Bone histomorphometry data were analyzed according to pre-specified plan. Summary statistics were used to calculate specific morphometric parameters and for between-group comparisons.

The proportions of women who dropped out of the study were calculated for each treatment. Between-group comparisons were made for the proportions of study drop-outs.

For continuous outcomes, ANOVA techniques were used to analyze BMD, biochemical bone turnover and metabolism parameters, vital signs, and certain laboratory safety parameters. Further details are provided in the NDA submission.

For dichotomous or discrete data (e.g., the proportion of patients with a given adverse event), comparisons among the treatment groups were performed using Fisher's exact test. Alternatively, other categorical data analysis techniques were used when appropriate.

The sponsor performed both ITT and per-protocol analyses.
The ITT populations included all patients who had a baseline and at least one on-treatment measurement. Missing data were replaced with data observed at the last on-treatment time point. For biochemical marker analyses, no data were carried forward.

For the BMD analyses, results from the per-protocol approach were compared with those from the ITT method. No data were carried forward in this analysis. If there were differences in conclusions from per-protocol vs ITT analyses, additional analyses were planned to attempt to discover the sources of disagreement.

The sponsor includes a power analysis, using a hypothetical 2% between-group difference in the primary comparison (ALN + CE vs CE alone) in mean percent lumbar spine BMD increase at 2 years. With a sample size approximately N=140 in each of the 2 groups at study end, there was 95% power to detect a 2% difference between mean % increases from baseline (details in Table 3 of the NDA).

8.3.2 Results

8.3.2.1 Populations enrolled/analyzed

Four hundred twenty-five women were randomized into the trial. The mean age was 61.3 years. The sponsor provides a table summarizing baseline characteristics of

this cohort. There were no significant differences among the 4 treatment groups. The PBO group had slightly greater mean body weight and BMI.

Characteristic	PBO (N=50)		ALN (N=92)		CE (N=143)		ALN+CE (N=140)	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Estimated daily dietary calcium intake (mg/day)*	50	999.4 (599.2)	91	966.1 (543.9)	142	902.5 (567.9)	138	1056.6 (641.3)
Weight (kg)	50	71.0 (15.3)	92	65.8 (12.1)	143	68.2 (13.3)	140	68.3 (11.0)
Height (mm)	50	1596.2 (55.9)	92	1591.5 (61.8)	143	1602.0 (58.9)	140	1604.2 (62.6)
Body mass index (kg/m^2)	50	27.9 (6.3)	92	26.0 (4.5)	143	26.6 (5.1)	140	26.6 (4.4)
Age (years)	50	61.5 (9.1)	92	61.0 (8.0)	143	60.5 (7.9)	140	62.1 (7.8)
Years since menopause	50	23.4 (11.0)	92	21.6 (7.8)	142	20.8 (8.0)	140	22.0 (8.8)

* Including calcium supplements, if any.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

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With one exception, there were no significant differences for categorical parameters, including use of cigarettes or ethanol, prior estrogen usage, family history of osteoporosis, or oophorectomy status. A higher proportion (58% vs about 42% for the other 3 groups) of PBO patients reported prior use of estrogen >30 days prior to randomization. There were no significant differences across groups in age distribution. The decade with the highest proportion of subjects was 60-69 (about 41% of each group).

There were no significant differences, across groups, in baseline BMD at any of the 7 anatomic sites (lumbar spine, total hip, femoral neck, trochanter, intertrochanteric, Ward's triangle, or total body). Details are provided in Table 9. Similarly, there were no differences, across the 4 groups in baseline biochemical efficacy parameters (BSAP, total AP, Ca, P, urine NTx/Cr).

There were no clinically meaningful differences, across groups, in secondary diagnoses, with two exceptions. There were more endocrine disorders in PBO vs ALN + CE (34% vs 15%). There were fewer musculoskeletal disorders in CE (42.5%) vs PBO (82.0%). A complete listing of secondary diagnoses is given in Table 11.

Comments: The ALN group seemed to have less arthritis, and the PBO group had more than the other groups. There was also more back pain in the PBO group. Examination of Table 11 shows no systematic difference between CE and ALN + CE, the primary comparison groups.

There were also no between-group differences in prior drug therapies or daily calcium intake. Across all groups, about 55% had an estimated daily calcium intake that was <1000 mg. The mean daily estimated intake for these individuals

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was about 600 mg. There were no significant between-group differences in vitamin intake.

