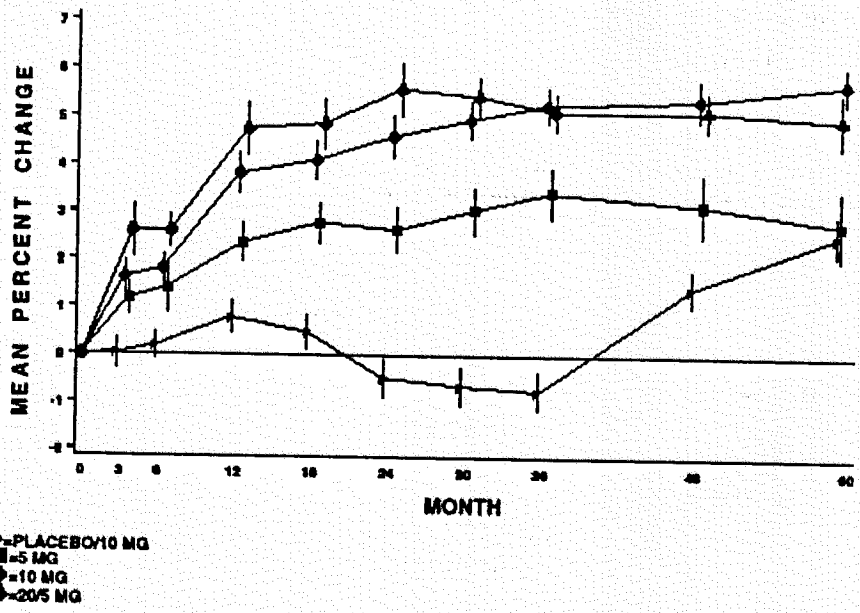
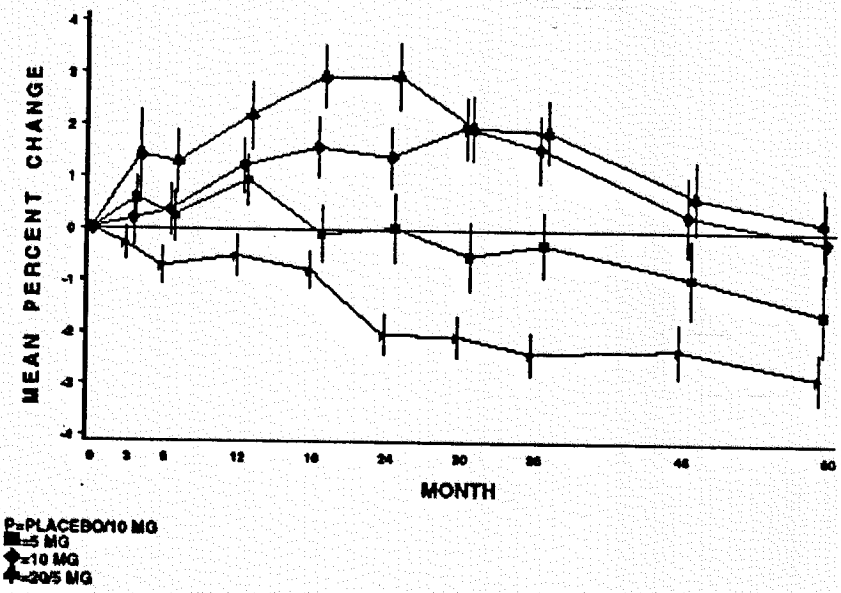
4.16.1: Alendronate Phase III Osteopenia Bone Density Study (Pooled 035/037)
Total Hip BMD
Mean Percent Change ±SE of the Mean
(Intention-to-Treat Approach)



Comments: The patterns of BMD change over time that were seen in these two secondary sites are similar to those observed in other anatomic locations, as described above.

However, for the ultra-distal wrist (radius + ulna), there was an initial rise in BMD, with a decline back to baseline by Month 60, in the 10-mg and 20/5-mg groups. The decline back to baseline BMD began around Months 24-30. In the placebo/10 and the 5-mg groups, there was a decline during the extension period, such that both groups ended the 60-month period with lower bone mineral densities than at baseline at the ultra-distal wrist, as shown in the figure below:

4.15.1: Alendronate Phase III Osteopenia Bone Density Study (Pooled 035/037)
UD Wrist (Radius+Ulna) BMD
Mean Percent Change ±SE of the Mean
"Intention-to-Treat" Approach



Analysis of these data is given in the table below:

4.15.2: (Pooled 035/037)
Forearm (Radius+Ulna) BMD
Analysis of Percent Change From Baseline at Month 60
(Intention-to-Treat Approach)

Treatment	N	Means (Observed) Baseline	Means (Observed) Month 60	Percent Change From Baseline Mean	S.D.	Adjusted Mean	LSD Interval	Pairwise Comparison 5 mg	Pairwise Comparison 10 mg
Placebo/10 mg	133	0.32	0.31	-2.83***	5.63	-2.78	(-3.55,-2.00)	.	.
5 mg	71	0.31	0.30	-1.59*	6.64	-1.61	(-2.62,-0.59)	.	.
10 mg	73	0.31	0.31	-0.20	6.46	0.08	(-0.92, 1.08)	0.093	.
20/5 mg	70	0.31	0.31	0.16	5.72	0.15	(-0.86, 1.17)	0.085	0.945

Within-Treatment Test Of Mean=0 ***:P<=.001 **: P<=.01 *: P<=0.05
Treatment-by-Protocol Interaction P-value: 0.686
Pooled SD: 5.98
Overall P-value: 0.001
Mean Difference 10-mg rel. 5-mg: 1.39, 95% Confidence Interval: -0.57 to 3.35

Comments: Both the placebo/10 mg and the 5mg groups experienced significant declines in BMD at this site by Month 60. The decline seen in the 10mg group was not statistically significant. Differences between the 5 and 10mg groups were not significant at 60 months.

