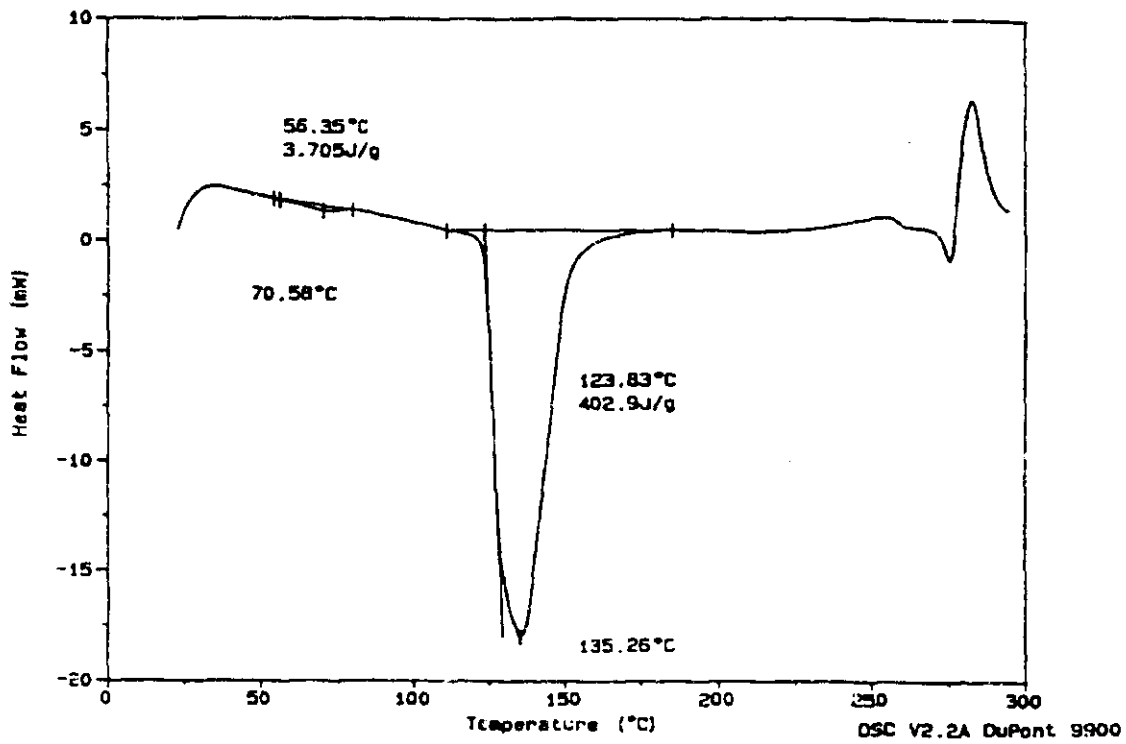
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Figure F-1 Differential Scanning Calorimetry
Curve for Alendronate Sodium
(Lot No. L-670,452-005Y032)



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Isothermal DSC tests under nitrogen in the 180-220°C region indicated small weight losses (0.6%/hour at 180°C, 0.7%/hour at 200°C and 1%/hour at 220°C). There was no visible evidence of sublimation, thus, it was concluded that the weight loss characterizes the onset of thermal degradation. Thermal degradation was confirmed by the slight darkening of the anhydrous salt at 220°C and was corroborated by subjecting a number of samples to 15-hour isothermal TG experiments under nitrogen for which, according to the weight loss curves obtained, a decrease in alendronate sodium content with increasing temperature (150-200°C) was observed.

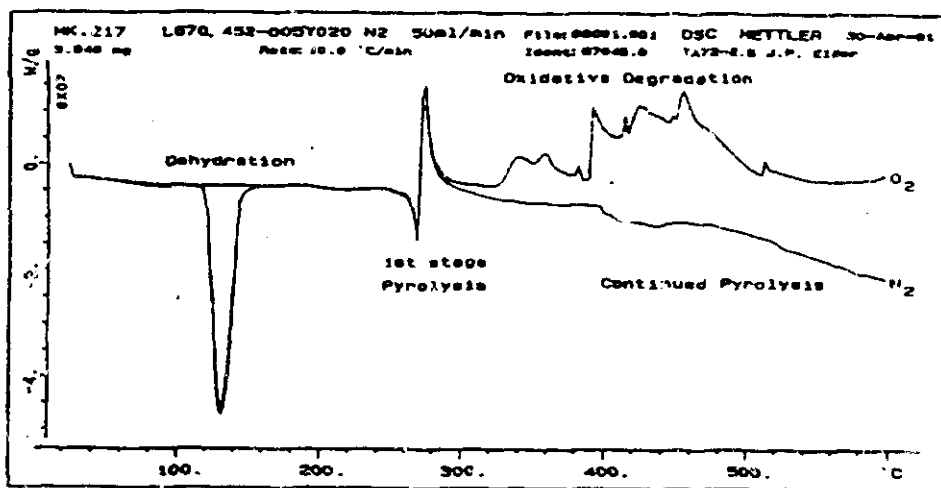
Thermal degradation commences at ~200°C, as indicated by the broad, shallow endotherm between 200-250°C (Figure F-3). At 250°C, visible evidence of this degradation is seen, the residue taking on a pale cream color. Between 260°C and the endotherm peak at ~268°C, sample temperature, $T_s = 266.8^\circ\text{C}$, the residue darkens from yellow to dark brown, while maintaining its shape. During the exothermic excursion, 271 to 277°C, the sample temperature increases from 266.8 to 275°C, the degrading salt takes on an orange-brown color, and continuously shrinks from the crucible wall. This behavior continues beyond the exothermic peak. At 280°C, the sample darkens further as pyrolysis continues

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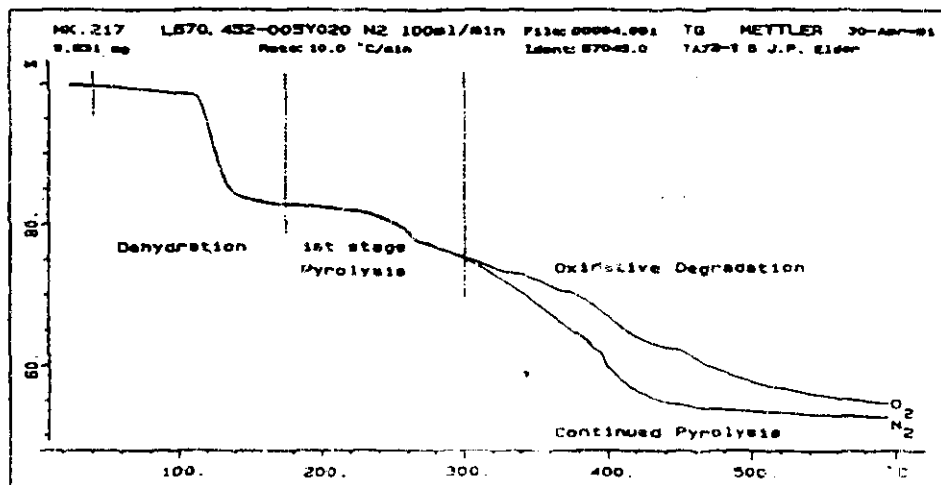
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Figure F-2 F-2a Differential Scanning Calorimeter (DSC) Response Between 25-600°C (2a, 2b)



