CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020560/S013

MEDICAL REVIEW(S)

NDA 20560-13
Alendronate (Fosamax)
Merck
Review Completed 4/28/99

Team Leader's Comments on Approvable Supplement to Approved Drug.

This drug is approved for treatment of Paget's Disease of bone, for treatment of postmenopausal osteoporosis, and for reduction of fractures in an osteoporotic population of postmenopausal women. It has been marketed for 3 years, and is estimated to be used in more than 2 million women. In the large population to which it is marketed, many episodes of upper GI disease are attributed to drug and reported to the sponsor and to FDA. However, in controlled studies conducted by Merck, the selected population does not exhibit an excess of these adverse events over events in placebo-treated patients.

This supplement contains the report of the 4th and 5th year of the studies conducted for the initial approval of alendronate for postmenopausal osteoporosis. The initial studies were double-blind and placebo-controlled. The placebo patients were switched to 10 mg Alendronate daily at the end of 3 years. During the first period (years 1-3) the 4 arms of the studies were dosed daily with placebo, 5 mg, 10 mg, or 20 mg (followed by 5 mg in year 3). This latter group and the 5 mg group continued through years 4 and 5 on 5 mg; the placebo group and the original 10 mg group continued on 10 mg alendronate daily.

Efficacy was based on BMD of the lumbar spine. Biochemical markers, calcium and phosphate were measured as secondary endpoints. Stature was also measured. Patients who had gastrointestinal disease within the past year, or used drugs to inhibit gastric acid secretion >2 weeks in the past 3 months were excluded. 727 subjects entered the extension. The ITT population evaluable for BMD of the lumbar spine at 60 months in protocols 035 and 037 was 131 and 138 in the placebo groups, 58-77 in treated groups, a total of 677 when the two studies are combined.

Recommendation Approvable with changes to proposed package insert. AP

The primary efficacy, mean change in BMD of the lumbar spine (035/037), month 36 to month 60: 6.4(placebo/10 mg), 1.0(5 mg), 0.9(10 mg), 0.3(20/5 mg); month 0 to month 60: 6.0 (placebo/10mg), 6.4(5 mg), 9.4(10 mg), 9.1 (20/5 mg). Changes from month 0 to month 60 were significant, but those from month 36 to month 60 were usually not (one in 5 mg and one in 10 mg group were significant) when the studies were examined separately, but were significant when pooled. The need to continue therapy during the last two years was not tested, and there was no placebo group, so it is not clear whether treatment during the last two years is beneficial. Perhaps it would be adequate to switch to vitamin D and calcium supplements to maintain gains from first year. It would have been useful to do a randomized withdrawal of the Alendronate at 36 months.

Biochemical markers continued to show reduction of bone turnover when drug was continued. Calcium and phosphate were not unduly altered.

Two other substudies were done. In one, BMD determination of the distal humerus showed a rise in BMD that seemed to plateau at about 24 months and to go back to baseline by 60 months. Actually, with 5 mg, the BMD went below baseline, but remained about parallel to the placebo decline. The adjusted mean percent change from baseline was –1.61 at 60 months. This site is important because it has a high content of cortical bone. It has been shown that with some treatments, improvement in BMD of the spine may be seen at the same time that BMD in the hip decreases. As important as they are, it is not usual to get data on peripheral fractures.

Another interesting efficacy measure is stature, an easily measured clinical endpoint that is one of the important outcomes for women with osteoporosis. All groups, drug-treated and placebo-treated, lost height at close to the same rate, and with no plateau effect. Although the decline in placebo patients was greater up to 36 months, after that time, the significance of the difference was lost for the 5 mg group. Only in a subgroup with incident spinal fractures was the mean difference more than a few millimeters. It is intriguing that the apparent benefit for stature is in a subgroup that seems to benefit less for fractures.

The studies were not designed to detect differences in fracture rate, but fracture incidence of the spine and non-vertebral rate were examined. Number of fractures, both vertebral and non-vertebral favored drug. Incident vertebral fractures were seen in 13=4.5% of patients treated with placebo/10 mg,

6=4.1% of 5 mg,

5=3.3% of 10 mg, and

9=6.3% of 20/ 5 mg,

Conclusions:

1. The mean percent change from baseline (month 0) in BMD of the lumbar spine is similar at 60 months to that at 36 months (5 and 10 mg subjects).