For the time interval Months 36-60,

4.15.4: (Pooled (035037)
Forearm (Radius+Ulna) BMD
Analysis of Percent Change From Month 36 to Month 60
(Intention-to-Treat Approach)

		Means(Observed)		Percent Change From Month 36				Pairwise Comparison	
Treatment	N	Month 36	Month 60	Mean	S.D.	Adjusted Mean	95 % CI	5 mg	10 mg
Placebo/10 mg	151	0.31	0.31	-0.22	4.30	-0.05	(-0.89, 0.79)	.	.
5 mg	81	0.31	0.30	-1.83**	5.58	-1.74	(-2.86,-0.62)	.	.
10 mg	78	0.31	0.31	-0.79	6.32	-0.79	(-1.92, 0.35)	0.232	.
20/5 mg	75	0.32	0.31	-1.70**	4.49	-1.75	(-2.91,-0.60)	0.991	0.236

Within-Treatment Test Of Mean=0 ***:P<=.001 **: P<=.01 *: P<=0.05
Treatment-by-Protocol Interaction P-value: 0.963
Pooled SD: 4.98
Overall P-value: 0.035
Mean Difference 10-mg rel. 5-mg: 1.04, 95% Confidence Interval: -0.52 to 2.59

Comments: Between 36 and 60 months, the BMD at this site declined significantly in the 5-mg and the 20/5-mg groups. There was also a decline in the 10-mg group that was not statistically significant. The difference between the mean changes in the 5- and 10-mg groups did not differ significantly. It is not clear why the 10mg group returned to baseline by Month 60. The lack of placebo control during the extension makes it difficult to assign long-term benefit to alendronate treatment at this anatomic site. However, there appears to have been an early benefit associated with 10mg alendronate, with a trend toward some protection in the alendronate 10mg group. Of some concern is the uncertainty regarding the trajectory of the BMD curve at this site, past 5 years. From the data available thus far, however, alendronate treatment does not appear to hasten the loss of BMD at this site.

Stature:

Comments: Loss of height is a clinically important consequence of vertebral osteoporosis. Analysis of stature should be a significant clinical outcome of interventional trials. As shown in the data below, increases in BMD that are associated with alendronate treatment do not suffice to prevent loss of stature. The degree to which alendronate treatment prevents loss of stature relative to that found in a placebo group is discussed below.

During the 60-month treatment period, all four treatment groups lost stature. The losses from baseline of 6.5, 4.1, 6.0, and 4.4 mm in the placebo/10-, 5-,10-, and 20/5-mg treatment groups were all statistically significant ($p<0.05$). The data are displayed in the tables and figure below:

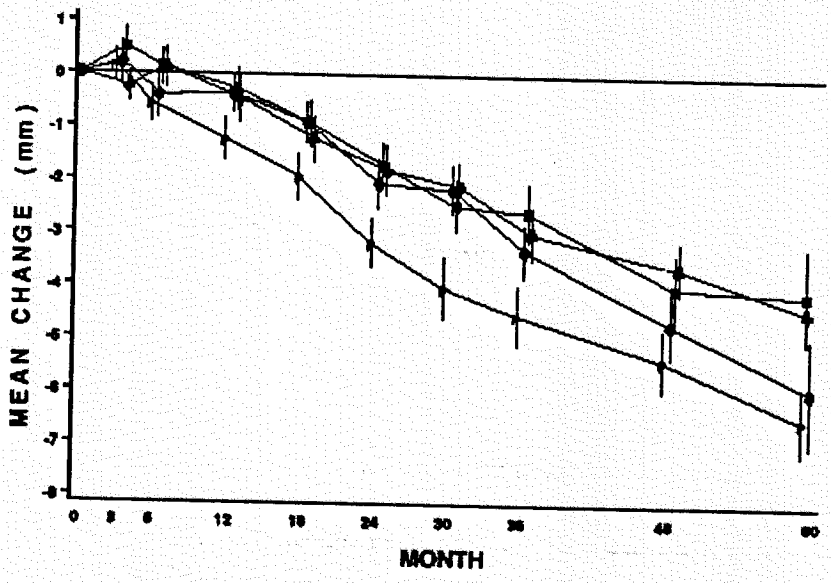
Summary of Stature Analyses
(Intention-to-Treat Approach)
(Pooled 035/037)

Alendronate Treatment	Change at Month 60 (mm)		Slope[†]
	Mean	Median	
Placebo/10 mg	-6.5	-5.8	
5 mg	-4.1	-3.7	-1.1
10 mg	-6.0	-3.9	-1.3
20/5 mg	-4.4	-4.3	
Pooled ALN	-4.9	-3.9	
5 mg vs. 10 mg Alendronate			
p-Value	0.114	0.232	0.355

[†] Mean yearly rate of change in mm.