F-2b Thermogravimetric (TG) Response Between 25-600°C



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without any further significant energetic activity. With the increase in temperature, the sample swells, then foams, finally bubbling as the gaseous pyrolysis products are released. Finally, at and above 400°C, char is produced.

In an inert atmosphere, the continuing pyrolysis through char to residual tar at 600°C proceeds endothermically. Under pure oxygen, char formation is retarded, possibly as a result of oxygen chemisorption, prior to exothermic combustion.

Total isothermal destruction of alendronate sodium can therefore be achieved at or above 400°C (752°F) in an oxidizing environment. A black, honey-combed residue was obtained at 400°C/10 minute residence, indicative of complete destruction beyond the gassing stage to the char state. A residence time of 3 minutes appears to be sufficient for destruction to occur. When analogous tests were carried out in a nitrogen atmosphere, the honey-combed residue was a light (3 minutes) to dark (10 minutes) brown, indicating incomplete char formation.

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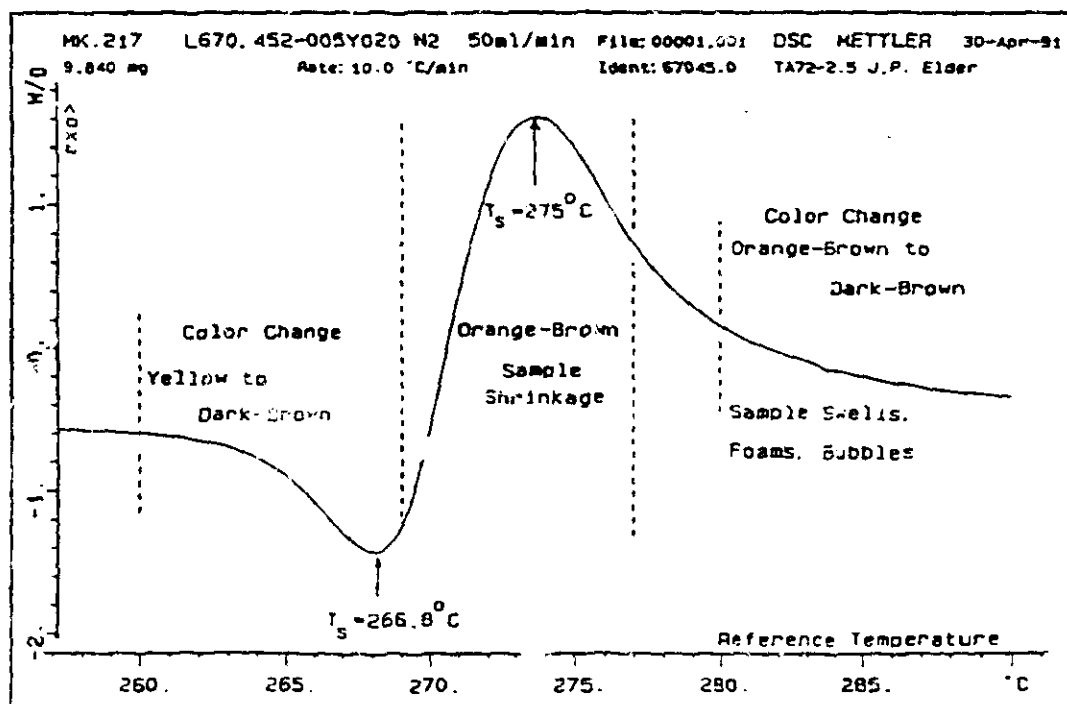
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Figure F-3

DSC Curve Showing
Thermal Degradative Behavior
of Alendronate Sodium



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7) UV-Visible Light Spectrum

Alendronate sodium, consistent with its assigned structure, exhibits no absorbance maxima in the 210-440 nm wavelength region.

b. Stability

The stability characteristics of alendronate sodium drug substance have been extensively evaluated, both for solid state material and in solution.

1) Solid State Stability

a) Ambient and Elevated Temperature and Relative Humidity Conditions

Samples of alendronate sodium were stored in double polyethylene liners inside a cardboard shipping container under ambient conditions of temperature and relative humidity (RH). Data from these studies show alendronate sodium to be stable for at least 28 months.

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b) Elevated Temperature and Relative Humidity Conditions

Stressed stability samples of alendronate sodium were stored in screw-capped glass vials protected from light at 80°C/ambient RH and in uncapped vials protected from light at 25°C and 75% RH. Data from these studies show alendronate sodium to be stable for four weeks at 25°C/75% RH and for at least eight weeks at 80°C.

2) Stability in Aqueous Solutiona) Hydrolysis

In a study conducted by Syracuse Research Corporation (Syracuse, NY), the stability of alendronate sodium in aqueous solution was evaluated at 25°C and pH 5 (0.001 M sodium acetate buffer), pH 7 (tris buffer: 50 mL Tris- [tris(hydroxymethyl)-aminomethane] and 46.6 mL 0.1M HCl) and pH 9 (0.025 M sodium tetraborate buffer) for a test period of 130 days. Using the criteria ($\geq 10\%$ hydrolysis in 28 days at 25°C) provided in the US FDA Technical Assistance Document, Section 3.09 (1987), the results from the pH 5, 7 and 9 hydrolysis testing indicate that alendronate sodium in water was not susceptible to hydrolysis.

The hydrolysis test results, however, suggest that a small amount of degradation had occurred over 130 days. (Test results were inconclusive because of variation in the HPLC assay over time). Evaluation of an

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alternate hypothesis which presumes that the data were not confounded by analytical variation and using only measured concentrations of the test article affords an estimate of the rate of hydrolysis. The hydrolysis rates and half-lives were calculated using the concentration of alendronate sodium determined at various sampling times. On this basis, the hydrolysis rates and half-lives estimated by linear regression from a plot of log concentration vs. time were 1.67×10^{-3} , 1.85×10^{-3} and 3.11×10^{-3} day⁻¹ and 413, 375 and 223 days at pH 5, 7 and 9, respectively.

b) Photochemical Stability

In a study conducted by Syracuse Research Corporation (Syracuse, NY), the photodegradation of alendronate sodium in an aqueous solution exposed to natural sunlight was studied at three different pH values for seven days.