Patient accounting:

Of the 425 who entered, 320 (75.3%) completed 24 months of treatment. The following table summarized patient accounting in this trial:

	Total	PBO	ALN	CE	ALN+CE
ENTERED:	425	50	92	143	140
Age range (years)	42 to 82	44 to 76	46 to 82	42 to 77	44 to 79
COMPLETED STUDY:	320	34	68	108	110
DISCONTINUED FROM STUDY:	105	16	24	35	30
Clinical adverse experience	38	5	6	14	13
Laboratory adverse experience	1	0	0	1	0
Lost to follow-up	17	4	5	5	3
Patient withdrew consent	40	7	10	12	11
Protocol deviation	9	0	3	3	3

PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

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For the primary efficacy analysis, lumbar spine BMD at Month 24, the number of subjects included/excluded in each group is shown in the table below:

	Total (N=425)	PBO (N=50)	ALN (N=92)	CE (N=143)	ALN+CE (N=140)
Total Included In:					
Intention-to-treat analysis	395	46	87	130	132
Per-protocol analysis	276	29	60	91	96
Total Excluded From:					
Intention-to-treat analysis[1]	30	4	5	13	8
Per-protocol analysis	149	21	32	52	44

[1] These patients were excluded from the intention-to-treat analysis for missing baseline and/or at least one posttreatment measurement.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

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Thus 149 were excluded from the per-protocol analysis and 30 were excluded from the ITT analysis. A subject was excluded from the ITT analysis if there were no data at baseline or if there was not at least one post-treatment measurement. Patients were excluded from the per-protocol analysis for a number of reasons, including: protocol violations, clinical or laboratory AE's leading to discontinuation, no data in the relative day range, no baseline data, withdrawal of consent, protocol deviation (discontinued, no data), lost to follow-up, or violation of off-drug rule (>25% of doses missed). A table summarizing the reasons for exclusions is provided by the sponsor. There were no significant between-group differences in reasons for exclusion from the per-protocol analysis of lumber spine BMD (Table 17 of the NDA)

8.3.2.2 Efficacy

Bone Mineral Density:

The primary efficacy outcome variable was % change in spinal BMD from baseline at Month 24, using an ITT approach. Key secondary endpoints were BMD changes from baseline, over the same period, at other skeletal sites. Results for each site are described below. For each ITT analysis, the sponsor performed a per-protocol analysis as well. Complete results of the per-protocol analysis are included in the NDA.

Main Result: The PBO group experienced a nonsignificant (0.6%) decrease in BMD at this site. All 3 other treatment groups had an increase in BMD, relative to baseline and PBO ($p \leq 0.001$ and $p < 0.001$, respectively). The mean increase in the ALN + CE group was statistically significantly ($p < 0.001$) greater than the increases observed in the CE or ALN groups. There was no significant difference between ALN and CE in mean % change in BMD ($p = 0.995$).

For ALN, CE, and ALN + CE, the mean increases from baseline were 6.00, 5.99, and 8.26%, respectively. There was no significant treatment-by-stratum (prior estrogen use) or treatment-by-center interaction. There were no significant treatment-by center or treatment-by-stratum interactions at any of the skeletal sites studied in this trial.

Results of the per-protocol analysis were essentially the same as for ITT, with significant ($p < 0.001$) BMD increases of 6.75, 6.70, and 9.05% ALN, CE, and ALN + CE groups, respectively.

The mean % change from baseline in lumbar spine BMD (ITT) is shown in the figure below:

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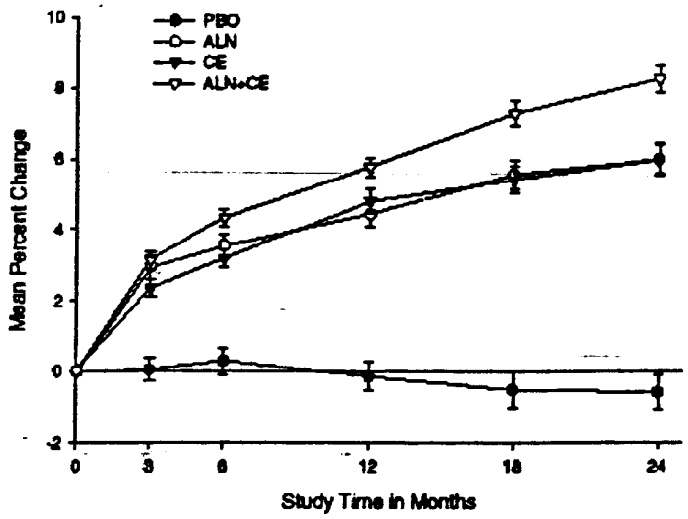