Data Source: [4.51]

Mean Change (±SE) in Stature
(Intention-to-Treat Approach)
(Pooled 035/037)



P=PLACEBO/10 MG
■=5 MG
◆=10 MG
◆=20/5 MG

Data Source: [4.51]

APPEARS THIS WAY ON ORIGINAL

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

Alendronate Treatment	n	Mean (Observed)		Change From Baseline				Pairwise Comparison	
		Baseline	Month 60	Mean	SD	Adjusted Mean	LSD Interval	5 mg	10 mg
Placebo/10 mg	275	1583	1577	-6.52***	10.47	-6.48	(-7.33, -5.63)	.	.
5 mg	129	1573	1569	-4.13*	10.36	-4.02	(-5.24, -2.80)	.	.
10 mg	141	1580	1574	-5.97***	12.12	-5.93	(-7.09, -4.77)	0.114	.
20/5 mg	135	1586	1581	-4.44***	6.01	-4.72	(-5.91, -3.53)	0.565	0.310
Pooled ALN	405	1580	1575	-4.88***	9.88	-4.92	(-5.62, -4.22)		

*,*** Within-treatment p-value: ≤0.050 and ≤0.001, respectively.
Treatment-by-protocol interaction p-value: 0.300.
Pooled SD: 9.90.
Placebo vs. pooled ALN p-value: 0.0259.
Mean difference 10 mg relative to 5 mg: -2.04, 95% CI: -4.33 to 0.26.
Data Source: [4.51]

There was no significant difference between the 10-mg and 5-mg groups in loss of stature from baseline to Month 60. Within the 5- and 10-mg treatment groups, slopes of -1.1 and -1.3 were significantly different ($p<0.001$) from zero, indicating an overall decreasing trend in stature from baseline to Month 60. The difference in slopes for the 5- and 10-mg groups was not significant. The comparison, placebo/10mg vs pooled alendronate (all three continuous alendronate treatment groups), was statistically significant for the differences from baseline to Month 60.

During the two-year extension (Months 36-60), a significant decrease of -2.0 ($p<0.001$), -1.7 ($p<0.050$), -2.4 ($p<0.010$), -1.7, and -1.9 mm ($p<0.001$) occurred in the placebo/10-, 5-, 10-, 20/5-mg, and pooled alendronate groups, respectively. There was no significant difference between the 5- and 10-mg treatment groups in changes from Months 36 to 60.

Comments: This trial lacked a placebo arm for the 2-year extension, and it is therefore not possible to draw conclusions regarding treatment effects during the last two years. The only statistically significant between-group comparison was between the placebo/10 mg and the pooled data from all three continuous treatment groups. This difference was small (about 1 mm). We do not know what the 60-month difference would have been if the placebo treatment had been continued until that time point; however, judging from the slope of the original (0-36 months) placebo-group stature curve, the maximum benefit of 10 mg alendronate would probably not have exceeded 2-3 mm at 60 months.

On the other hand, the effects of alendronate on height may be far greater among those with an incident vertebral fracture (i.e., one that occurs during the treatment period). In the analysis at 36 weeks, there was a significant difference in height between alendronate and placebo groups among patients with a new vertebral fracture (about 6% of the population in the placebo arm), but only a small effect of treatment in patients with no new fracture (for all patients at 36 weeks, –3.0mm in treated group vs –4.6mm in

placebo; for those with new fracture, –5.9 mm in treated group vs – 23.3 mm in the placebo). This may mean that the fractures were worse in the placebo patients, or that there were more fractures per patient in that group, or both. The stature data at 36 months can be summarized as:

HEIGHT LOSS

	PLACEBO	POOLED ALENDRONATE
+ NEW FX	23.3 mm	5.9 mm
– NEW FX	3.3 mm	2.3 mm

Thus the benefits of alendronate on stature may be substantial but limited to a subgroup of patients who experience new fractures during a defined period.

Considerations regarding placebo notwithstanding, it is particularly noteworthy that, despite the consistent and highly significant increases in spine BMD in the 10mg group (increases that were present in almost all of the 10-mg-treated patients throughout the five years of the study), alendronate did not prevent loss of stature in this or in any of the treatment groups over the 60 months. Furthermore, there was no apparent dose effect in preventing or slowing the loss of height, despite significant and substantial differences in BMD between the 5- and 10mg dose groups. Since loss of stature is clinically important and not a surrogate, the relationship between BMD measurements and this clinically meaningful outcome warrants further consideration. Further discussion of stature changes appears below, in Sections 10 and 12.

Biochemical Efficacy:

Comments: The biochemical efficacy end points were studied to increase our knowledge of the pharmacology of alendronate; they do not serve as surrogate outcomes for BMD, nor were they intended to do so by the sponsor. The serum and urinary markers provide information on the effect of alendronate on bone formation, bone resorption, and mineral homeostasis in this patient population.