This is indicative of maintenance of gains, but no, or very little, gain in BMD during months 36 to 60.

2. Efficacy in preventing fractures cannot be determined from this study, but has been studied separately in a population of women with spinal fractures and found to reduce the incidence of spinal fractures by a very small amount.
3. Efficacy was lacking when stature was the parameter that was measured, and was reversed during the 4th and 5th years when BMD of the distal humerus was evaluated.
4. Efficacy was not shown by measurement of stature, which decreased similarly in treated and in placebo patients.
5. Safety was similar to that seen during the first 3 years, with upper gastro-intestinal events having the most serious and frequent reports in spite of selection of patients with no history of upper gastro-intestinal disease.
6. The package insert should be modified as suggested by Dr. Schneider.
7. The proposed change in the package insert for alendronate may be approved.

/S/ [redacted]

Gloria Troendle

Cc: NDA 20560
HFD-510 Division File
HFD-510 GTroendle, BSchneider, RHedin

[redacted]
APPEARS THIS WAY ON ORIGINAL

MEDICAL OFFICER'S REVIEW

March 22, 1999

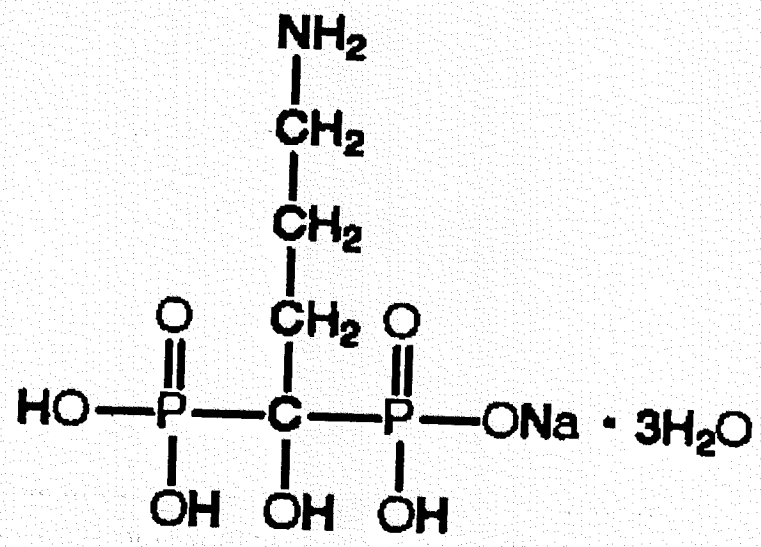
sNDA # 20-560-013

DRUG NAME: Fosamax®

GENERIC NAME: Alendronate Sodium Tablets

PROPOSED TRADE NAME: Fosamax®

CHEMICAL STRUCTURE:



Alendronate sodium

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

1.4 PHARMACOLOGIC CATEGORY: Alendronate sodium (4- amino- 1-hydroxybutylidene bisphosphonic acid monosodium salt trihydrate, $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$, f.w. 325.12) is an aminobisphosphonate. Bisphosphonates, synthetic analogs of pyrophosphate, bind to hydroxyapatite in bone. Alendronate specifically inhibits osteoclast- mediated bone resorption.

1.5 INDICATION: Prevention and treatment of postmenopausal osteoporosis. In this sNDA, the sponsor proposes revisions to the current labeling. The revisions are based on efficacy and safety data that support the use of the drug for an additional two years (from the currently-labeled three years, to five years).

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

1.7 NDA DRUG CLASSIFICATION: Bisphosphonate, oral

1.8 IMPORTANT RELATED DRUGS: Etidronate, pamidronate, clodronate,

1.9 RELATED REVIEWS:
Statistics review

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3 **MATERIAL REVIEWED:** All clinical data in the eight-volume submission sNDA 20-560-013. The data were reviewed both from a CANDA (electronic submission) and from paper sources.

