Patients were instructed to remain fasting (water only) until 30 minutes after taking their alendronate each morning.

Comments: 500-mg calcium supplementation is generally inadequate for postmenopausal women. The lack of vitamin D supplementation could further limit the bioavailability of calcium and place these patients in negative calcium balance. For postmenopausal women, the recommended doses of calcium and vitamin D are at least 1000 mg as supplement (if the patient consumes an added 500 mg in her diet, otherwise 1200-1500 mg/day), plus 400-800 IU vitamin D per day. Inadequate calcium and vitamin D supplementation leave patients in negative calcium balance and increase the rate of bone loss. Conclusions regarding efficacy of any antiresorptive agent must take patients' calcium balance into account.

Concurrent treatment (cont.): concurrent medications. Other drugs that were prohibited were fluoride (>1 mg/day), calcitonin, estrogen, anabolic steroids, glucocorticoids, progestin, large doses of vitamin A (> 5000 IU/day) or vitamin D (> 1000 IU/day), phosphate-binding antacids, or anticonvulsants. If there was a clinical indication for any of these medications, this was to be discussed with the investigator and clinical monitor. If these and/or any other additional medications were used, the use was noted (drug, dates of administration, dose) in case report forms.

8.1.1.3.2 Endpoints
Efficacy
Efficacy endpoints were: 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 of the PA lumbar spine (L1-L4) at the end of 5 years of treatment. This was expressed as percent BMD change from original 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 also 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, intact PTH, and 1,25-dihydroxyvitamin D.

Stature: Stature was measured using Harpenden stadiometer readings. Three to five measurements were taken on a given day, and the average of these was computed. Change from baseline to Month 60 was calculated. Assessment of stature data was similar to the assessment of change in BMD, including definition of baseline values (range of Days –100 to 14).

Comments: These parameters are appropriate to answer the questions posed in the hypothesis and also to meet proposed labeling claims. More important and far-reaching clinical questions, such as long-term treatment effects on fracture endpoints, await the results of further investigation. Since it is proposed that alendronate is to be given for many years, and since alendronate remains in bone for very long periods, long-term safety issues will ultimately need to address such clinically important aspects of bone biology as fracture healing. For the present purposes, however, the methodology is suitable to answer the questions posed in the hypothesis. The overall approach appears to be careful and adequate to meet the goals of the project.

Safety:
The safety of long-term alendronate treatment (up to 5 years) was evaluated clinically, biochemically, and radiologically. At each visit, patients were questioned by investigators about adverse events. These were assessed in terms of severity, duration, seriousness of the event, proposed relationship to study drug, and outcome.

Investigators monitored weight, pulse, and systolic and diastolic blood pressure. Percent change from baseline at Month 60 was calculated and recorded for all vital signs. Baseline was defined as an average of all values in the range of days from -100 to 1.

Clinically and radiographically demonstrable new fractures and vertebral compression fractures were reported as adverse experiences.

Hematology, serum chemistry, and urinalysis were performed at Months 36, 48, and 60. The hematology safety parameters were: basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, monocytes, neutrophils, platelet count, and white blood cell (WBC) count. Chemistry parameters were: corrected alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), serum albumin, serum alkaline phosphatase, serum calcium, serum creatinine, serum glucose, phosphate, potassium, and sodium.

Clinically important predefined limits of change from baseline were generated and are provided in Appendix [4.50.1]. Laboratory adverse experiences were evaluated with regard to seriousness, proposed relationship to the drug, and outcome.

Comments: This is a standard and reasonable plan for evaluating clinical adverse events. The sponsor is certainly aware of the concern, in the medical community, over gastrointestinal adverse events. These are evaluated separately in the Results sections, below.

The absence of a placebo-control group limits the interpretation of adverse events in any study.

8.1.1.3.3 Statistical Considerations

Standard statistical planning and analytical methodology was used in this trial. A separate statistics review accompanies the medical review.