Serum alkaline phosphatase and bone-specific alkaline phosphatase (BSAP) concentrations provide indices of bone formation activity. Urinary DPyr/Cr and NTx/Cr serve as markers for bone resorption. As predicted from the known pharmacology of alendronate, both the bone formation and bone resorption indices decreased early in treatment. Bone resorption indices decreased more

rapidly than formation indices. Following this decline in both formation and resorption indices, the marker excretion rates stabilized, as a new (low-turnover) balance was achieved.

To evaluate the influence of alendronate on calcium and mineral homeostasis, the sponsor measured serum calcium, PTH, 1,25- dihydroxyvitamin D, and phosphate concentrations. Upon initiation of alendronate treatment, serum calcium and phosphate decreased rapidly, followed by a gradual return toward baseline levels. A rapid rise in concentration, followed by a gradual return toward baseline, was observed for 1,25-dihydroxyvitamin D and PTH.

Comments: These changes, described in more detail below, are predictable on the basis of diminished bone resorption, associated with alendronate treatment.

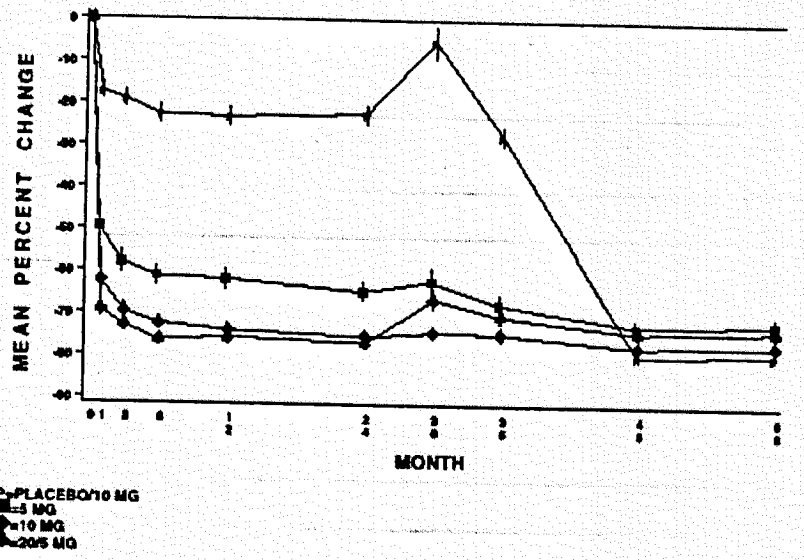
Analysis of bone resorption markers:

At the end of Month 60, there were significant ($p<0.001$) decreases in urine DPyr/Cr in all treatment groups, relative to baseline. Decreases from baseline of 52.0, 40.7, 46.4, and 42.3% were seen in the placebo/10-, 5-, 10-, and 20-/5-mg groups, respectively. At the end of the fifth year, there was no difference in effects of 5, 10, and 20/5 mg of alendronate on urine DPyr/Cr. Following initiation of alendronate, 10 mg, to the placebo group at Month 36, DPyr/Cr decreased to levels observed in the group treated with 10 mg continuously for 5 years. During the two-year extension, the DPyr/Cr levels in the other treatment groups remained at levels observed in the first 3 years of the study. These ranged from -41 to -46% of baseline. The intention-to-treat results were similar to the per-protocol results.

Similar results were found for N-telopeptide/Cr. During Years 4 and 5, NTx/Cr in the 5-, 10-, and 20-/5-mg groups remained at levels that had been observed in the first 3 years of the study. With the institution of alendronate treatment, NTx/Cr levels in the placebo/10-mg group abruptly decreased to the level observed in patients treated with 10 mg continuously for 5 years. At the end of Month 60, significant changes in NTx/Cr excretion ($p<0.001$) of -79.1, -72.0, -76.9, and -73.6% were seen in the placebo/10-, 5-, 10-, and 20-/5-mg groups, respectively. The decrease observed in the 10-mg group was significantly ($p=0.030$) lower than that in the 5-mg group. The intention-to-treat results were similar to the per-protocol results.

Changes in NTx/Cr over time are shown in the graph below:

Mean Percent Change (±SE) in Urine N-Telopeptide/Cr (nmoL BCE/mmoL Cr)
Transformed From ln (Fraction of Baseline)
(Per-Protocol Approach)
(Pooled 035/037)



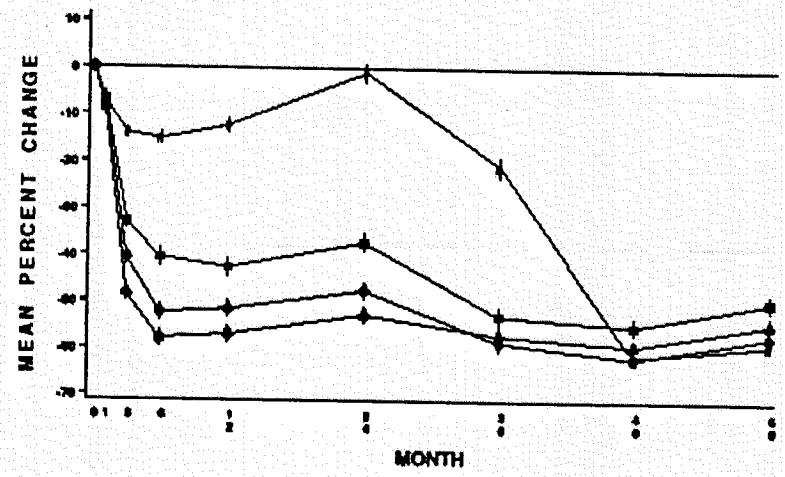
P=PLACEBO/10 MG
=5 MG
=10 MG
=20/5 MG

Data Source: [4.45.1]