Alendronate sodium was not susceptible to photolysis under clear sky conditions. The active drug substance was stable in pH 5 (0.001 M sodium acetate), pH 7 (tris buffer: 50 mL 0.01M Tris-[tris(hydroxymethyl)-aminomethane] and 46.6 mL 0.1M HCl) and pH 9 (0.025 M sodium tetraborate) buffered solutions for seven days. The nominal (i.e. - calculated) initial concentration and the measured final concentrations were compared. The nominally calculated initial concentration was 21.2 mg/L. The final concentrations of 20.1 mg/L $\pm$ 3.7, 19.7 mg/L $\pm$ 3.4 and 22.3 mg/L $\pm$ 2.9 were determined at pH 5, 7

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and 9. The final concentrations were similar to concentrations determined in the dark controls.

c. Biodegradability

Alendronate sodium does not appear to be readily biodegradable when exposed to an unacclimated mixed microbial population (activated sludge). Presence of an easily metabolizable cosubstrate, such as glucose, failed to induce transformation or degradation of alendronate sodium. The average recovery of the drug substance at the completion of the 28-day study was 88.6%. Virtually no hydrolysis of alendronate sodium was observed during the 28-day test which was performed using phosphate buffer. An average of 87.9% of the drug substance was recovered.

A biodegradation study was conducted by Syracuse Research Corporation, Syracuse, NY. The study was conducted to assess the susceptibility of alendronate sodium to aerobic biodegradation in water. Three attempts to develop an acclimated microbial population in the presence of alendronate sodium were unsuccessful. Microbes were isolated from a single source of soil and secondary effluent, then from a composite of four soil sources and another secondary effluent and finally from a composite of two different soil samples.

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In all three attempts, acclimated microbes metabolized glucose for growth as evidenced by the presence of turbidity within 30 hours of the inoculation. In the acclimation step, there was no evidence indicating the degradation of alendronate sodium.

d. Aquatic Toxicity

1) Toxicity to *Daphnia magna*

Results obtained from a 48-hour *Daphnia magna* static acute aquatic toxicity study with alendronate sodium, based on nominal concentrations, yielded an LC₅₀ of 21.8 mg/L with a 95% confidence interval of 18.7 to 25.5 mg/L.

2) Toxicity to *Pimephales promelas* (Fathead Minnows)

Results obtained from a 48-hour *Pimephales promelas* static acute aquatic toxicity study with alendronate sodium, based on nominal concentrations, yielded an LC₅₀ of 1450 mg/L with a confidence interval of 1247 to 1717 mg/L. The assay was conducted in soft water in an attempt to assess the toxicity of alendronate sodium in solutions with a reduced level of divalent cations (e.g. Ca⁺⁺ and Mg⁺⁺ ions), which otherwise chelate the drug substance. Analytical determinations of test substance concentrations by High Pressure Liquid Chromatography were performed at the start and end of the test. The measured concentration of the

compound was 92.8 - 99.9% of the nominal at the start and 97.6 - 113.3% at the conclusion of the test.

3) Toxicity to *Oncorhynchus mykiss* (Rainbow Trout)

The static acute toxicity of alendronate sodium to rainbow trout, *Oncorhynchus mykiss* fry, was determined in laboratory toxicity tests conducted by Syracuse Research Corporation, Syracuse, NY. The 96-hour median lethal and effective concentration (I.C₅₀ and EC₅₀) could not be calculated because of lack of mortalities and inadequate level of effects during the two 96-hour screening tests. There were no mortalities and an insignificant level of effects (≤10%) observed among test fish exposed to calculated concentrations of ≤500 mg/L alendronate sodium (average measured concentration of ≤172 mg/L) after 96 hours in a preliminary screening test conducted in standard laboratory water with a hardness of 124-140 mg/L (as CaCO₃).

A secondary assay was conducted in soft water in an attempt to assess the toxicity of alendronate sodium in solutions with a reduced level of divalent cations (e.g. Ca⁺⁺ and Mg⁺⁺ ions) which otherwise chelate the drug substance. There were no mortalities or effects observed among test fish exposed to calculated concentrations of ≤1000 mg/L alendronate sodium (average measured concentration of ≤1033 mg/L) after 96 hours in the secondary screening test conducted in standard laboratory water adjusted to a hardness of 50 mg/L (as CaCO₃).

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4) Photobacterium Phosphoreum (Microtox®)

An EC₅₀ of 385 mg/L was obtained for alendronate sodium at 30 minutes and 15°C using the standardized Microtox® indicator organism (Photobacterium phosphoreum).

5) Chronic Toxicity to Green Alga, Selenastrum capricornutum

The chronic toxicity of alendronate sodium to the green alga, Selenastrum capricornutum was conducted by Syracuse Research Corporation, Syracuse, NY. The chronic toxicity was determined in laboratory toxicity tests under the conditions of various algal media and test substance stock solution hardnesses. Test concentrations ranged from 1-1000 mg/L alendronate sodium in standard screening tests and from 0.0625 to 1.0 mg/L in a definitive test. An inhibition/lethality assessment test was also conducted to determine if effects of the test substance on cultures of S. capricornutum were inhibitory or toxic. The criterion for effect was reduction in cell growth. Algal cell counts were used to determine the no-observed-effect-level (NOEL) and the minimum-inhibitory-concentration (MIC) after one- to two-week incubation periods. Comparisons of cell concentrations and specific growth rates in each test substance treatment with the control treatment for each observation day was determined by Dunnett's (1-sided) test.

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The chronic toxicity test conducted in unmodified algal media (media hardness of ~40 mg/L) revealed a no-observed-effect-level (NOEL) and lowest-observed-effect-level (LOEL) of 0.5 and 1.0 mg/L nominal alendronate sodium after 14 days under culture. Consequently, the minimum inhibitory concentration (MIC) for S. capricornutum cultured in the presence of the test substance for 14 days under these conditions is $0.5 \leq 1.0$ mg/L.