Briefly, for evaluation of efficacy:

Null hypothesis: daily alendronate, 10 mg p.o. continuously for 5 years in postmenopausal women, would not result in a greater increase in spine BMD from baseline than that achieved with alendronate 5 mg.

Alternative hypothesis: alendronate 10 mg continuously for 5 years would result in a greater increase in spine BMD from baseline than that achieved with alendronate 5 mg.

Power calculations: were based on projected sample sizes and standard deviations of the lumbar spine BMD as assessed at the 2-year interim analysis. For each of the two original studies, 350 patients were projected to continue until Month 60. For each of the four treatment groups— 5, 10, and 20/5 mg— the projected number of patients was 80. Based on the standard deviation (approx.4.37), the pooled studies had 90% power to detect a between group BMD difference of 1.59% change from baseline.

For safety, the null hypothesis was that daily alendronate, 5 or 10 mg, for up to 5 years in postmenopausal women, would be sufficiently safe and well tolerated to permit the long-term use of these doses in the treatment of postmenopausal osteoporosis.

The alternative hypothesis was that daily alendronate, 5 or 10 mg, for up to 5 years in postmenopausal women, would not be sufficiently safe and well tolerated to permit the long-term use of these doses in the treatment of postmenopausal osteoporosis.

Statistical significance was designated at the 5% level (two-sided). This significance level was used to make conclusions for the primary efficacy outcomes. Secondary analyses were used to support the primary analyses, and thus no multiplicity adjustment was applied.

There were a few deviations from the original Data Analysis Plan. Originally, analyses of biochemical efficacy parameters were not included, because of drift in the assays of biochemical markers during the first 3 years of the study. However, the sponsor believes that studies of biochemical parameters yield important information on the pharmacology of alendronate, and the only assay identified with drift was deoxypyridinoline in Protocol 037. These data were excluded from the extension protocol, and analyses from Baseline, Month 24, and Months 36 to 60 were performed to determine whether effects of alendronate on bone metabolism differ between treatment groups, and to determine whether changes in biochemical markers over 5 years of treatment is significant.

In addition, the sponsor performed subgroup analyses to determine whether the treatment effect was different for various pre-specified groups.

Primary analyses of the BMD parameters were based on the intention-to-treat approach. This approach was modified to exclude patients who chose open-label therapy after Month 36. In addition, dropouts were included by carrying forward the last observation on treatment for all time points subsequent to dropout. For patients who did not drop out but had no data in the day range, the last observation prior to the time point being analyzed was used in the analysis. Patients with data from multiple time points in a day range had only the last time point used in the analysis.

No data from the original 3-year study were carried forward to Month 36 (extension baseline) for any assessment of change, nor were any data carried forward from the extension baseline to the active phase of the extension for any analyses including that of repeated measures.

In addition to the ITT analysis, per-protocol analyses were performed to corroborate the ITT approach. The per-protocol analyses excluded patients based on prespecifed criteria. No data were carried forward in the per-protocol analyses. Open label-treated patients were excluded from this analysis.

All biochemical data were analyzed on a per-protocol basis.

For efficacy analysis of data pooled across studies, the sponsor used a two-way ANOVA model, which included treatment, protocol, study center nested within protocol, and treatment-by-protocol interaction as factors. Across all protocols, significant treatment-by-protocol interactions were investigated using plots of treatment group versus treatment effect. Homogeneity of variance and normality were tested by Levene's test and the Kolmogorov D statistic. Nonparametric tests were used to corroborate parametric analyses, when appropriate.

For pairwise comparisons, the ANOVA F-statistic for overall treatment effect was examined,using a modification of the least significant difference (LSD) test, in order to provide greater protection against false-positive results. For all efficacy parameters, two-tailed (a=0.050) tests were used. The sponsor notes that the patients in the treatment groups at Months 24 or 36 are not quite as comparable as at the time of randomization of the original study. The comparison of two means should therefore be interpreted as a conditional comparison, i.e., conditional on the patient's choice of remaining in the study after Months 24 and/or 36, which is related to the treatment effect.