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Data for changes in lumbar spine BMD are summarized in the table below:

Treatment	N	Observed Mean (g/cm²)		Percent Change From Baseline at Month 24						
						Adjusted		Pairwise Comparison p-Value		
		Baseline	Month 24	Mean	SD	Mean	95% CI	ALN	CE	ALN+CE
PBO	46	0.77	0.77	-0.60	3.36	-0.73	(-1.63, 0.17)	<0.001	<0.001	<0.001
ALN	87	0.77	0.82	6.00***	4.27	5.85	(5.19, 6.51)		0.995	<0.001
CE	130	0.75	0.80	5.99***	4.64	5.86	(5.31, 6.40)			<0.001
ALN+CE	132	0.77	0.83	8.26***	4.43	8.13	(7.58, 8.67)			

Within-treatment test of mean = 0 ***: p≤0.001 **: p≤0.010 *: p≤0.050.
p-Value for consistency of treatment across centers: 0.845.
p-Value for consistency of treatment across strata based on prior use of estrogen: 0.968.
Overall treatment effect p-value: <0.001.
Pooled SD: 4.31.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

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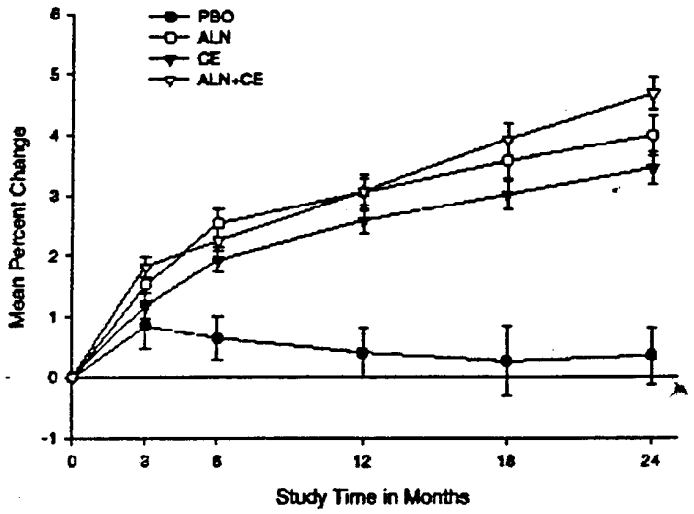
Total Hip BMD:

All groups except the PBO had a significant increase in total hip BMD from baseline over the 24 months. The ALN + CE group had a significantly (p=0.001) greater increase in total hip BMD, compared with the CE group. There was no

significant difference between ALN and CE (p=0.207), or between ALN and ALN + CE (p=0.110) in this parameter. The groups ALN, CE, and ALN + CE had significant (p<0.001) increases from baseline of 3.99, 3.45, and 4.66%, respectively. For all 3 active-treatment groups the increases from baseline were significantly greater than the mean increase (0.35%,ns from baseline) in PBO (p<0.001).

Per-protocol results were similar to ITT, except for a significant (p=0.046) difference between the ALN + CE and ALN.

Results for the ITT analysis for Total Hip BMD are shown in the figure and table below:



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Treatment	N	Observed Mean (g/cm²)		Percent Change From Baseline at Month 24						
		Baseline	Month 24	Mean	SD	Adjusted Mean	95% CI	Pairwise Comparison p-Value ALN	CE	ALN+CE
PBO	45	0.77	0.77	0.35	3.22	0.29	(-0.36, 0.94)	<0.001	<0.001	<0.001
ALN	86	0.75	0.78	3.99***	3.03	3.90	(3.43, 4.37)		0.207	0.110
CE	130	0.73	0.76	3.45***	3.17	3.36	(2.97, 3.75)			0.001
ALN+CE	131	0.75	0.78	4.66***	3.05	4.58	(4.19, 4.97)			