The known chelating properties and mode-of-action of the test substance led to a supplementary set of tests in which the hardness of the algal media and test substance was increased in an attempt to minimize the effect of chelation of nutrients that were present in the algal media and which are required for algal growth. Abbreviated screening tests were conducted in algal media with CaCO₃-adjusted hardnesses of ~150 and 300 mg/L. Under these conditions, the NOELs increased to ≥ 1.0 mg/L after 8- and 10-day incubation periods, respectively. Since the design of the screening tests utilize orders of magnitude differences in test concentrations, the LOELs for both of these tests were ≤ 10 mg/L alendronate sodium. Addition of 4.62 mg CaCO₃ to 10 mg of alendronate sodium in 100 mL of algal media prior to the preparation of test solutions did not influence the results of the subsequent screening test relative to no treatment at all. The NOEL and LOEL for S. capricornutum under these conditions were both ≤ 1 mg/L after a 9-day incubation period.

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The final screening test conducted in this study attempted to determine if the effects of alendronate sodium on cultures of S. capricornutum were inhibitory or toxic. Algal cells incubated in the presence of 10 mg/L alendronate sodium for 7 days were used to inoculate fresh algal media without alendronate sodium. Whereas there was no growth observed in the culture incubated with 10 mg/L alendronate sodium for 7 days, an aliquot used as inoculum from this culture and incubated in algal media for a subsequent 7-day period exhibited growth similar to that observed in control cultures. The combined results of these tests suggest that the mechanism of action for alendronate sodium with respect to effects on algal culture growth is inhibitory rather than directly toxic. Also of interest was the presence of an algal contaminant in the 10 mg/L alendronate sodium treatment of this last assay tentatively identified as Oocystis pusilla, another green algae. This green algae is reported to have grown well in zinc contaminated systems at concentrations beyond the tolerance level of other algal and invertebrate species.

Analytical determinations of test substance concentrations by High Pressure Liquid Chromatography were performed only in the initial screening and definitive test conducted with unmodified algal media and test substance stock. These analyses revealed poor recoveries for alendronate sodium relative to nominal test concentrations at both the start and end of each test although percent recovery was positively related to the calculated test substance concentration. Mean recovery of alendronate sodium observed in the screening test ranged from 16.8-88.2%. Percent recovery values in the definitive test are probably

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irrelevant because of the proximity of the test concentrations to the analytical detection limits for the method in use.

6) Chronic Toxicity to Bluegreen Alga, *Microcystis aeruginosa*

Attempts to assess the chronic toxicity of alendronate sodium to the blue green alga, *Microcystis aeruginosa* were pursued through laboratory tests conducted by Syracuse Research Corporation, Syracuse, NY. Algal cell concentrations of *M. aeruginosa* were determined at varying intervals during the course of a test by manual counting methods.

No-observed-effect-levels (NOELs) and minimum-inhibitory-concentrations (MICs) could not be determined because of persistent contamination of test cultures by the green alga, *Selenastrum capricornutum* that appeared to interfere with growth of the test species (*M. aeruginosa*). Modification to both the experimental design set forth in the original sponsor-approved study protocol and experimenter techniques failed to prevent the introduction of algal contaminants to the test flasks. Despite these developments, the lack of growth of *M. aeruginosa* in test solutions at concentrations at which *S. capricornutum* was inhibited suggests that *M. aeruginosa* is equally or more sensitive to the inhibitory effects of alendronate sodium as *S. capricornutum*.

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e. Microbial Inhibition

A range-finding or screening test was conducted at Syracuse Research Corporation, Syracuse, NY, to define the concentration range within which alendronate sodium produces complete inhibition on six different microorganisms. The criterion for the effect was complete inhibition of growth.

1) Growth Inhibition

Microbial growth inhibition by alendronate sodium in agar plates was conducted with six pure culture microorganisms, viz., Scenedesmus quadricauda, Aspergillus niger, Azotobacter paspali, Trichoderma hamatum, Selenastrum capricornutum and Pseudomonas putida. These microbes were obtained from culture collections such as American Type Culture Collection (ATCC) and grown in the presence of alendronate sodium at various concentrations up to 1 g/L of medium. When the microbes demonstrated a sensitivity to the alendronate sodium, then the lowest concentration of test substance that inhibited the growth of the microbial cultures was determined. The minimum inhibitory concentration for alendronate sodium was ≤ 1 g/L and >0.5 g/L using Azobacter paspali as the test organism. At 1g of alendronate sodium in the agar plates, Scenedesmus quadricauda, Aspergillus niger, Trichoderma hamatum, and Pseudomonas putida were able to grow. The

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minimum inhibitory concentration for alendronate sodium was ≤ 0.5 g/L and > 0.1 g/L using Selenastrum capricornutum as the test organism.

2) Microbial (Activated Sludge) Inhibition

The maximum non-inhibitory effect concentration (MNIEC) procedure is based on the "Activated Sludge, Respiration Inhibition Test," which is described in OECD Guidelines for Testing of Chemicals, 1984, Method 209. The purpose of this test is to provide a rapid screening method whereby substances which may adversely affect aerobic microbial treatment plants can be identified and the maximum non-inhibitory effect concentration of the test substance determined. This method assesses the effect of different concentrations of the test substance on heterogeneous microorganisms by measuring the respiration (i.e. - oxygen uptake) under defined conditions. The MNIEC value is the maximum concentration of the test substance which does not inhibit oxygen uptake by the activated sludge culture. Inhibition is indicated by a decrease in the respiration rate of the microbes present in a test solution as compared to that exhibited in the controls. Using this procedure, nominal concentrations up to 4.20 mg/L of alendronate sodium did not exert an inhibitory effect.

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8. Environmental Effects of Released Substancesa. Bulk Chemical Production1) Alendronate sodium

Environmental concentrations of alendronate sodium as a result of manufacturing operations, use and disposal are estimated to be well below levels of environmental significance. See Section 7 for a summary of the environmental effects of alendronate sodium.

Appendix II (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. Production of alendronate sodium will take place at the Merck Ballydine, Kilsheelan, Ireland facility to supply the U. S. and International markets (kg annually). Estimated maximum concentrations of the drug-substance-equivalent leaving the on-site wastewater treatment plant will be approximately mg/l. As a result of the on-site wastewater treatment and subsequent dilution, maximum receiving water concentrations of drug substance will be approximately mg/l.

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Aquatic concentrations of alendronate sodium will be far below the levels which would cause environmental effects. The low environmental (aquatic) concentrations coupled with the low toxic effects at these concentrations and a propensity to complex with divalent cations indicate that the drug substance will have little impact on the aquatic environment.