Summary statistics (sample size, mean, standard error, median, minimum and maximum) for percent change from baseline, Month 24, and Month 36 were computed for all efficacy parameters. Graphical representations of changes observed over 5 years' duration are also presented.

As an exploratory analysis, the time course was examined to evaluate how treatment effects changed over time. The analysis of time-response profiles, based on fitting the appropriate (curvi-) linear function to the actual BMD data, was performed. All patients with at least one on-treatment observation were included in the analysis. The function was estimated using all data available across time points for each patient. Based on 2-year data for lumbar spine, it was observed that the rates of increase in the active treated groups slowed down gradually over time.

Safety

The sponsor notes that statistical hypothesis testing for safety parameters must be interpreted cautiously and that the usual hypothesis testing paradigm and the resulting p-values are appropriate for a limited number of prespecified hypotheses for which there is reasonable power to detect clinically important effects.

As the sponsor notes, the analysis of safety data is a screening experiment, a post-hoc exercise. In this context, significant p-values are useful for identifying parameters that require further study. They cannot be interpreted as an indication of a "real" treatment effect, either positive or negative.

For laboratory safety analysis, the sponsor used the predefined limits of change. The proportion of patients outside the predefined limits was compared in each treatment group using Fisher's exact test. If a significant result ($p<0.050$) was observed for a given variable, a summary table and analysis of change/percent change from baseline at Month 60, using the intention-to-treat approach, was provided for that variable. Between-treatment differences in the proportion of patients experiencing clinical adverse experiences in the 5- and 10-mg groups was tested using Fisher's exact test, and only significant results ($p\leq0.050$) were reported.

Drug-related adverse experiences, such as abdominal pain and upper gastrointestinal (GI), results approaching significance (p-value ≤0.100) were also reported and discussed.

To assess baseline comparability across treatment groups, patients who entered the Years 4 and 5 extension were compared with those who did not enter the extension or were not eligible for the extension, using change from the original baseline at Month 36.

8.1.1.4 Results

8.1.1.4.1 Populations enrolled/analyzed:

Patient accounting: As described above, 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. These data are summarized as follows:

	# PATIENTS
A) ENTERED ORIGINAL STUDY (035 + 037):	**994**
B) COMPLETED ORIGINAL (36-M0NTHS STUDY):	**824 (83% OF A)**
C) AGREED TO ENTER 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)**

The sponsor provides an extensive analysis of characteristics of patients who entered into the extension study, compared with those of patients who did not enter or were ineligible. Patient characteristics at baseline included age, lumber spine BMD, body mass index, estimated calcium intake, height, number of years since menopause, weight, and percent change in lumbar spine BMD from baseline to Month 36. Summary (mean, SD, median, and range) of these variables for these three groups is presented in Table 7 of the NDA. Characteristics did not differ between patients who entered the extension and those who did not or were ineligible. The only exception was that the percent change in lumbar spine BMD over the first 3 years was generally smaller in patients not eligible for extension as compared to those who either did not enter extension, or entered the extension studies for all treatment groups except placebo/10 group [redacted]

A between-group analysis was done for those who entered the extension study. There were no differences among treatment groups at baseline for any of the variables, except body mass index (Table 8 of NDA). Using the F-test, the BMI of patients in treatment groups differed significantly (p=0.033), but the differences were clinically insignificant. For convenience, and to display some of the salient characteristics of patients in this study, the following tables are reproduced (these appear within Table 8 of the NDA):

Treatment	N	Mean	SD	Median	Range	p-Value
Age (Years)						
Placebo/10 mg	288	63.3	7.2	63	44.0 to 79.0	0.950
5 mg	145	63.6	7.4	64	45.0 to 82.0	
10 mg	151	63.2	6.3	63	46.0 to 77.0	
20/5 mg	142	63.3	6.3	64	45.0 to 76.0	
Baseline Lumbar Spine BMD (gm/cm^2)						
[redacted]						
Placebo/10 mg	165	0.71	0.08	0.72	0.38 to 0.84	0.734
5 mg	89	0.71	0.09	0.72	0.48 to 0.93	
10 mg	88	0.70	0.08	0.71	0.42 to 0.83	
20/5 mg	83	0.71	0.08	0.73	0.47 to 0.85	
[redacted]						
Placebo/10 mg	107	0.82	0.09	0.84	0.54 to 0.95	0.504
5 mg	47	0.82	0.08	0.83	0.62 to 0.95	
10 mg	57	0.82	0.06	0.83	0.66 to 0.93	
20/5 mg	47	0.80	0.10	0.82	0.45 to 0.93	