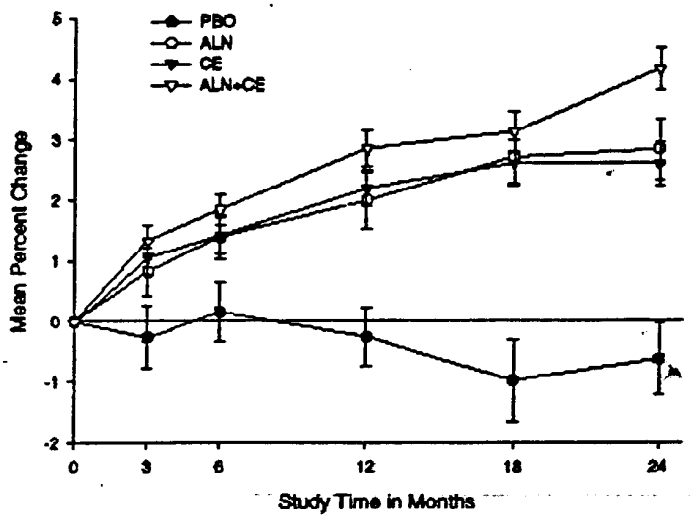
Within-treatment test of mean = 0 ***: p≤0.001 **: p≤0.010 *: p≤0.050.
p-Value for consistency of treatment across centers: 0.890.
p-Value for consistency of treatment across strata based on prior estrogen use: 0.856.
Overall treatment effect p-value: <0.001.
Pooled SD: 3.07.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

Femoral Neck BMD:

At the femoral neck, the PBO group lost a nonsignificant 0.62% BMD over 24 months. The other 3 groups, ALN, CE, ALN + CE, had significant ($p<0.001$) increases of 2.86, 2.62, and 4.17%, respectively; all 3 of these values were statistically significantly greater ($p<0.001$) than PBO.

Main result: ALN + CE had statistically significantly greater increases than either ALN ($p=0.022$) or CE ($p=0.003$). There was no significant difference between ALN and CE ($p=0.685$).

Per-protocol results were essentially the same. ITT results for the femoral neck are shown in the figure and table below:



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Treatment	N	Observed Mean (g/cm²)		Percent Change From Baseline at Month 24						
		Baseline	Month 24	Mean	SD	Adjusted Mean	95% CI	Pairwise Comparison p-Value: ALN	CE	ALN+CE
PBO	46	0.66	0.66	-0.62	4.11	-0.66	(-1.53, 0.22)	<0.001	<0.001	<0.001
ALN	87	0.63	0.65	2.86***	4.72	2.88	(2.24, 3.52)		0.685	0.022
CE	130	0.62	0.64	2.62***	4.01	2.64	(2.11, 3.18)			0.003
ALN+CE	132	0.63	0.66	4.17***	3.99	4.21	(3.68, 4.74)			

Within-treatment test of mean = 0 ***: $p\leq0.001$ **: $p\leq0.010$ *: $p\leq0.050$.
p-Value for consistency of treatment across centers: 0.606.
p-Value for consistency of treatment across strata based on prior use of estrogen: 0.934.
Overall treatment effect p-value: <0.001.
Pooled SD: 4.18.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

Trochanter BMD:

At the trochanter, the PBO group group gained 0.49% in BMD over 2 years (ns). In the ALN, CE, or ALN + CE groups, there were significant (p<0.001) increases from baseline of 5.89, 4.26, and 6.53%, respectively. All 3 of these groups gained significantly more than PBO (p<0.001).

Main result: ALN + CE had a significantly greater increase (p<0.001) than did CE alone. ALN + CE did not differ significantly in BMD changes from ALN (p=0.260). The mean BMD increase in the ALN group was statistically significantly greater than in CE (p=0.004).

Per-protocol results were similar to the ITT results, except that the difference between ALN and CE was not statistically significant (p=0.071).

The ITT results for trochanter BMD are summarized in the table below:

Treatment	N	Observed Mean (g/cm²)		Percent Change From Baseline at Month 24						
		Baseline	Month 24	Mean	SD	Adjusted Mean	95% CI	Pairwise Comparison p-Value		
								ALN	CE	ALN+CE
PBO	46	0.56	0.57	0.49	3.80	0.62	(-0.23, 1.47)	<0.001	<0.001	<0.001
ALN	87	0.55	0.59	5.89***	4.39	5.93	(5.31, 6.55)		0.004	0.260
CE	130	0.54	0.57	4.26***	3.88	4.30	(3.78, 4.82)			<0.001
ALN+CE	132	0.55	0.59	6.53***	4.11	6.56	(6.05, 7.08)			

Within-treatment test of mean = 0 ***: p≤0.001 **: p≤0.010 *: p≤0.050.
p-Value for consistency of treatment across centers: 0.938.
p-Value for consistency of treatment across strata based on prior use of estrogen: 0.592.
Overall treatment effect p-value: <0.001.
Pooled SD: 4.07.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

BMD in intertrochanteric region:

The PBO group had a nonsignificant gain of 0.05% in BMD at this site over the 24 months. The ALN, CE, and ALN + CE groups all had significant (p 0.001) BMD increases of 3.28, 3.26, and 4.16%, respectively, and the increases in all 3 of these groups were significantly different from PBO (p<0.001). ALN + CE had a significantly greater increase than did CE (p=0.030). ALN + CE and ALN did not differ significantly (p=0.062), nor did ALN and CE (p=0.939). Per-protocol results were essentially the same.