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

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

6 **CLINICAL BACKGROUND:** Alendronate is a potent bisphosphonate that was approved in 1995 by FDA for the treatment of postmenopausal osteoporosis. The drug works by binding to hydroxyapatite and inhibiting osteoclastic bone resorption at this site. In addition, alendronate does not appear in inhibit bone mineralization directly, and there is no evidence that alendronate use causes osteomalacia. By inhibiting bone resorption, alendronate reverses the loss of bone mineral that accompanies estrogen-deficient states, such as menopause. Consequently, bone mineral density increases at several skeletal sites, particularly those areas that are rich in trabecular bone. The preferential effect of alendronate on trabecular bone is due to the relatively high mineral turnover in this type of bone after menopause. Alendronate resides in bone for many years. The terminal elimination half-life of the drug is 10 years. Nonetheless, the drug has to be administered continuously in order to maintain inhibition of bone resorption.

Once initiated, postmenopausal osteoporosis is a condition that is present for the remainder of the lifespan; thus current anti-resorptive therapy will have to be continued for many years. Data derived from the initial three years of a placebo-controlled trial of alendronate were published in 1995 and 1996. These data relate to biochemical and BMD efficacy, as well as a pooled analysis of vertebral fracture incidence. There has been a need to extend these studies to determine the effects of prolonged treatment with this drug. The data contained in the present sNDA result from a protocol that extended for an additional two years treatment for patients completing the original studies (035 and 037). Data from these studies were pooled, since the protocol designs and patient characteristics did not differ from each other.

7 **DESCRIPTION OF CLINICAL DATA SOURCES:** Clinical data were obtained from patients who completed the sponsor's Protocols 035 and 036 (3 years) and were accepted into a two-year extension study. Further details are provided below.

8 **CLINICAL STUDIES:** This application is based on a single multicenter two-year extension study, in which patients were recruited from two three-year trials (#'s 035 and 037).

8.1 Reviewer's Trial #1, Sponsor's Protocol # 035-10 and 037-10

"A 2-Year, Double-Blind, Multicenter Extension Study to Evaluate the Safety and Effect on Bone Density of Daily Oral Alendronate in Osteoporotic Postmenopausal Women"

8.1.1.1 Objectives: This trial had five objectives. As stated by the sponsor, these were:

(1) "To obtain safety and tolerability data in postmenopausal women treated continuously with oral alendronate for up to 5 years;

(2) To assess the relative effects of alendronate 5 and 10 mg daily for 5 years to increase bone mineral density (BMD) of the spine, hip, forearm, and total body;

(3) To evaluate and compare the changes in BMD of the spine, hip, forearm, and total body between Months 24 and 60 in the groups receiving either 5 or 10 mg continuously for 5 years or 20 mg for 2 years followed by 5 mg in the last 3 years;

(4) To determine the effects of alendronate on biochemical markers of bone turnover and calcium and phosphate metabolism;

(5) To assess whether the vitamin D receptor allele may have utility in predicting the baseline (Month 0) BMD and/or the rate of bone loss in placebo-treated patients."

The results of objective #5 are not presented in the NDA document.

8.1.1.2 Study Design

This was a multi-center, double-blind, randomized, parallel-group extension study involving 18 centers in the United States and 18 multinational centers. The overall objectives were to evaluate the use of long-term treatment with alendronate, 5 or 10 mg daily, in terms of safety, tolerability, and ongoing effects on BMD and biochemical markers of bone turnover. The study was designed to test several hypotheses that are relevant to the daily use of 5 or 10 mg oral alendronate for up to five years in women with postmenopausal osteoporosis. The hypotheses, as stated by the sponsor, were:

1) "Daily oral administration of alendronate, 5 or 10 mg, for up to 5 years in postmenopausal women, will be sufficiently safe and well tolerated to permit these doses to be used long-term in the treatment of postmenopausal osteoporosis.

2) Daily oral administration of alendronate, 10 mg continuously for 5 years in postmenopausal women, will result in a greater increase in spine bone mineral density (BMD) from the original pretreatment baseline than achieved following treatment with alendronate 5 mg for 5 years.

3) Daily oral administration of alendronate, 10 mg continuously for 5 years in postmenopausal women, will result in a greater increase in hip, forearm, and total body BMD from the original pretreatment baseline than achieved following treatment with alendronate 5 mg for 5 years.