Treatment	N	Mean	SD	Median	Range	p-Value
Body Mass Index (kg/m^2)						
Placebo/10 mg	271	24.3	3.5	23.9	15.9 to 36.5	0.033
5 mg	136	24.8	3.8	24.1	18.1 to 36.0	
10 mg	143	23.6	2.9	23.3	17.3 to 31.9	
20/5 mg	134	24.4	3.4	24.0	17.9 to 33.9	
Estimated Calcium Intake (mg/day)						
Placebo/10 mg	288	736	506	650	0 to 2959	0.820
5 mg	144	736	470	653	0 to 2196	
10 mg	150	773	650	613	62 to 4800	
20/5 mg	140	715	471	576	7 to 2318	
Height (mm)						
Placebo/10 mg	271	1584	69	1587	1352 to 1781	0.497
5 mg	136	1573	72	1572	1348 to 1741	
10 mg	143	1583	62	1588	1374 to 1728	
20/5 mg	134	1584	64	1588	1381 to 1722	

Treatment	N	Mean	SD	Median	Range	p-Value
Number of Years Since Menopause						
Placebo/10 mg	288	16.3	7.9	16.0	4.0 to 42.0	0.906
5 mg	145	15.9	8.1	15.0	1.0 to 47.0	
10 mg	151	15.9	7.5	15.0	4.0 to 40.0	
20/5 mg	142	16.4	8.2	15.0	4.0 to 46.0	
Weight (kg)						
Placebo/10 mg	288	61.0	9.5	60.0	32.7 to 99.3	0.225
5 mg	145	61.5	10.4	61.0	37.9 to 88.8	
10 mg	151	59.5	8.5	58.4	41.0 to 90.0	
20/5 mg	142	61.5	9.0	61.3	43.1 to 94.0	

The sponsor performed a similar analysis of patient demographic characteristics. Baseline demographics included cigarette smoking, ethanol intake, family history of osteoporosis, oophorectomy status, race, renal status, and prevalent vertebral fracture status.

Comparing those who entered the extension, those who did not enter, and those who were ineligible, there were no clinically meaningful differences in responses. The percent of cigarette smokers was lowest in the group of patients not entering the study, compared to those who entered and those who were ineligible. The vertebral fracture prevalence was lowest in ineligible patients.

These data appear in the sponsor's Table 9 of the NDA, sections of which are reproduced here, with modifications in column headings:

RACE	TREATMENT TOTAL	N		(%)
Caucasian				
Not eligible for extension	All	181	156	(86.2)
Did not enter extension	All	87	70	(80.5)
Entered extension	All	726	643	(88.6)
Other				
Not eligible for extension	All	181	25	(13.8)
Did not enter extension	All	87	17	(19.5)
Entered extension	All	726	83	(11.4)

VERTEBRAL FRACTURE PREVALENCE				
Not eligible for extension	All	167	29	(17.4)
Did not enter extension	All	86	27	(31.4)
Entered extension	All	698	168	(24.1)

For patients who entered the extension study, the percent of cigarette smoking patients differed significantly (p=0.011) between treatment groups, and the percent of patients with prevalent vertebral fracture was also significantly (p=0.030) different between treatment groups. There were no other demographic variables with significant differences between treatment groups in patients who entered the extension study.