BMD at Ward's triangle:

The sponsor used non-parametric methods to analyze data at this anatomic site, because normality assumptions were violated according to the (pre-defined) Shapiro-Wilk test (p=0.001).

All 3 active treatment groups showed significant (p<0.010) BMD increases at 24 months. ALN + CE had a significantly (p<0.001) greater increase in BMD than either PBO, ALN, or CE. ALN did not differ significantly from PBO or CE; however, CE increased BMD significantly, (p=0.041), compared to PBO. The data for BMD changes at Ward's triangle are shown in the table below:

Treatment	N	Observed Median (g/cm²)		Percent Change From Baseline			Pairwise Comparison p-Value		
		Baseline	Month 24	Median	SE (Median)	Range	ALN	CE	ALN+CE
PBO	46	0.45	0.46	0.13	1.53	(-13.15, 43.54)	0.185	0.041	<0.001
ALN	87	0.45	0.46	3.49**	0.84	(-15.47, 22.00)		0.423	<0.001
CE	130	0.44	0.46	3.54**	0.74	(-12.17, 27.00)			<0.001
ALN+CE	132	0.45	0.48	7.47**	0.82	(-10.96, 32.15)			

Within-treatment test of median = 0 ***: p≤0.001 **: p≤0.010 *: p≤0.050.
p-Value for consistency of treatment across centers: 0.536.
p-Value for consistency of treatment across strata based on prior estrogen use: 0.193.
Overall treatment effect p-value: <0.001.
Pooled SD: 0.97.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

Total body BMD:

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For technical reasons, there were fewer subjects with total body BMD results than for the other skeletal sites.

In addition, the normality assumptions on %change in total body BMD were violated (Shapiro-Wilk test, p<0.001), and a nonparametric rank test method was employed. Results from this analysis appear in the sponsor's table below. Results of a parametric analysis are included in the NDA submission.

Main results: For total body BMD, ALN, CE, and ALN + CE all had statistically significant (p<0.010) increases in BMD at 24 months. All 3 of these active-treatment groups had greater increases than did PBO (p≤0.006). There were no significant differences in BMD changes among the 3 active-treatment groups (p≥0.219). Results from the parametric analysis differed from the nonparametric, in that ALN did not differ from PBO (p=0.120).

Nonparametric analysis of % change in total body BMD at month 24 is shown in the following table:

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TOTAL BODY BMD

Treatment	N	Observed Median (g/cm²)		Percent Change From Baseline			Pairwise Comparison p-Value		
		Baseline	Month 24	Median	SE (Median)	Range	ALN	CE	ALN+CE
PBO	33	0.97	0.98	0.06	0.42	(-7.29, 22.63)	0.006	<0.001	<0.001
ALN	66	0.96	0.97	1.33**	0.36	(-2.73, 14.52)		0.354	0.219
CE	95	0.97	0.99	1.74**	0.34	(-10.52, 21.59)			0.748
ALN+CE	101	0.96	0.98	2.03**	0.27	(-3.84, 16.27)			

Within-treatment test of median = 0 ***: p≤0.001 **: p≤0.010 *: p≤0.050.
p-Value for consistency of treatment across centers: 0.600.
p-Value for consistency of treatment across strata based on prior estrogen use: 0.043.
Overall treatment effect p-value: <0.001.
Pooled SD: 0.85.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

Biochemical efficacy:

Based on the known pharmacology of bisphosphonates, the anticipated changes are decreases in calcium, phosphate, NTx, and BSAP, and increases in PTH and 1,25-dihydroxyvitamin D.

A per-protocol approach was used to analyze changes in biochemical markers from baseline at 24 months.