Alendronate sodium is non-toxic to aquatic organisms at the expected environmental concentrations. It is neither toxic nor inhibitory to biological oxidation of other, more easily metabolized carbon sources, such as glucose, by an activated sludge system; although, alendronate sodium itself is not readily biodegradable by an unacclimated activated sludge culture. Alendronate sodium is very stable in aqueous solution. It was observed in the aquatic toxicity studies that due to its mode of action, alendronate sodium strongly chelates with divalent cations (e.g. Ca^{++} and Mg^{++}). The chelated form of the drug is less bioavailable. This is consistent with the low aquatic toxicity exhibited by the chelated compound. Given its propensity to complex with divalent cations, alendronate sodium will not cause an adverse environmental impact, especially at the expected environmental concentrations from production and use.

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Alendronate sodium is practically nontoxic to aquatic indicator organisms (fish, daphnia) and does not inhibit the activity of a marine bacteria and unacclimated mixed microbial population (activated sludge) at expected environmental concentrations. Alendronate sodium does not inhibit the growth of a number of representative microorganisms up to 0.5 or 1 g/L. Alendronate sodium is inhibitory to the green alga, Selenastrum capricornutum and blue green algae Microcystis aeruginosa. However, there are no observable effects at the expected environmental concentrations.

Little or no introduction of alendronate sodium to the terrestrial environment will occur. Thermal studies indicate alendronate sodium is not volatile at ambient temperatures and, thus, transport of the drug substance to the air compartment is not deemed to be significant.

a) Chemical Operations

Chemical manufacturing operations will be conducted in the Merck facility at Ballydine, Kiilsheelan, Ireland. The environmental impacts of the emitted substances from the production of bulk drug and dosage form have been assessed through material balance considerations, and physico-chemical and biological characterization of the emitted waste streams. Parameters considered include pH, oxygen demanding materials, nitrogenous materials, organic carbon, solids concentration, hydraulic and organic waste loading, extent of biodegradation, inhibitory effects on the

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mixed microbial population of the activated sludge system and aquatic toxicity.

Characterization of the waste streams indicate them to be biodegradable after prolonged acclimation of a mixed microbial population of activated sludge origin.

b) Tablets Alendronate Sodium

FOSAMAX[®] ingredients when taken orally will enter the environment primarily in urine which is highly diluted during normal wastewater processing and treatment. 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 is estimated to be less than mcg/L - equivalent to mcg/L free acid - (ppb) based on projected fifth year production levels for the U. S. market and do not include any environmental depletion. This assumes a uniform distribution throughout the U. S. population, a per capita water usage of 150 gallons per day, excretion of 100% of drug activity and that 74% of the drug administered will be discharged in domestic sewage. Lifetime exposure to this concentration (2 L/day, for 365 days/year over a 70 year lifetime) would result in ingestion of less than a single mg daily dose. Use of the drug is not expected to result in emissions to the atmospheric or terrestrial compartments.

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c) Animal Toxicology

(1) Acute Toxicity

The oral LD₅₀ values of alendronate in female rats and mice were 552 mg/kg (3256 mg/m²) and 966 mg/kg (2898 mg/m²) (2760 and 4830 times the recommended dose for the treatment of osteoporosis in postmenopausal women, based on a patient weighing 50 Kg), respectively. In male rats and mice, 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/m²) (1000 times the recommended dose for the treatment of osteoporosis in postmenopausal women).

(2) Chronic Toxicity

Alendronate-related changes in the repeated dose-toxicity studies of up to one year in rats and three years in dogs consisted of retention of primary spongiosa of bone in areas of endochondral bone formation, sustained reduction of alkaline phosphatase activities, and transient reduction in serum calcium and phosphate concentrations. These are related to the desired pharmacologic activity of alendronate. The species most sensitive to nephrotoxicity (dogs) required at least 10 times the recommended dose for the treatment of osteoporosis in postmenopausal women to manifest nephrotoxicity. Rats also showed evidence of this effect at higher doses.

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Gastrointestinal toxicity was seen in rodents only. This appears to be due to a direct effect on the mucosa and occurred only at doses greater than 2.5 mg/kg/day.

(3) Carcinogenicity/Mutagenesis

No evidence of carcinogenic effect was observed in a 105-week study in rats receiving oral doses up to 3.75 mg/kg/day and in a 92-week study in mice receiving oral doses up to 10 mg/kg/day.

Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation. Similarly, no evidence of mutagenicity was observed in an *in vitro* mammalian cell mutagenesis assay, an *in vitro* alkaline elution assay in rat hepatocytes, and in *in vivo* chromosomal aberration assay in mice at IV doses up to 25 mg/kg/day (75 mg/m²). 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. This is of no relevance to safety in humans since similar concentrations are not achievable *in vivo* at therapeutic doses. Furthermore, clear negative results in four of five genotoxicity studies, including the most relevant studies for human carcinogenic potential (the *in vivo* chromosomal aberration assay and the microbial mutagenesis assay), and negative carcinogenicity studies in rats and mice lead to the conclusion that there is no evidence of genotoxic or carcinogenic risks from alendronate in humans.

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(4) Reproduction/Development

Alendronate had no effect on fertility or reproductive performance (male or female) in rats at doses up to 5 mg/kg/day. The only drug-related effect seen in these studies was difficulty in parturition in rats, which is directly related to pharmacologically mediated hypocalcemia. This effect can be prevented in rats by calcium supplementation. Furthermore, a clear no-effect level of 1.25 mg/kg/day was established. As humans do not typically become hypocalcemic during pregnancy and since alendronate use is not indicated in pregnant women, this effect is not relevant to safety in humans.

In developmental toxicity studies, there were no adverse effects at doses up to 25 mg/kg/day in rats and 35 mg/kg/day in rabbits.

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d) Pharmacokinetics

(1) Absorption

Relative to an intravenous (IV) reference dose, the oral bioavailability of alendronate was 0.7% for doses ranging from 5 to 40 mg when administered after an overnight fast and two hours before a standardized breakfast. Bioavailability was decreased similarly (by approximately 40%) whether alendronate was administered one or one-half hour before a standardized breakfast. However, in the two large controlled studies that demonstrated efficacy, FOSAMAX[®] 10 mg/day was administered one hour before the first food or beverage of the day. Therefore, bioavailability and therapeutic response should be similar to that seen in the studies if FOSAMAX[®] is taken as directed.

Animal studies have demonstrated that FOSAMAX[®] is highly concentrated in bone and only minimally in soft tissue. No metabolites have been detected. Although alendronate is bound approximately 78% to plasma protein in humans, its plasma concentration is so low after oral dosing that only a small fraction of plasma-binding sites is occupied.

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(2) Distribution

Preclinical studies show that alendronate transiently distributes to soft tissues following 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 for analytical detection (less than 5 ng/mL). Protein binding in human plasma is approximately 78%.