For BSAP, a similar temporal pattern of change was observed. In the 5-, 10-, and 20-/5-mg groups, the mean percent changes from baseline at Months 48 and 60 were similar to that observed at Month 36. Significant decreases ($p<0.001$) of 59.0, 49.8, 57.3, and 54.5% were observed in the placebo/10-, 5-, 10-, and 20-/5-mg treatment groups, respectively. The decrease in the 10-mg group from baseline at Month 60 was significantly greater than that in the 5-mg group ($p<0.001$). Summary statistics by time point were similar for the per-protocol and intention-to-treat approaches and are in the Appendices [4.33.13 ff].

Changes in BSAP over time are shown in the figure below:

Mean Percent Change (±SE) in Serum Bone-Specific Alkaline Phosphatase (ng/mL)
Transformed From ln (Fraction of Baseline)
(Per-Protocol Approach)
(Pooled 035/037)



P=PLACEBO/10 MG
=5 MG
=10 MG
=20/5 MG

Data Source: [4.45.1]

Comments: The changes in bone resorption and formation markers are in keeping with the known action of alendronate. The data very nicely demonstrate the ability of alendronate to slow bone turnover, irrespective of the time at which the drug is introduced into the trial population. Complete statistics for these studies are presented in the NDA Appendices.

Mineral homeostasis:

Serum calcium concentrations, which at Month 36 were close to pre-treatment baseline levels, decreased minimally in all 4 treatment groups from Months 36 to 60. The geometric mean percent change in the 4 groups ranged from -0.6 to -2.0% and the change of -2.0, -1.0, and -1.1% in placebo/10-, 10-, and 20-/5-mg treatment groups were significant with $p<0.001$, $p<0.050$, and $p<0.010$, respectively. There was no significant difference between the 5- and 10-mg treatment groups over 5 years. Details of analysis of change from baseline (Months 24 and 36) at Month 60 and summary statistics are in Appendices [4.32.10 to 4.32.12] and [4.33.20 to 4.33.22].

There were statistically significant increases of 20 and 15% in serum PTH levels from Months 36 to 60 in the placebo/10- and 10-mg groups, respectively. These increases were similar to those observed in the

10-mg group from baseline to Month 24. While the geometric mean percent increase from baseline to Month 60 in the placebo/10-mg group was significant, the corresponding increase in the 10-mg group (7.6%) was not significant [data in Appendix 4.32.17]. Neither the percent change from baseline nor Month 36 were significant in the 5- and 20-/5-mg groups.

Comments: These changes were numerically small, transient, and clinically insignificant. By 60 months, there were certainly no clinically significant changes in mean PTH levels.

Assessment of 1,25-dihydroxyvitamin D was made for Protocol 035-10 only because levels were not determined at Months 48 and 60 in Protocol 037-10. At Month 36 the concentrations of 1,25-dihydroxyvitamin D were close to pretreatment baseline levels. These concentrations increased in all 4 treatment groups from Months 36 to 60. The geometric mean percent increase in the 4 groups ranged from 19.5 to 22.5% and all were significant. Details of analyses of changes over time and summary statistics are in Appendices [4.32.19- 4.32.21 and 4.33.29 - 4.33.31].

Serum phosphate levels declined by about 3-7% in all alendronate-treated groups, but not in placebo, during the initial 18 months of treatment and then returned to baseline by 36 months. The serum phosphate levels did not deviate significantly from original baseline during the two-year extension period.

Comments: Changes in major parameters of mineral homeostasis are mostly expected from known action of the drug, combined with secondary effects of perturbations in calcium and PTH. These changes are numerically small, transient, and clinically insignificant at Month 60.

Subgroup Analysis:

The sponsor also preformed an efficacy analysis of treatment effect for certain prespecified patient subgroups. This included percent change from baseline and Month 36 for lumbar spine BMD. Intention-to-treat summary statistics are provided for categorical and continuous subgroup variables (Appendices [4.34] and [4.35]). Renal insufficiency was defined as creatinine clearance (24-hour urine sample) less than 60 mL/min. The continuous variables included age, baseline lumbar spine BMD, and baseline NTx/Cr. A baseline age of 65 years was the cutoff point for the 2 subgroups. The subgroups were defined according to tertiles for lumbar spine BMD and NTx/Cr at baseline.

The most significant results of this analysis were that percent change in lumbar spine BMD from baseline at Month 60 was relatively higher in patients with age ≥65 years and for patients having urine creatinine clearance ≥60 mL/min for placebo/10-, 5-, 10-, and 20-/5-mg treatment groups. However, the percent

change of lumbar spine BMD from Months 36-60 was not different between the 2 subgroups based on age and renal status.