4) Daily oral administration of alendronate, 5 and/or 10 mg continuously for 5 years, in postmenopausal women, will preserve (no statistically significant loss) or increase spine, hip, forearm, and total body BMD from Months 24 to 60.

5) Reduction in the daily total dose of oral alendronate from 20 to 5 mg after 2 years will result in increased bone turnover (assessed by biochemical markers of bone turnover) and a smaller increase in spine BMD (from Months 24 to 60) than that observed over the same period in postmenopausal women treated with 10 mg continuously for 5 years."

The patients enrolled in the present study had met all exclusionary/inclusionary criteria for enrollment in the original trials and had completed either of the two 3-year, double blind studies of alendronate in postmenopausal osteoporosis (Protocol 035 or 037). All patients in the present study were given alendronate, either 5mg or 10 mg, daily for the two years (Years 4 and 5). Patients who had been taking alendronate, 5mg or 10 mg, in the initial study were kept on that dose for Years 4 and 5. Patients who had been given 20-mg alendronate during Years 1 and 2 of the initial study had been switched to 5 mg for Year 3. These patients were kept on 5 mg for Years 4 and 5. Patients who had been taking placebo for Years 1-3 were switched to alendronate 10 mg. for Years 4 and 5.

The blinded status of patients and investigators was maintained as follows: Those patients who had previously received active treatment with Alendronate during the original three-year study period were blinded to assigned dose (5 or 10 mg) and to their previous dose. (Those patients who had been given placebo during the first 3 years were switched to alendronate 10 mg during Years 4 and 5.) Midway through Years 4 and 5, all patients were informed whether they had received placebo or alendronate (dose not revealed) during the

first 3 years. Therefore, patients in the original placebo group became aware that they were receiving the 10-mg dose during Years 4 and 5. This information became available to investigators as well.

All patients in the trial were placed on alendronate following the final visit in the original 3-year study. The dose allocation schedule is summarized in the sponsor's table below*:

Year 1	Year 2	Year 3	Years 4 and 5
Placebo	Placebo	Placebo	10 mg
5 mg	5 mg	5 mg	5 mg
10 mg	10 mg	10 mg	10 mg
20 mg	20 mg	5 mg	5 mg

*Tables and graphs appearing in this review are those of the sponsor, unless indicated otherwise. Reviewer's modifications to sponsor's tables are indicated as they occur.

Treatment of patients in open-label arms: Two groups of patients received open-label alendronate during this two-year study. These were patients who refused to be treated blindly and patients who had received open-label alendronate, 5 mg, during the third year. Both groups of patients were switched to alendronate, 10 mg, for the 2-year extension study. All data for patients in these two groups of patients who received open-label drug are presented separately from data derived from patients who had double-blind treatment. The dose allocation schedule for patients who had received open-label alendronate during the third year of the initial study is shown in the table below:

Double Blind (Years 1 and 2)	Open Label (Year 3)	Open Label (Years 4 and 5)
Placebo	5 mg	10 mg
5 mg	5 mg	10 mg
10 mg	5 mg	10 mg
20 mg	5 mg	10 mg

Each center attempted to enroll as many of their patients as successfully completed the initial 3-year study phase.

In performance of this study, the sponsor obtained multiple radiological, biochemical, and clinical baseline parameters at the end of Year 3 and at scheduled times for the next two years (details below).

Efficacy was assessed using bone mineral density measurements at several anatomic sites, biochemical parameters, and stature.

Bone Mineral Density: The primary efficacy end point was the change in BMD at the end of 5 years of treatment. This was expressed as percent BMD change from baseline of the posterior-anterior lumbar spine (L1 to L4).

To assess the change in lumbar spine BMD due to an additional 2 years of therapy, the sponsor measured the percent change in lumbar spine BMD from Months 36 to 60.

To compare the change in lumbar spine BMD following the dose reduction from 20 to 5 mg after 2 years of treatment with the change in patients who received 10 mg continuously over the same five-year period, the sponsor measured the percent BMD change from Months 24 to 60.