(3) Metabolism

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

(4) Elimination

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 100 mL/min. The terminal half-life in humans is estimated to exceed 10 years.

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(5) Characteristics in Patients

Preclinical studies show that the drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after chronic dosing with cumulative IV doses up to 35 mg/kg in animals. 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

9. Use of Resources and Energy

The raw materials utilized to manufacture the drug substance and dosage form are common chemicals all of which are in ample commercial supply. Energy input for dosage form production is nominal and not excessive. Only very small increases in the utilization of energy is anticipated since production occurs at existing facilities. For U. S. facilities, no effects upon endangered species and upon property listed in or eligible for listing in the National Register of Historic Places are anticipated.

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10. Mitigation Measures

No potential adverse environmental impacts are foreseen from the production and use of the drug substance and product. The manufacture, distribution and use of the product takes place under highly regulated and controlled conditions which act to further mitigate against negative environmental consequences.

A variety of pollution prevention initiatives were evaluated during development of the current bulk drug manufacturing process and, where appropriate, incorporated into the process. A continuous reactor design was chosen due to superior safety and environmental control features of the process. Continuous mode of operation minimizes active reactor volume, offers better control of operating conditions and increases productivity. Additionally, the cumulative effect of many small process improvements resulted in yield improvement which implies less raw material usage per unit of product and less waste generated. In addition, a number of process changes were introduced during the course of the laboratory and pilot plant development; many of which further improved the environmental profile of the current process.

The single complex waste stream, containing methanesulfonic acid (MSA), sodium phosphite (Na_2PO_3) and dimethyldisulfide (DMDS), posed a number of significant environmental challenges for which solutions were conceived, developed and demonstrated. DMDS is

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effectively treated by adsorption on granular activated carbon and/or oxidation with sodium hypochlorite. Activated sludge treatment plant operational constraints for the effective treatment of MSA and Na_2PO_3 were determined.

Methane Sulfonic Acid (MSA), the major carbonaceous chemical present in the waste stream, has been shown to be biodegradable by an acclimated activated sludge (Forman et al., 1994). Concentrations of MSA up to 1000 mg/L were found to undergo ~100% biodegradation by the acclimated activated sludge alone, as well as in the presence of additional carbon sources. MSA was found to be inhibitory and toxic (alone, as well as in the presence of other carbon sources) to activated sludge at a concentration of 2000 mg/L. However, the activated sludge could be revived by restarting the reactor without MSA and reintroduction following a few days of good growth. Also, the rate of reacclimation was found to be faster than the initial acclimation. A minimum hydraulic residence time (HRT) of 50 hours is required for degradation of MSA. The Ballydine wastewater treatment plant (WWTP) which operates at a HRT of ~60 hours is capable of degrading the waste from the alendronate process. The MSA level in the influent will be maintained <1000 mg/L.

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The major inorganic constituent, phosphorous, present in the waste may be removed prior to sewerage to the WWTP (Magliette et al., 1994a). A simple laboratory procedure for PO_x (PO_4+PO_3) precipitation using calcium chloride and lime followed by neutralization prior to filtration has been developed and may be used at the Ballydine plant when warranted by production level. The procedure produces a filter cake which is virtually free of MSA and a filtrate which is devoid of alendronate. The calcium filter cake containing the phosphorous and the drug substance would be disposed off-site in accordance with existing regulations.

In addition, a batch as well as continuous process for the recovery of MSA and Na_2PO_3 have been conceived and design parameters established (Magliette et al., 1994b). The recovery process will also be considered for implementation when the production levels warrant.

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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.

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.

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M.S. - Biochemical Engineering, 1980

Indian Institute of Technology, New Delhi, India

M.Phil/Ph.D. - Chemical and Biochemical Engineering,
1982/1984

M.S. - Microbiology, 1988

Rutgers University, New Brunswick, NJ

Research Fellow, Developmental Technology

Merck Research Laboratories

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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.

Philip T. Woodrow

Philip T. Woodrow, D. Eng.

Executive Director, Chemical Engineering
R&D Operations

Merck Research Laboratories

9/15/94

Date

Lawrence J. Maldi

Lawrence J. Maldi

Executive Director, Environmental Affairs
Merck & Co., Inc.

9/12/94

Date

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14. Literature Cited

Forman, A. L., E. S. Venkataramani, P. F. McKenzie, R. J. Magliette, G. B. Quick, D. McKinney, W. Vaughn and R. Boyle, 1994, "Environmentally Proactive Pharmaceutical Process Development," AIChE Summer National Meeting, Denver, Colorado.

R. J. Magliette, D. McKinney, E. S. Venkataramani and A. L. Forman, 1994a, "Process for Removing Waste POx, Alendronate and Byproducts," U. S. Patent Applied For, Case #19223.

R. J. Magliette, E. S. Venkataramani, A. L. Forman and W. Vaughn, 1994b, "Process for Recovery and Recycle of Methanesulfonic Acid and Phosphorous Acid," U. S. Patent Applied For, Case #19224.

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APPENDICES

APPENDIX I - DRUG SUBSTANCE INFORMATION SUMMARY

APPENDIX II - ENVIRONMENTAL DESCRIPTIONS FOR MANUFACTURERS
OTHER THAN MERCK & CO., INC.

APPENDIX III - CHEMICALS SUBJECT TO PROPOSED ACTION

APPENDIX IV - MATERIAL SAFETY DATA SHEET FOR DRUG SUBSTANCE

APPENDIX V - ENVIRONMENTAL STUDY REPORTS

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APPENDIX I

A. Drug Substance Information Summary1. 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

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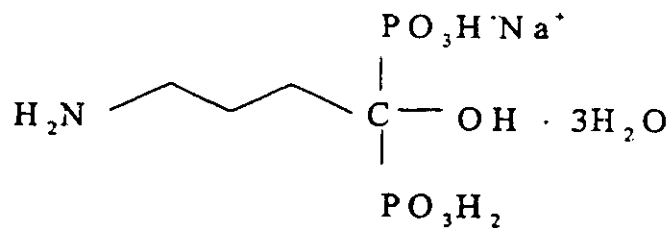
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APPENDIX I (CON'T)

2. Description

Structural Formula



Molecular Formula



Molecular Weight

325.1

3. Environmental Fate

a. Solubility, aqueous

40 mg/mL @25°C

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APPENDIX I (CONT)

b. Dissociation Constant

$$pK_a = 6.9$$

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.