For subgroup analysis based on initial lumbar spine BMD, no apparent subgroup effect on percent change in BMD was observed in the 5-, 10-, or 20-/5-mg treatment groups. In the placebo/10-mg treatment group, patients belonging to the subgroup with lowest lumbar spine BMD at baseline had the highest percent increase at that site baseline and from Month 36 at Month 60 and vice versa.

8.1.1.4.3 Safety outcomes

As this extension study lacked a placebo control, the sponsor's safety analysis was based on evaluation of clinical and laboratory adverse experiences (AE's) and comparing these AE's across all 4 active treatment groups. The treatment groups were compared for the percent of patients reporting at least one AE, the percent with AE's within each body system, and the percent of patients with each specific AE. Patients who opted for open-label treatment with 10mg alendronate were not included in the analysis, and were analyzed separately. The data for these patients are provided in Appendix [4.49]. In addition, safety was assessed by analyzing changes in weight, blood pressure, and pulse rate for within- and between-group differences from baseline. The percent of patients exceeding predefined limits of change in laboratory variables were also determined and analyzed.

Clinical adverse experiences:

During Months 36 to 60, 78.1% of the 727 patients had clinical adverse experiences recorded. The sponsor has compared these with those that were recorded during the first 36 months. During that period, 89.4% (889 of the total sample of 994 patients) had clinical adverse experiences. The sponsor notes some of the pitfalls inherent in making these comparisons. For example, the periods of observation differed in duration (2 vs 3 years); also, not all patients participated in the 2-year extension study. It should also be noted that after Month 36 of the study, both the investigators and the patients were unblinded to whether patients were initially randomized to placebo or alendronate (but not to the alendronate dose).

During the extension period, 98 patients (13.5%) had adverse experiences that were considered serious. These included five deaths. Sixty-three patients (10.8, 6.9, 8.6, and 6.3% of the patients in the placebo/10-, 5-, 10-, and 20-/5-mg groups, respectively) had AE's that were considered possibly, probably, or definitely drug related by the investigators; none were serious. Nineteen patients discontinued the study due to a clinical adverse experience. Seven of the 19

patients discontinued the study due to clinical adverse experiences considered to be drug related by the investigators.

Comments: The sponsor defines a "drug-related adverse event" as one in which the investigator thought that the event might be related to study drug. This is a usual convention. However, after this point, the unmodified term "drug-related" assumes the legitimacy and import of objective truth. It would be more accurate to define the relationship of each adverse event to drug use as an interpretation or judgment call. Based on clinical data, the medical reviewer or reader may be able to decide whether there was any relationship between a given event and use of a drug.

According to table 56 in the NDA, and associated data, there was no difference among the 4 groups in the number of patients with one or more AE's, or with serious AE's. There was no difference, across groups, in the percent of patients who withdrew from study due to AE's. Across all groups, the percent of patients with serious AE's was about 15%. According to the investigators, none of these events was drug-related. Across all groups, the number of patients withdrawn for adverse experiences (about 1.4-3.5 %) or for serious AE's (1.4-2.1%) was the same. About 1% of patients withdrew from treatment because of "drug-related" AE's, and none (0%) withdrew because of "drug-related" serious AE's.

Overall data are provided in the table below:

Clinical Adverse Experience Summary—Patient Count (%)

Number (%) of patients:	PBO/ALN 10 mg (N=288)		ALN 5 mg (N=145)		ALN 10 mg (N=151)		ALN 20/5 mg (N=143)	
with one or more adverse experiences	227	(78.8)	112	(77.2)	118	(78.1)	111	(77.6)
with drug-related adverse experiences[1]	31	(10.8)	10	(6.9)	13	(8.6)	9	(6.3)
with serious adverse experiences	35	(12.2)	22	(15.2)	20	(13.2)	21	(14.7)
with serious drug-related adverse experiences[1]	0		0		0		0	
withdrawn from therapy due to an adverse experience	10	(3.5)	3	(2.1)	4	(2.6)	2	(1.4)
withdrawn from therapy due to a serious adverse experience	6	(2.1)	2	(1.4)	2	(1.3)	2	(1.4)
withdrawn from therapy due to a drug-related adverse experience[1]	4	(1.4)	1	(0.7)	2	(1.3)	0	
withdrawn from therapy due to a serious drug-related adverse experience[1]	0		0		0		0	
Patients who died	3	(1.0)	2	(1.4)	0		0	

This table does not include those adverse experiences that occurred during the first 3 years of treatment.
[1] Considered possibly, probably, or definitely drug related by the investigator.

Clinical adverse experiences by body system are presented below. The table shows the number of (double blind) patients in each treatment group having at least one AE in a given body system. Patients were counted more than once if AE's occurred in > 1 system, but not if there were multiple AE's in one system.