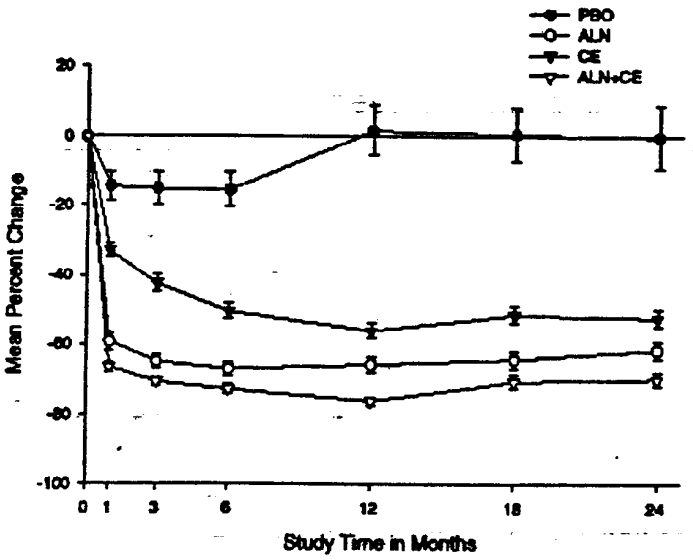
Main results: For NTx/Cr and BSAP, there were significant declines in all 3 active-treatment groups, with the greatest decline in ALN+CE.

For urinary NTx/Cr, the excretion of this marker of bone resorption reached a nadir at 6 months in all three active-treatment groups (ALN, CE, and ALN + CE). The PBO group had a nonsignificant decrease of 0.21% by Month 24. ALN, CE, and ALN + CE all had significant decreases relative to both baseline ($p<0.001$) and PBO ($p<0.001$) at Month 24 (decreases were 61.44, 52.20, and 69.69%, for ALN, CE, and ALN + CE, respectively). ALN + CE differed significantly from both ALN ($p=0.005$) and CE ($p<0.001$). ALN also differed significantly from CE ($p=0.009$).

In the biochemical studies, there were no significant treatment-by-center or treatment-by-stratum interaction.

Changes in NTx/Cr over time (mean % change) in the 4 groups are graphed below:

NTx?Cr



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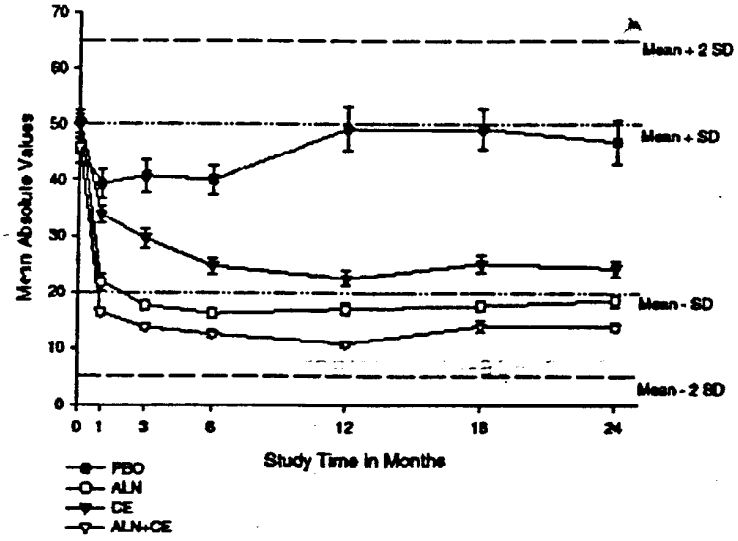
And in the following graph are depicted the mean changes in absolute values for NTx/Cr. The mean ± 1 and 2 SD reference values for premenopausal women are included in the figure.



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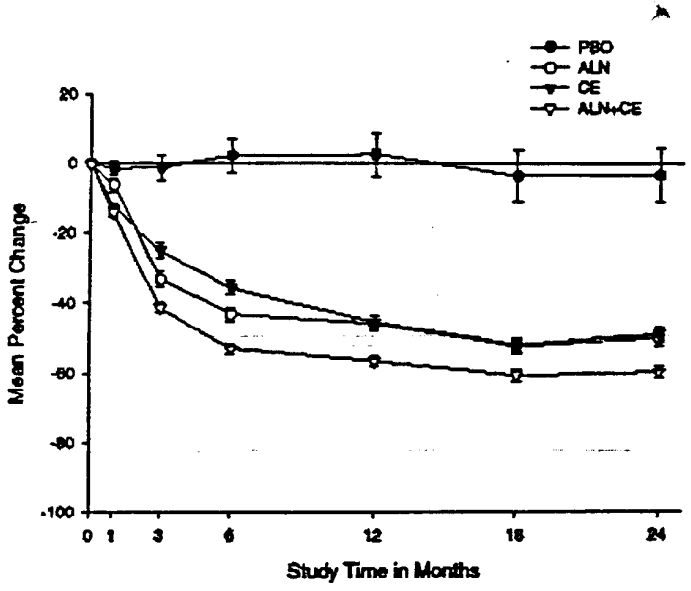
Note: The reference ranges depicted here (mean ±1 SD, and mean ±2 SD) are for premenopausal women.