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REPRODUCTION PROHIBITED
 BY THE U.S. GOVERNMENT

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)	t _{1/2} ~413 days
pH 7 (tris buffer)	<10% (28 days)	t _{1/2} ~375 days
pH 9 (borate buffer)	<10% (28 days)	t _{1/2} ~223

h. Photolysis

Alendronate sodium is not susceptible to photolysis under clear sky conditions.

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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

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NOVOC SEARF AND DOMS (IE) LTD., BALLINAH, KILSHANN,
 CLONMEL, COUNTY TIPPERARY, IRELAND

***** MATERIAL SAFETY DATA SHEET *****

LABEL NAME: SODIUM ALENDRONATE PURE SBT PLANT MINS CODE
 Emergency Telephone Number: 951-640411 BA-028

SECTION 1 - MATERIAL IDENTIFICATION

Chemical Name----- (4-Amino-1-hydroxybutylidene)
 bisphosphonic acid, monosodium salt,
 trihydrate

Synonyms (Common)----- MG-217, Alendronate
 (Chemical)----- None

Material Statistical Number----- 2-80987, 2-80988, 2-80989, 2-80990

Material Product Number----- SP2239

Chemical Classification----- Pharmaceutical active

Intended Use----- Bone resorption inhibitor

SECTION 2 - PRINCIPAL HAZARDOUS COMPONENT(S)

Component	Molecular Formula	Molecular Weight	CAS Number	Percent (%)
Sodium Alendronate	C ₁₈ H ₁₈ N ₂ O ₁₀ P ₂	325.13	121268-17-5	100

SECTION 3 - PHYSICAL PROPERTY DATA

Appearance----- Clean, white free-flowing crystalline powder.

Odor/Threshold Level (ppm)----- Not available

Boiling Point (°C/°F)----- Not applicable

Freezing Point (°C/°F)----- Not applicable

Melting Range (°C/°F)----- Decomposes 250-280°C/482-536°F

pH ----- 4.3

Solubility in water----- Hydrate: 2.68 (w/w) @ 10°C

Specific Gravity (Water = 1)----- Not applicable

REPRODUCTION
 BY APPLICANT

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MERCK SHARP AND DOHME (IPL) LTD.; BALLINIDGE, KILSHEPPAN,
CLONMEL, COUNTY TIPPERARY, IRELAND

***** MATERIAL SAFETY DATA SHEET *****

LABEL NAME: SODIUM ALENDRONATE PURE DRY

PLANT MSDS CODE
BA-026

Emergency Telephone Number: 031-640411

Hazardous Polymerizations----- None known

SECTION 6 - EMERGENCY AND FIRST AID PROCEDURES

Eye Contact----- Immediately flush eyes with plenty of
water for 15 minutes. Seek medical
attention immediately.

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
reaction 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

SECTION 7 - HEALTH HAZARD DATA

Component	OSHA Permissible Exposure Limit (PEL)	ACGIH-1992-93 Threshold Limit Value (TLV)	Merck Exposure Control Limit (ECL)
Sodium Alendronate	Not established	Not established	0.1 mg/m ³ *

Carcinogen Designation----- Not listed as a carcinogen by IARC, NTP or
OSHA.

*At a no-effect-level of 1 mg/day (established during human clinical trials),
effects on bone density are considered clinically irrelevant. Given the fact
that absorption is significantly less than 100%, no additional safety factors
are necessary.

*** Continued on next page ***

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MERCK SHARP AND DOHME (IRL) LTD., BALLINIER, KILSEKELAN,
 CLONSILLA, COUNTY TIPPERRARY, IRELAND

***** MATERIAL SAFETY DATA SHEET *****

LABEL NAME: SODIUM ALENDRONATE POWD DRY

PLANT MSDS CODE
BA-028

Emergency Telephone Number: 051-646411

Effects of Acute Exposure

Eye Contact----- Severely irritating to the eyes.
 Skin Contact----- Severely irritating. Reaction may be
 delayed several days.
 Inhalation----- Manufacturing experience indicates it may
 cause irritation.
 Ingestion----- Moderately toxic by the oral route.
 Compound causes gastric and renal toxicity
 which is related to this class of
 compounds. When administered by the
 intravenous route compound will cause a
 reduction in serum calcium and phosphorus.

Effects of Chronic Exposure

Based upon mutagenicity and genotoxicity
 assays, there is no risk of genotoxicity
 in man at therapeutic doses.

No fetal changes were noted independent of
 maternal toxicity (but the pharmacologic
 activity of MK-217 inhibits Ca⁺⁺
 mobilization from bone necessary for
 normal fetal development in late
 gestation).

Slight focal renal tubular degeneration
 (NOEL = 0.05 mg/kg/dy), abnormal
 endochondral bone maturation (LOEL = 0.01
 mg/kg-dy) and focal gastritis (NOEL = 0.1
 mg/kg-dy) were noted in animal studies.

Quantitative Toxicity Data

TEST	SPECIES	ROUTE	RESULT
LD50	Mouse (F)	Oral	978 mg/kg
LD50	Rat (F)	Oral	552 mg/kg
LD50	Rabbit	Dermal	Extremely irritating
Eye	Rabbit	Direct	Extremely irritating

*** Continued on next page ***

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REDACTIONS MADE
BY [unclear]

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MERCK SHARP AND DOHME (IREL) LTD.; BALLYSHEAR, KILSHEERLAW,
CLOSHEL, COUNTY TIPPERRARY, IRELAND

***** MATERIAL SAFETY DATA SHEET *****

LABEL NAME: SODIUM ALENDRONATE POWD ERX

PLANT NEEDS CODE
NA-028

Emergency Telephone Number: 051-640411

SECTION 8 - SPILL/LEAK/DISPOSAL PROCEDURES

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 9). Follow
all fire prevention procedures (Section
4).

For additional assistance, CHEMTREC provides a toll-free Hotline for
chemical emergencies regarding spills,
leaks, exposure or accidents:
1-800-424-9300.

Environmental Data----- 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)

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
federal, state and local regulations.

SECTION 9 - SPECIAL PROTECTION INFORMATION

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 engineered
controls to control employee exposure
below the exposure limit.

*** Continued on next page ***

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REDUCTIONS MUST
BE APPLIED

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WELCK SHARP AND DOWNS (IREL) LTD.; BALLYDINE, KILBENELAN,
CLOMEL, COUNTY TIPPERARY, IRELAND

***** MATERIAL SAFETY DATA SHEET *****

LABEL NAME: SODIUM ALENDRONATE FOUR DUST

PLANT MSDS CODE
BA-028

Emergency Telephone Number: 051-640411

Hands/Arms----- DEPRIV CONTACT MUST BE AVOIDED. 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----- Full-face protection required if potential exists for direct exposure to dusts or splashes.