	PBO/ALN 10 mg (N=288)		ALN 5 mg (N=145)		ALN 10 mg (N=151)		ALN 20/5 mg (N=143)	
Body as a whole/site unspecified	59	(20.5)	20	(13.8)	33	(21.9)	29	(20.3)
Cardiovascular system disorders	45	(15.6)	26	(17.9)	28	(18.5)	22	(15.4)
Digestive system disorders	87	(30.2)	40	(27.6)	52	(34.4)	32	(22.4)
Endocrine disorders	3	(1.0)	3	(2.1)	2	(1.3)	3	(2.1)
Hemic and lymphatic disorders	4	(1.4)	7	(4.8)	3	(2.0)	1	(0.7)
Metabolic, nutritional, immune disorder	9	(3.1)	8	(5.5)	12	(7.9)	8	(5.6)
Musculoskeletal disorders	131	(45.5)	65	(44.8)	73	(48.3)	75	(52.4)
Nervous system and psychiatric disorder	61	(21.2)	37	(25.5)	34	(22.5)	26	(18.2)
Respiratory system disorders	97	(33.7)	52	(35.9)	63	(41.7)	40	(28.0)
Skin and skin appendage disorders	56	(19.4)	36	(24.8)	30	(19.9)	30	(21.0)
Special sense disorders	36	(12.5)	16	(11.0)	13	(8.6)	15	(10.5)
Urogenital system disorders	46	(16.0)	29	(20.0)	20	(13.2)	20	(14.0)

This table does not include those adverse experiences that occurred during the first 3 years of treatment.

Comments: The 5- and 10-mg groups did not differ in % of patients experiencing clinical AE's in all body systems.

Adverse experiences that occurred during the extension study with an incidence of at least 5% in one or more treatment groups are the table below. Data from the first 36 months are not given here. Patients were counted only once if they had multiple episodes of the same AE but more than once if they had more than one type of AE. A significant difference was observed between the groups taking 5 and 10 mg during Years 4 and 5 for abdominal pain (p=0.027) and sinusitis (p=0.052). No other statistical differences were found between the 5- and 10mg treatment groups in most commonly reported clinical AE's.

Most Common Clinical Adverse Experiences Reported in ≥5% of Patients—Patient Count (%)

	PBO/ALN 10 mg (N=288)		ALN 5 mg (N=145)		ALN 10 mg (N=151)		ALN 20/5 mg (N=143)	
Number (%) of patients with one or more clinical adverse experiences	227	(78.8)	112	(77.2)	118	(78.1)	111	(77.6)
Body as a Whole/Site Unspecified								
Pain, abdominal	14	(4.9)	4	(2.8)	14	(9.3)	8	(5.6)
Digestive System Disorders								
Diarrhea	9	(3.1)	10	(6.9)	7	(4.6)	5	(3.5)
Dyspepsia	15	(5.2)	3	(2.1)	7	(4.6)	6	(4.2)
Musculoskeletal Disorders								
Pain, back	33	(11.5)	18	(12.4)	25	(16.6)	15	(10.5)
Pain, hip	8	(2.8)	9	(6.2)	8	(5.3)	8	(5.6)
Pain, leg	9	(3.1)	5	(3.4)	7	(4.6)	8	(5.6)
Pain, neck	10	(3.5)	9	(6.2)	3	(2.0)	4	(2.8)
Pain, shoulder	10	(3.5)	4	(2.8)	7	(4.6)	11	(7.7)
Nervous System and Psychiatric Disorders								
Headache	24	(8.3)	16	(11.0)	15	(9.9)	8	(5.6)
Respiratory System Disorders								
Bronchitis	19	(6.6)	16	(11.0)	15	(9.9)	6	(4.2)
Infection, respiratory, upper	44	(15.3)	19	(13.1)	25	(16.6)	16	(11.2)
Influenza	9	(3.1)	9	(6.2)	9	(6.0)	7	(4.9)
Sinusitis	12	(4.2)	3	(2.1)	11	(7.3)	8	(5.6)
Urogenital System Disorders								
Infection, urinary tract	22	(7.6)	15	(10.3)	7	(4.6)	8	(5.6)

Although a patient may have had two or more adverse experiences, the patient is counted only once in "Number (%) of patients with one or more adverse experiences."

This table does not include those adverse experiences that occurred during the first 3 years of treatment.

The most common drug-related (ie.,judged by investigator to be drug-related) AE's were digestive system disorders. The occurrence of AE's in this category was never more than 2.1% in any treatment group. There were no dose-related difference in occurrence of any AE's that were considered to be drug-related. During the two-year extension trial (Months 36-60), 98 patients (13.5%) had one or more serious AE, while 154 patients (15.5%) had one or more such events during the first 3 years of treatment. Thirty-five (12.2%), 22 (15.2%), 20 (13.2%), and 21 (14.7%) patients had a serious AE in the placebo/10-, 5-, 10-, and 20-/5-mg treatment groups, respectively. None of the serious adverse experiences were considered drug related by the investigator. The 5 deaths, 3 in the placebo/10-mg group and 2 in the 5-mg group, were not considered drug related [4.41]. There were no clinically meaningful differences between the U.S. and multinational cohorts in the report of serious clinical adverse experiences.