Changes in BMD at the proximal femur (femoral neck, total hip, trochanter, and Ward's triangle), forearm [ultra-distal forearm and one-third distal forearm (radius + ulna)], and total body were assessed as secondary end points. To assess the effects of five years of treatment with alendronate, the percent BMD changes from baseline, from Month 24, and from Month 36 were calculated from the Month 60 measurements. The pretreatment baseline BMD was defined as the average of values obtained in Days -100 to 14 of the original study.

Biochemical end points: To study the effects of alendronate on bone formation, bone resorption, and mineral homeostasis, multiple biochemical parameters were obtained at baseline, (month 36), and at Months 48 and 60. These included serum alkaline phosphatase, serum bone-specific alkaline phosphatase (BSAP), urinary deoxypyridinoline corrected for creatinine (DPyr/Cr), N-telopeptides of type I collagen, also corrected for creatinine (NTx/Cr), serum calcium, phosphate, PTH, and 1,25-dihydroxyvitamin D.

Stature: Stature was measured with a stadiometer. Three to five measurements were taken on a given day, and the average of these was computed. Assessment of stature data was similar to the assessment of change in BMD.

Full details on methodology employed in obtaining efficacy outcome measurements are presented below, in **8.1.1.3.2.**

Safety was assessed clinically (adverse events, reported and detected on physical examination) and radiologically (fractures). In addition, standard clinical laboratory data were obtained at Months 36, 48, and 60. Details of the safety

analysis are presented below, in sections **8.1.1.3.2** (methods) and **8.1.1.4.3** (results).

Comments: This extension study lacked a placebo arm. Consequently, the cogency of safety data is reduced.

8.1.1.3 Protocol [redacted] APPEARS THIS WAY ON ORIGINAL

8.1.1.3.1.1 Population: The patients studied were postmenopausal women who had completed two prior 3-year alendronate trials (sponsor's Protocols # 035 and 037). Patients had been postmenopausal for at least 5 years prior to the initiation of the original study and also had a lumbar spinal BMD ≤ 0.92 g/cm^2 by [redacted] or ≤0.80 g/cm^2 by [redacted] at the beginning of the original study. The patients had met all other initial exclusion/inclusion criteria (detailed below). They had all completed (without protocol deviation) the initial 3-year protocols and were "otherwise in good health."

Inclusion/exclusion criteria for the present study were:

1) The patient met all initial inclusion and exclusion criteria, participated in and completed without deviation from the alendronate Protocols 035 or 037 (36-month visit).

2) The patient understood the procedures of the study, had been informed of potential alternative treatments of osteoporosis, and was willing to give informed consent.

3)The patient was in good health, based on medical history, physical examination, and laboratory evaluation.

Criteria for exclusion were:

1) The patient was withdrawn from Protocols 035 or 037 for any reason prior to completing the study (36-month visit). If the entry into the extension study was delayed by more than 2 months (not to exceed 6 months), then the exclusion criteria of the original protocol applied to the lag period as well.

2) The patient completed the original study protocol more than 2 months prior to the start of the extension study and failed to meet the entry criteria stipulated in the original protocol (035-03 or 037-03).

3) The patient was mentally or legally incapacitated or otherwise unable to give informed consent.

4) The patient had significant abnormalities at extension baseline on clinical or laboratory examinations or a history of, or evidence for, significant end-organ disease, e.g., genitourinary, cardiovascular, hepatic, psychiatric, renal, or pulmonary disease, which either posed additional risk to the patient or might have complicated the analysis of the data obtained from this extension study.

5) The patient had a history of, or evidence for, a disorder of skeletal turnover (other than postmenopausal bone loss) including, but not limited to, hyper- or hypoparathyroidism, Paget's disease of bone, and osteomalacia.

6) The patient had received any other treatment that might have influenced bone turnover for more than 2 weeks within 6 months prior to the start of the extension study, including estrogen, anabolic steroid, glucocorticoid, progestin, vitamin A (≥5000 IU/day), vitamin D (≥1000 IU/day), anticonvulsants, or regular use of phosphate-binding antacids. (Topical [vaginal] estrogen cream for the treatment of local symptoms of estrogen deficiency used up to two times per week was acceptable.)