The vertebral fracture prevalence among women who entered the study is given below (data taken from sponsor's Table 10, with column heading modifications):

 # OF PATIENTS WITH VERTEBRAL FRACTURES/# PATIENTS IN TREATMENT GROUP)

TREATMENT	TOTAL	N	(%)	p-VALUE
Placebo/10 mg	276	78	(28.3)	0.030
5 mg	142	30	(21.1)	
10 mg	143	23	(16.1)	
20/5 mg	137	37	(27.0)	

Baseline and Month 36 clinical efficacy parameters are analyzed by treatment group (Tables 11 and 12 of NDA). Statistics are provided overall and by densitometer type for lumbar spine, femoral neck, trochanter, total body, Ward's triangle, total hip, ultra-distal forearm, and one-third distal forearm (radius+ulna) BMD.

Among the four treatment groups, the mean baseline and 36-month BMD values were essentially the same at each anatomic site, and at each of the two time points (data presented in sponsor's Tables 11 and 12).

To give an indication of the nature and consistency of the baseline data, portions of Tables 11 and 12 are presented below:

SUMMARY OF BASELINE CLINICAL EFFICACY PARAMETERS

BMD Site	Densitometer	Alendronate Treatment	n	Mean	SD	Median	Range
Femoral Neck BMD (g/cm^2)	Hologic/Norland	All	410	0.61	0.08	0.60	0.39 to 0.92
		Placebo/10 mg	155	0.61	0.08	0.61	0.42 to 0.89
		5 mg	87	0.60	0.10	0.59	0.39 to 0.86
		10 mg	84	0.59	0.07	0.58	0.46 to 0.74
		20/5 mg	84	0.62	0.09	0.62	0.42 to 0.92
	Lunar	All	209	0.74	0.09	0.74	0.47 to 0.98
		Placebo/10 mg	85	0.75	0.08	0.74	0.58 to 0.98
		5 mg	40	0.76	0.10	0.78	0.59 to 0.95
		10 mg	42	0.72	0.09	0.71	0.53 to 0.93
		20/5 mg	42	0.72	0.08	0.73	0.47 to 0.89
Lumbar Spine BMD (g/cm^2)	Hologic/Norland	All	425	0.71	0.08	0.72	0.38 to 0.93
		Placebo/10 mg	165	0.71	0.08	0.72	0.38 to 0.84
		5 mg	89	0.71	0.09	0.72	0.48 to 0.93
		10 mg	88	0.70	0.08	0.71	0.42 to 0.83
		20/5 mg	83	0.71	0.08	0.73	0.47 to 0.85
	Lunar	All	258	0.81	0.08	0.83	0.45 to 0.95
		Placebo/10 mg	107	0.82	0.09	0.84	0.54 to 0.95
		5 mg	47	0.82	0.08	0.83	0.62 to 0.95
		10 mg	57	0.82	0.06	0.83	0.66 to 0.93

For femoral neck and lumbar spine at Month 36:

BMD Site	Machine	Alendronate Treatment	n	Mean	SD	Median	Range
Femoral Neck BMD (g/cm^2)	Hologic/Norland	All	397	0.62	0.09	0.62	0.39 to 0.98
		Placebo/10	151	0.61	0.08	0.61	0.39 to 0.87
		5	85	0.62	0.10	0.62	0.45 to 0.89
		10	81	0.62	0.07	0.62	0.47 to 0.78
		20/5	80	0.64	0.09	0.63	0.44 to 0.98
	Lunar	All	205	0.74	0.09	0.74	0.52 to 1.02
		Placebo/10	82	0.73	0.09	0.72	0.57 to 1.02
		5	40	0.77	0.10	0.77	0.58 to 0.99
		10	42	0.74	0.09	0.73	0.54 to 0.93
		20/5	41	0.73	0.09	0.74	0.52 to 0.91
Lumbar Spine BMD (g/cm^2)	Hologic/Norland	All	419	0.74	0.09	0.75	0.36 to 0.97
		Placebo/10	165	0.71	0.08	0.73	0.36 to 0.90
		5	87	0.75	0.10	0.76	0.50 to 0.97
		10	87	0.77	0.09	0.78	0.50 to 0.92
		20/5	80	0.77	0.08	0.77	0.53 to 0.92
	Lunar	All	257	0.84	0.09	0.85	0.44 to 1.04
		Placebo/10	106	0.81	0.09	0.83	0.44 to 0.98
		5	47	0.86	0.09	0.86	0.61 to 1.04
		10	57	0.87	0.08	0.89	0.65 to 1.02
		20/5	47	0.86	0.08	0.87	0.62 to 1.00