These data are summarized in the following table:

Treatment	N	Observed Mean (nmol BCE/mmol Creatinine)		Percent Change From Baseline at Month 24			
					Pairwise Comparison p-Value		
		Baseline	Month 24	Mean[†]	ALN	CE	ALN+CE
PBO	28	48.12	46.92	-0.21	<0.001	<0.001	<0.001
ALN	56	49.28	18.65	-61.44***		0.009	0.005
CE	86	50.21	24.44	-52.20***			<0.001
ALN+CE	94	45.70	13.89	-69.69***			

[†] Transformed from ln (fraction of baseline).
Within-treatment test of mean = 0 ***: p≤0.001 **: p≤0.010 *: p≤0.050.
p-Value for consistency of treatment across centers: 0.958.
p-Value for consistency of treatment across strata based on prior use of estrogen: 0.447.
Overall treatment effect p-value <0.001.
Pooled SD: 0.50.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

For BSAP, the 3 active treatment groups significantly decreased levels of this bone formation marker (relative to both baseline and to PBO, p≤0.001) throughout the 24 months. The PBO group showed a nonsignificant decrease of 3.27% during this period. For the 3 active-treatment groups, ALN, CE, and ALN + CE, the decreases were 50.05, 49.09, and 59.72%, respectively. ALN + CE differed significantly from both ALN (p=0.002) and CE (p<0.001), but there was no difference between ALN and CE. The percent and absolute changes are depicted in the following two figures:



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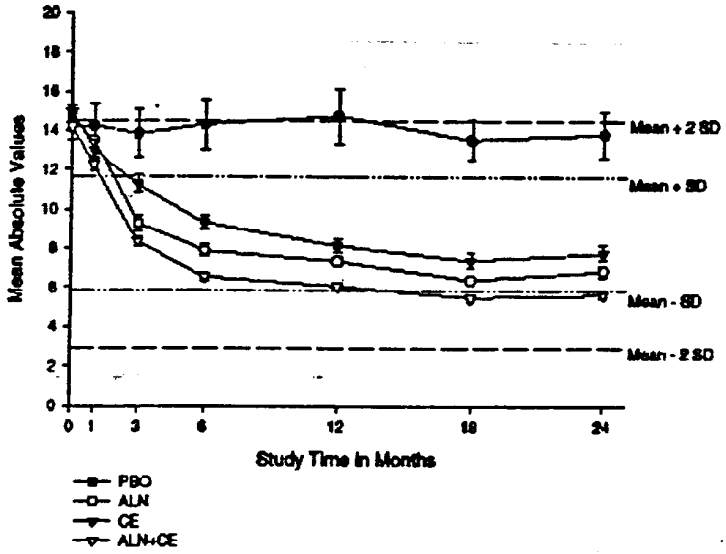
BSAP



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The data for BSAP are summarized in the table below:

Treatment	N	Observed Mean (ng/mL)		Percent Change From Baseline at Month 24			
					Pairwise Comparison p-Value		
		Baseline	Month 24	Mean*	ALN	CE	ALN+CE
PBO	27	13.55	13.22	-3.27	<0.001	<0.001	<0.001
ALN	59	13.73	6.88	-50.05***		0.649	0.002
CE	88	14.35	7.46	-49.09***			<0.001
ALN+CE	95	13.73	5.67	-59.72***			

* Transformed from ln (fraction of baseline).
Within-treatment test of mean = 0 ***: p≤0.001 **: p≤0.010 *: p≤0.050.
p-Value for consistency of treatment across centers: 0.649.
p-Value for consistency of treatment across strata based on prior use of estrogen: 0.944.
Overall treatment effect p-value <0.001.
Pooled SD: 0.39.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

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Total serum alkaline phosphatase: Levels of this enzyme followed a similar pattern to that of BSAP. While subjects in the PBO group had a small nonsignificant increase in alkaline phosphatase (2.76%), all three active-treatment groups had decreases of 25.34, 22.30, and 31.13%, for ALN, CE, and ALN + CE, respectively. ALN + CE differed significantly from both ALN (p=0.012) and CE (p<0.001). However, there was no significant difference between ALN and CE.