Additional Protective Equipment----- Wear suitable disposable suit.

Ventilation----- Use local exhaust ventilation.

SECTION 10 - SPECIAL PRECAUTIONS

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

SECTION 11 - BASIC TRANSPORTATION DESCRIPTION

U.S. DOT----- Not available

ICAO/IATA----- Not available

IMO----- Not available

Hazardous Substance Reportable Quantity (RQ)--- Not available

SECTION 12 - INTER-PLANT COMMUNICATION

List all other MSD plants requiring a copy of this MSDS: None

*** Continued on next page ***

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MERCK SHARP AND DOHME (IRL) LTD.: BALLYDINE, KILSEKILIAN,
CLOMEL, COUNTY TIPPERARY, IRELAND

***** MATERIAL SAFETY DATA SHEET *****

LABEL NAME: SCOTUM ALENDRONATE PURE DRY

PLANT MSDS CODE
BA-029

Emergency Telephone Number: 051-640417

SECTION 13 - MSDS PREPARATION - Revision February 1992, E. Sargent
Revision April 1992, D. Mahoeck

- E. DePaer
Safety-----Date: October 14, 1992
- D. Barry-Walsh
Technical Operations-----Date: November 26, 1992
- L. Kingley
Central Environmental Resources-----Date: October 6, 1992
- R. Cutre
Technical Operations Administration-----Date: October 1, 1992
- E. Sargent, Ph.D.
Central Safety & Industrial Hygiene-----Date: December 7, 1992

SECTION 14 - MERCK DISCLAIMER

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.

MK0217EA NDA

SEPTEMBER 84

NDA 20-560

Fosamax (alendronate) 10 and 40 mg Tablets

Merck Research Laboratories

This section is not applicable at this time.

MICROBIOLOGY

NDA 20-560
Fosamax (alendronate) 10 and 40 mg Tablets
Merck Research Laboratories

This section is not applicable at this time.

FRC

END



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J.H.M. RESEARCH & DEVELOPMENT, INC. 5776 SECOND STREET, N.E. WASH. DC 20011

20-560 EA MISSING PAGES

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APPENDIX I (CON'T)

b. Microbial Inhibition

<i>Azotobacter paspali</i>	MIC > 500 ≤ 1000 mg/L
<i>Scenedesmus quadricauda</i>	MIC > 1000 mg/L
<i>Trichodeme hamatum</i>	MIC > 1000 mg/L
<i>Aspergillus niger</i>	MIC > 1000 mg/L
<i>Pseudomonas putida</i>	MIC > 1000 mg/L
<i>Selanastrum capricornutum</i>	MIC > 100 ≤ 500 mg/L

Photobacterium phosphoreum (Microtox®)

EC₅₀ (30 min, 15°C) = 385 mg/L

c. Maximum Non-Inhibitory Effect Concentration (Activated Sludge)

= 4320 mg/l.

d. Algal Toxicity (14 day)

	NOEL	MIC
	Hardness (mg/L)	(mg/L)
<i>S. capricornutum</i>	~40 mg/L ¹	0.5 >0.5 ≤ 1.0
<i>S. capricornutum</i>	150-300 mg/L ²	≥ 1.0 ≥ 1.0 ≤ 10

¹Unmodified algal media

²Hardness adjusted with CaCO₃

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APPENDIX IV

MATERIAL SAFETY DATA SHEET

ALENDRONATE SODIUM

1K0217EA.NDA

SEPTEMBER 04

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MERCK SHARP AND DOHME (IRL) LTD.; BALLINACREE, KILSHERRILLAN,
 CLOMEL, COUNTY TIPPERARY, IRELAND

***** MATERIAL SAFETY DATA SHEET *****

LABEL NAME: SODIUM ALENDRONATE PURE DRX PLANT MFGS CODE
 Emergency Telephone Number: 051-640411 BA-028

SECTION 1 - MATERIAL IDENTIFICATION

Chemical Name----- (4-Amino-1-hydroxybutylidene)
 bisphosphonic acid, monosodium salt,
 trihydrate
 Synonyms (Common)----- MK-217, Alendronate
 (Chemical)----- None
 Material Statistical Number---- 2-80987, 2-80988, 2-80989, 2-80990
 Material Product Number----- J82239
 Chemical Classification----- Pharmaceutical active
 Intended Use----- Bone resorption inhibitor

SECTION 2 - PRINCIPAL HAZARDOUS COMPONENT(S)

Component	Molecular Formula	Molecular weight	CAS Number	Percent (%)
Sodium Alendronate	C ₈ H ₁₀ NO ₆ NaO ₁₀ P ₂	325.13	12166-17-5	100

SECTION 3 - PHYSICAL PROPERTY DATA

Appearance----- Clean, white free-flowing crystalline
 powder.
 Odor/Threshold Level (ppm)----- Not available
 Boiling Point (°C/°F)----- Not applicable
 Freezing Point (°C/°F)----- Not applicable
 Melting Range (°C/°F)----- Decomposes 230-280°C/462-536°F
 pH ----- 4.3
 Solubility in water----- Moderate: 2.4% (w/w) @ 10°C
 Specific Gravity (Water = 1)--- Not applicable
 Vapor Density (Air=1)----- Not applicable
 Vapor Pressure (mm Hg @ °C/°F)- Not applicable

*** Continued on next page ***

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MERCK SHARP AND DOHME (Ireland) LTD.; BALLYDINE, KILSHEKLAN,
CLOONEL, COUNTY TIPPERARY, IRELAND

***** HAZARDOUS SAFETY DATA SHEET *****

LABEL NAME: SODIUM ALENDRONATE POWDER DRY

PLANT MSDS CODE
BA-028

Emergency Telephone Number: 051-648411

Volatile Components (% w/w)---- 04

SECTION 4 - FIRE AND EXPLOSION HAZARD DATA

Flash Point (°C/°F)----- Not applicable

Flash Point Test Method----- Not applicable

Autoignition Temperature (°C/°F)- Not available

Flammable Limits -LEL (%)----- Not applicable

-UEL (%)----- Not applicable

Combustibility Information----- The match flame test created no reaction.
The burner flame produced a light
grey 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 available

Extinguishing Media----- Water, CO₂, dry chemicalSpecial Fire Fighting Procedures-- Firefighters should wear SCBAs and
protective clothing.

Fire/Explosion Hazards----- Not available

Hazardous Decomposition Products Resulting From A Fire-- CO, CO₂, and
oxides of nitrogen and phosphorous may be
released in a fire.

SECTION 5 - REACTIVITY DATA

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.

*** Continued on next page ***