Summaries of baseline and Month 36 biochemical efficacy parameter values are also provided. Among the four treatment groups, there were no differences in mean values for alkaline phosphatase, bone-specific alkaline phosphatase, serum calcium, phosphorus, PTH, 1,25-dihydroxyvitamin D, urine N-telopeptide/Cr, or urine deoxypyridinoline/Cr. Complete summary data are provided in Tables 13 and 14 of the NDA.

Secondary diagnoses and prior drug therapies: Of the 727 patients who entered the extension study, 696 (96%) had at least one secondary diagnosis at the time of entry. Complete listings of these disorders are presented in the NDA (Table 15 and Appendix 4.6.1). There were no significant differences among the treatment groups in the prevalence of any specific disorder. Similarly, there were no clinically meaningful differences between treatment groups for prior drug therapies. Full data are also provided in the NDA Table 16 and Appendices 4.8.1, 4.8.2, and 4.8.3.

Similar analyses for concomitant therapies revealed no differences between groups in any drug category.

Note that a few patients in each group were receiving ranitidine. In the Appendix, the percent of patient in each group who were taking ranitidine concomitantly were: placebo/10 mg, 3.1%; 5mg, 2.1%;10 mg, 9.3%; 20mg/5mg, 4.9%.

Patient accounting: A total of 715 (91%) of the 788 patients who entered the study at the end of Month 36 completed Years 4 and 5 of treatment. Patient accounting data are summarized in the table below:

	Total	PBO/ALN 10 mg	ALN 5 mg	ALN 10 mg	ALN 20/5 mg
ENTERED EXTENSION: Total (age range, years)	788 (44 to 82)	316 (44 to 79)	156 (45 to 82)	161 (46 to 77)	155 (45 to 77)
Entered—Double blind (percent*)	727 (73%)	288 (73%)	145 (72%)	151 (77%)	143 (72%)
Entered—Open label	61	28	11	10	12
DISCONTINUED: Total	73	33	16	9	15
Clinical adverse experience	23	12	4	4	3
Patient withdrew consent	36	14	10	4	8
Protocol deviation	6	4	1	0	1
Lost to follow-up	8	3	1	1	3
COMPLETED: 60 months†	715*	283	140	152	140

† Includes 61 patients who elected open-label treatment during extension period (Years 4 and 5) only, or continued on open label from Year 3 to Years 4 and 5.
* Percent of originally randomized population.

Comments: In order to clear up potential confusion introduced by the inclusion of the 61 patients who elected open-label treatment, the data can be summarized as follows:

The completion rates are essentially the same across all four treatment groups. 79% of the initially randomized patients entered the extension

study. 73% of the initially randomized patients entered the study double-blind. This number (73%) was essentially the same across all treatment groups. Of the 788 who entered the study, 91% completed, including the 61 open-label-treated patients. This number, 715 (91%), included completers from the group of 61 open- label-treated patients. Thus fewer than 700 patients provided the basis for analysis of each of the efficacy outcomes. For example, analysis of BMD at the lumbar spine included 644 individuals, or 65% of the patients originally randomized into 035 and 037.

Detailed accounting of patients in the analyses is provided in the NDA Appendices.

For the ITT analyses, patients were excluded for one or more of the following reasons: no efficacy data at baseline, no efficacy data at both Months 48 and 60, and/or the patient was receiving therapy open-label.