7) The patient had a history of recent (within the past year) major gastrointestinal disease, including, but not limited to, peptic ulcer, malabsorption and esophageal disease, or the patient had used a drug to inhibit gastric acid secretion for more than 2 weeks within 3 months of entry into the extension.

Comments: Across all centers, 727 patients were enrolled in the two-year double blind extension study. According to data presented in Table 6 in the Results section, this represents 73% of those randomized into the original protocol. This is an excellent retention/recruitment rate. From the patient data presented in the Appendices, apparently, 995 patients were originally randomized into the 3-year studies. Of these, 824 (83%) completed the trials. Of the 824 completers, 788 (96%) agreed to enter the extension study, but 61 elected open-label protocol. Thus 727 of the 824 completers (88%) entered the double blind extension trial. I have summarized these data as follows:

	# PATIENTS
A) ENTERED ORIGINAL STUDY (035 + 037):	994
B) COMPLETED ORIGINAL (36-M0NTHS STUDY):	824 (83% OF A)
C) ENTERED EXTENSION STUDY	788 (96% OF B)
D) ENTERED TWO-YEAR EXTENSION (DOUBLE BLIND):	727 (88% OF B)
E) ENTERED TWO-YEAR EXTENSION (OPEN LABEL)	61 (7% OF B)

Additional Comments: The population enrolled in a clinical trial should be as representative of the intended treatment population as possible. For

many reasons, perfect representation is never achieved. The present and future markets for alendronate run in the tens of millions, comprising most postmenopausal women with osteopenia and osteoporosis. The present alendronate extension trial studied 727 postmenopausal women in 36 centers in the United States and abroad. The sponsor employed strict inclusion/exclusion criteria for entry; consequently, efficacy/safety conclusions can be drawn only from the population of patients who met these criteria.

Procedures:

Individual investigators explained the nature of the extension study to patients and obtained written informed consent. On the 36-month visit of the original study, the investigator elicited an adverse experience history and performed a complete physical examination. Samples of blood and urine were obtained in accordance with the original protocol. Also in accord with the original protocol, BMD measurements and lateral lumbar and thoracic spine x-rays were obtained.

If a subject had finished the original study more than 1 month before enrollment in the extension study, then additional safety laboratory tests were obtained, as well as a complete clinical examination. The interval between the end of the original study and the initiation of the extension trial was not to exceed 6 months.

Following the initial examination, subjects returned to the clinic at Weeks 42, 48, 54, and 60. During these visits, all unused study drugs (or empty containers) were returned and tablet counts were made. At each visit, patients were questioned as to adverse events and concomitant medications. Physical examinations were performed as needed. A limited physical examination was performed on everyone during the last visit.

There was no replacement of dropouts. It was anticipated that over 85% of patients initially enrolled would complete the extension study.

A schedule of procedures for this protocol is presented in the sponsor's table below:

Visit:	Last Visit Prior Study (Month 36) 11	11E[†]	42 12	48 13	54 14	60 15
Informed consent	X	X				
Height/weight[†]	X	X	X	X	X	X
Limited physical examination[‡]	X	(X)	(X)	(X)	(X)	X
History and adverse experience inquiry[*]	X	X	X	X	X	X
Tablet count	X		X	X	X	X
BMD (spine, hip, forearm, and total body)	X			X		X
Safety laboratories[†] (serum chemistry, urinalysis, complete blood count)	X	(X)		X		X
PTH 1,25 vitamin D[¶]	X			X		X
Biochemical markers (OSTEOMARK, OSTASE, osteocalcin) (Alkaline phosphatase, pyridinolines)	X	(X)		X		X
Vitamin D receptor alleles[¶]	X			X		X
Archive serum[†] (6 mL/urine (15 mL)	X		(X)			
L/T spine x-rays	X	(X)		X		X

Note: ( ) denotes that the study is done based on circumstances detailed below.

† For patients entering more than 1 month after the completion of the previous protocol, an adverse experience inquiry and height/weight was recorded. In addition, serum and urine was obtained for safety laboratories, biochemical markers, and the aliquots of urine and serum archived.

‡ Minimum of height/weight, vital signs, Visit 11 (and 15—Protocol 035-10) and at investigator's discretion for all other visits.