The following is a complete listing of serious AE's that occurred during the study as appear in Table 63 in the NDA:

Serious Clinical Adverse Experiences

Study Number	AN	Sex/Age	Drug/Total Daily Dosage at Time of AE	Study Day	Adverse Experience	Duration	Intensity	Drug Relation	Therapy Discontinuation
Placebo/Alendronate 10 mg									
035002	0204	F/71	D/10 mg	1166	Neoplasm, skin, malignant	66 days	Mild	Def not	No
			Off D 1 day/10 mg	1790	Pneumonia	29 days	Moderate	Def not	No
035003	0178	F/62	D/10 mg	1358	Neoplasm, skin, malignant	22 days	Mild	Prob not	No
			D/10 mg	1469	Neoplasm, malignant	1 day	Mild	Prob not	No
			D/10 mg	1807	Melanoma	28 days	Mild	Prob not	No
035004	0078	F/76	Off P 22 days/1 Tab	1099	Fracture, hip, rt	2 days	Severe	Def not	No
			D/10 mg	1415	Fracture, pelvis	195 days	Severe	Def not	No
035004	0085	F/60	D/10 mg	1168	Neoplasm, skin, malignant	20 days	Mild	Def not	No
			D/10 mg	1412	Neoplasm, skin, malignant	1 day	Mild	Def not	No
			D/10 mg	1433	Melanoma	1 day	Mild	Def not	No
035005	0102	F/77	D/10 mg	1140	Implant, breast, complication	16 days	Moderate	Def not	No
035005	0108	F/77	D/10 mg	1281	Death	1 day	Severe	Def not	NA
			D/10 mg	1281	Trauma	1 day	Severe	Def not	Yes
035005	0119	F/61	Off D 1 day/10 mg	1812	Laceration	14 days	Severe	Def not	No
035005	0120	F/66	D/10 mg	1424	Myocardial infarction	39 days	Moderate	Prob not	No
035008	0017	F/78	D/10 mg	1722	Fracture, hip, rt	5 days	Severe	Def not	No
035011	0424	F/68	D/10 mg	1135	Arteritis	9 days	Severe	Prob not	No
035011	0434	F/63	Off D 1 day/10 mg	1698	Dizziness	3 days	Severe	Prob not	No
			Off D 1 day/10 mg	1706	Dizziness	5 days	Severe	Prob not	No
035012	0456	F/60	D/10 mg	1677	Cholelithiasis	22 days	Severe	Def not	No
035012	0467	F/71	Off D 2 days/10 mg	1581	Osteoarthritis, hip	6 hours	Severe	Def not	No
035013	0411	F/69	D/10 mg	1750	Pain, chest	4 days	Severe	Prob not	No
			D/10 mg	1750	Dyspnea	4 days	Severe	Prob not	No
035013	0416	F/54	D/10 mg	1794	Neoplasm, ovary	36 days	Severe	Def not	No

Study Number	AN	Sex/Age	Drug/Total Daily Dosage at Time of AE	Study Day	Adverse Experience	Duration	Intensity	Drug Relation	Therapy Discontinuation
Placebo/Alendronate 10 mg (Cont.)									
035015	0305	F/65	Off D 1 day/10 mg	1809	Appendicitis w/peritonitis	1 day	Severe	Def not	No
			Off D 1 day/10 mg	1820	Infection, postoperative	6 days	Severe	Def not	No
035016	0370	F/72	D/10 mg	1687	Degeneration, macular	133 days	Severe	Prob not	No
035016	0383	F/78	D/10 mg	1750	Prolapse, rectal	54 days	Moderate	Def not	No
037001	2103	F/73	D/10 mg	1464	CVA	9 days	Severe	Def not	No
037001	2113	F/71	Off D 1 day/10 mg	1589	Septicemia	30 days	Severe	Def not	No
			Off D 1 day/10 mg	1589	Meningitis	30 days	Severe	Def not	No
			D/10 mg	1765	Fracture, femur, rt	38 days	Severe	Def not	No
037004	2293	F/65	D/10 mg	1186	Transient ischemic attack	15 days	Mild	Def not	No
037004	2294	F/75	D/10 mg	1162	Cataract, senile	NA hr	Mild	Def not	No
037004	2514	F/52	D/10 mg	1582	Cartilage disorders	31 days	Mild	Def not	No
037005	2458	F/66	D/10 mg	1661	Neoplasm, breast, malignant	15 days	Severe	Def not	Yes
037006	2412	F/73	D/10 mg	1660	Pneumonia	15 days	Severe	Def not	No
037010	2363	F/74	D/10 mg	1718	Neoplasm, breast, malignant	4 days	Severe	Def not	Yes
037011	2006	F/61	D/10 mg	1216	Neoplasm, skin, malignant	57 days	Mild	Prob not	No
037013	2176	F/61	Off D 19 days/10 mg	1845	Encephalopathy	29 days	Moderate	Def not	No
037013	2450	F/58	Off D 115 days/10 mg	1810	Neoplasm, intestinal, malignant	2 days	Severe	Def not	No
037014	2561	F/65	Off D 1 day/10 mg	1294	Claudication, intermittent	2 days	Moderate	Prob not	No
			Off D 1 day/10 mg	1294	Ulcer, skin	9 days	Mild	Prob not	No
			D/10 mg	1329	Lymphocele	56 days	Moderate	Def not	No
037014	2565	F/62	Off D 1 day/10 mg	1261	Colitis	4 days	Severe	Def not	No
			Off D 5 days/10 mg	1265	Colitis	78 days	Severe	Def not	Yes