For the per-protocol analyses, the sponsor provides the following list of exclusion criteria:

1) Protocol violations, including estrogen use (other than topical vaginal preparation); glucocorticoid therapy, (oral/parenteral: dose ≥5 mg oral prednisone or equivalent for >2 weeks; or inhaled: >4 puffs/day for >2 weeks); 25-hydroxyvitamin D ≤10 ng/mL at screening (and either one or more of abnormal PTH, alkaline phosphatase, serum calcium), calcitonin therapy, laminectomy, tamoxifen, TSH below detectable limits of assay for two consecutive visits, hyperthyroidism, high screening lumbar spine BMD (>1.01 g/cm2 for sites using Lunar machines and>0.88 g/cm2 for sites using non-Lunar machines).

2) Clinical adverse experience (discontinued).
3) Laboratory adverse experience (discontinued).
4) No data in the relative day range.
5) No baseline.
6) Patient withdrew consent.
7) Protocol deviation (discontinued, no data).
8) Lost to follow-up.
9) Violation of the off-drug rule)pt. off drug for more than 25% of the time spent in the study. The patient was excluded from the per-protocol analyses beginning on the study day when more than 25% of the expected total number of doses had been missed.
10) Patients who did not consent to third-year double-blind treatment and those who did not consent to 2-year extension studies.
11) Multiple violations (more than one of the above).

For the biochemical efficacy analyses, patients were not included for one or more of the reasons listed above or for one of the following reasons:

1) Violation of the biochemical off-drug rule: Under the biochemical off-drug rule, an observation was excluded from the per-protocol analysis at a specific time point if the patient was off drug for more than 15 days during the 45 days prior to a visit.

2) Urine calcium/creatinine data were excluded at a specific time point if there was a dose of any diuretic within 2 weeks of that time point (also in the intention-to-treat approach).

For the lumbar spine BMD analysis at Month 60, the accounting of all patients is given in the table below:

	PBO/ALN 10 mg	ALN 5 mg	ALN 10 mg	ALN 20/5 mg
Total Entered	316	156	161	154†
Total Included In				
Intention-to-treat analysis (percent*)	257 (81%)	123 (79%)	142 (88%)	122 (79%)
Per-protocol analysis (percent*)	211 (67%)	103 (66%)	118 (73%)	106 (69%)
Total Excluded From				
Intention-to-treat analysis	59	33	19	32
Per-protocol analysis	105	53	43	48
Discontinued				
Clinical adverse experience	10	4	3	3
Lost to follow-up	2	1	1	3
Deviation from protocol	4	1	0	0
Patient withdrew consent	12	10	4	5
No Data In				
Baseline day range	13	8	5	11
Month 60 day range	8	3	2	2
Protocol Violations				
Off-drug rule	0	0	0	0
Estrogen use	3	3	3	2
Glucocorticoid use	13	2	3	5
Low vitamin D use	7	4	7	2
TSH below detection for two consecutive visits	2	3	0	3
Tamoxifen use	1	1	0	0
Calcitonin therapy	1	0	2	0
Multiple violations	9	2	5	3
High BMD	0	1	0	0
Open label	20	10	8	9

† One patient (AN 2624) is not counted in this treatment group as she continued only to follow-up and accounted for no data in the analysis.

* Percent of total patients who entered Years 4 to 5 extension only.

This table contains counts of patients. Although a patient may have been excluded from analysis for more than one reason, the patient is counted only once.

Comments: The dropout/retention rates are essentially the same across the four treatment groups.

8.1.1.4.2 Efficacy endpoint outcomes

Data from patients who elected to be treated open-label with 10 mg alendronate are not included in the following efficacy analyses.