¶ Blood was obtained and sent to a central laboratory for DNA extraction and subsequent assessment of vitamin D receptor allele status at either the 36- or 42-month visit.

[Tests performed at the start of the 2-year extension depended on the timing of Visits 11 and 11E.

- When Visit 11 and 11E occurred at the same date workbooklets and case report forms noted this. Only extension informed consent, extension biochemical markers, and vitamin D receptor allele testing were additional.
- When Visit 11E occurred 1 month or more after Visit 11, all marked evaluations were repeated. For Protocol 037-10, vitamin D receptor allele status was not repeated, and lateral thoracic and lumbar spine x-rays were repeated only if height was decreased ≥1 cm since visit.

* Protocol 035-10 only.

The primary efficacy endpoint, BMD of the PA lumbar spine, was determined by dual energy x-ray densitometry. These studies were performed at Months 36 (baseline entry value for the extension study), 48, and 60. Measurements were made with either: [redacted] densitometers. The type of densitometer used for each patient was the same as in the original protocol. Changes between models were permitted only after appropriate validation (validation protocol available from Merck).

BMD was calculated according to standard procedures (e.g., for spine, BMC/area for evaluable vertebrae L1-L4). If a vertebra became fractured during the study, data derived from that structure were not included in analysis. Each anatomic site provided quality control using hydroxyapatite phantoms. Quality control was also assured by having scans reviewed by the QA center.

Similar procedures were followed for BMD studies of the other anatomic sites. For the proximal femur studies BMD were measured at Months 48 and 60, using the same femur as in the original protocol, unless there had been significant new trauma to that bone. In this case, the scan was not done. BMD measurement sites included: total, neck, trochanteric, intertrochanteric, and Ward's triangle.

Forearm sites included total, ultra-distal, mid, and one-third distal radius and ulna. The forearm BMD studies were done at the same time as the proximal femur measurements. Studies included the forearm that was originally scanned. In the event of new trauma to that forearm, scanning was not performed. Within the forearm, BMD of ultra distal radius and ulna gives the most information regarding the status of peripheral mixed cortical/trabecular bone. BMD of the one-third distal forearm provides the most information regarding peripheral cortical bone.

The sponsor estimates that the total radiation exposure to the regions of interest throughout the trial were approximately 50 mREM (exposure to each site is about 2-5 mREM per study).

Lateral radiograms of the spine were obtained at Months 36 and 60 to exclude the presence of vertebral crush fractures and/or other spinal deformities that could affect the precision and accuracy of the BMD studies. The incidence of vertebral fractures during this interval was determined by comparing the films taken at both dates. Vertebral fracture determinations were made as safety endpoints in this study. For this purpose, an incident fracture was defined as a reduction in vertebral height, compared to baseline, that was diagnosed as a fracture by a radiologist. Only new fractures were interpreted as adverse experiences. In addition, anterior wedge compression, end plate deformity, and symmetrical crush fractures were all considered as vertebral compression fractures, for the purpose of adverse event reporting.

(In the future, if a vertebral endpoint study is to be performed, it will be based on formal morphometric criteria measured via digitization of x-ray images at a central site. This will be the subject of a protocol amendment.)

Biochemical measures of bone turnover and calcium homeostasis were obtained at 36, 48, and 60 months. These included: serum alkaline phosphatase and serum bone-specific alkaline phosphatase (BSAP, to indicate bone formation activity), and urinary deoxypyridinoline corrected for creatinine (DPyr/Cr) and N-telopeptides of type I collagen, also corrected for creatinine (NTx/Cr), to indicate bone resorption activity. Serum osteocalcin was not measured at Month 60, due to a change in the assay kit. To evaluate effects of alendronate on mineral metabolism, the sponsor measured serum calcium, phosphate, intact PTH, and 1,25-dihydroxyvitamin D. Samples were kept frozen (-70°C) until assay. All samples were assayed in a central laboratory facility.

Concurrent treatment: Throughout the study, patients consumed a "normal" diet. Presumably this means that they were on *ad libitum* food intake with no special instructions. They all received 500-mg supplemental elemental calcium, as calcium carbonate, per day. No vitamin D supplementation was prescribed.