a) Bone Mineral Density

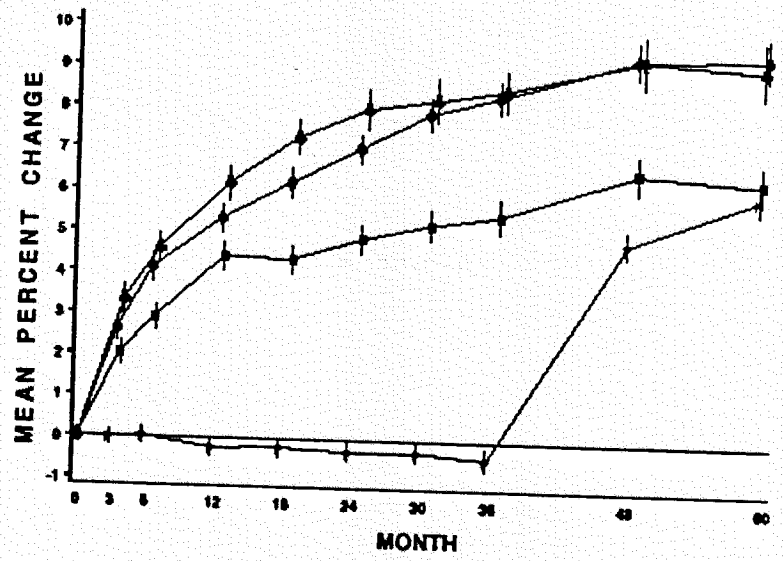
The statistics for efficacy analysis are based on combined data from Protocols 035-10 and 037-10, unless the sponsor detected evidence of differential treatment effects. For completeness, the sponsor has also included analyses of individual studies separately in the Appendix of the NDA. Conclusions based on per-protocol analyses corroborate those derived from the ITT data and are also given separately in the appendices.

1) Lumbar spine BMD

Changes over the 5-year period:

Over the 5-year period, all 4 treatment groups (placebo/10 mg, 5 mg, 10 mg, and 20/5 mg) showed significant increases in lumbar spine BMD over baseline ($p \leq 0.001$). All groups receiving alendronate experienced increases in BMD, from baseline, early in the treatment period. In contrast, patients in the placebo/10-mg treatment group decreased BMD during the first 3 years (when on placebo) then had a sharp increase in BMD during the last two years, when they were treated with 10mg alendronate. At Month 60, significant ($p<0.001$) increases from baseline of 6.0, 6.4, 9.4, and 9.1% were seen in the placebo/10-, 5-, 10-, and 20-/5-mg groups, respectively. The mean percent increase in lumbar spine BMD in the 5-mg alendronate group was significantly smaller than that in both the 10- and 20-/5-mg groups ($p<0.001$). The data are presented in the following figure, reproduced from the NDA:

Mean Percent Change (±SE) in Lumbar Spine BMD
(Intention-to-Treat Approach)
(Pooled 035/037)



Comments: This figure demonstrates the consistent, early, and robust effects of alendronate treatment on spinal bone mineral density in postmenopausal women. Following what appear to be maximum increases in BMD at 24-36 months (depending on dose treatment group), the effects were maintained or increased during the next two years (by Month 60). The 5-mg and 10-mg groups diverged early in the course of treatment. The BMD in the 5-mg group remained less than that in the 10-mg group for the duration of the 60-month period.

Statistics on the baseline and 60-month lumbar spine BMD data are summarized in the following table:

Analysis of Percent Change in Lumbar Spine BMD From Baseline at Month 60
(Intention-to-Treat Approach)
(Pooled 035/037)

Alendronate Treatment	n	Mean (Observed)		Percent Change From Baseline				Pairwise Comparison	
		Baseline	Month 60	Mean	SD	Adjusted Mean	LSD Interval	5 mg	10 mg
Placebo/10 mg	257	0.75	0.80	6.00***	5.70	5.97	(5.44, 6.50)	.	.
5 mg	123	0.74	0.79	6.36***	5.11	6.31	(5.57, 7.06)	.	.
10 mg	142	0.75	0.82	9.39***	5.91	9.37	(8.67, 10.06)	<0.001	.
20/5 mg	122	0.75	0.81	9.12***	7.48	8.96	(8.21, 9.71)	<0.001	0.576

*** Within-treatment p-value: ≤0.001.
Treatment-by-protocol interaction p-value: 0.177.
Pooled SD: 5.86.
Overall p-value: <0.001.
Mean difference 10 mg relative to 5 mg: 3.03, 95% CI: 1.61 to 4.45.