Comments: The data convincingly demonstrate that the combination ALN + CE suppress markers of formation and resorption to a greater extent than is achieved with either agent alone. These changes are certainly in accord with the BMD changes. However, there remain long-term safety concerns associated with this degree of suppression. In a following section, the results of the histomorphometry sub-study are reviewed. The histomorphometry data suggest a more profound local suppression of bone remodeling than is demonstrated by the marker data. This issue is discussed further in both the *safety* and *integrated safety* sections of this review.

Calcium and phosphorus:

All three active-treatment groups, ALN, CE, and ALN + CE, had small declines in average serum calcium levels from Month 3 onward. The declines in calcium are consistent with the mechanism of action of bisphosphonates. The small decline in total calcium in the groups receiving CE is in accord with prior literature on the effects of estrogen replacement on total and ionized calcium. The reason for the decline in the PBO group at 24 months is unclear; thus it is difficult to draw conclusions regarding the causes of these changes in any of the treatment groups. At Month 24, the declines were ($p<0.001$ for all 4 groups) 2.17, 2.81, 3.69, and 4.12% in PBO, ALN, CE, and ALN + CE, respectively. Inter-group differences were small; the statistical significance of each of these comparisons is given in the table below.

CHANGES IN SERUM CALCIUM LEVELS: BASELINE-24 MONTHS

Treatment	N	Observed Mean (mg/dL)		Percent Change From Baseline at Month 24			
					Pairwise Comparison p-Value		
		Baseline	Month 24	Mean[1]	ALN	CE	ALN+CE
PBO	28	9.37	9.17	-2.17***	0.324	0.036	0.006
ALN	61	9.38	9.12	-2.81***		0.169	0.024
CE	91	9.37	9.03	-3.69***			0.327
ALN+CE	97	9.41	9.02	-4.12***			

[1] Transformed from ln (fraction of baseline).
Within-treatment test of mean = 0 ***: p≤0.001 **: p≤0.010 *: p≤0.050.
p-Value for consistency of treatment across centers: 0.039.
p-Value for consistency of treatment across strata based on prior use of estrogen: 0.342.
Overall treatment effect p-value 0.016.
Pooled SD: 0.03.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

Serum Phosphate:

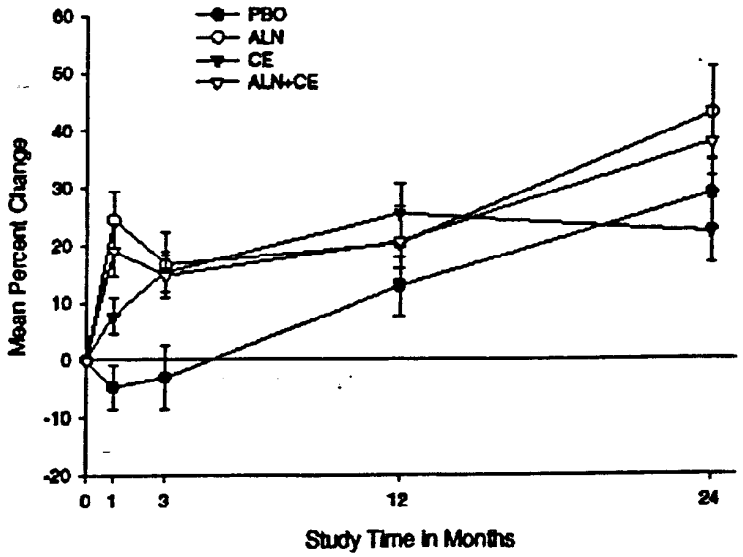
The PBO group had a significant ($p<0.010$) decrease in phosphate of 7.88% by Month 24. ALN, CE, and ALN + CE also had significant ($p<0.001$) decreases of 7.31, 8.11, and 9.73%, respectively, during this period. The serum phosphate fell more rapidly in the 3 active-treatment groups than in PBO, where the decline took place in the last half of the trial. The reasons for the decline in serum phosphate during this part of the trial are not known.

Serum Parathyroid Hormone:

All 4 treatment groups experienced statistically significant increases in serum PTH levels from baseline at Month 24. These were: 29.06, 43.10, 22.34, and 37.92% in PBO, ALN, CE, and ALN + CE respectively. Although the increases in PTH are consistent with the decreases in serum calcium (as a result of the actions of CE and ALN), all groups demonstrated a substantial upward trend in levels of this hormone, after Month 3. The reasons for this are not apparent.

Comments: Therefore, on the basis of this trial, conclusive statements about the effects of combined ALN+CE treatment on PTH cannot be made.

The % changes in PTH in all 4 groups during the trial period are shown in the figure below:



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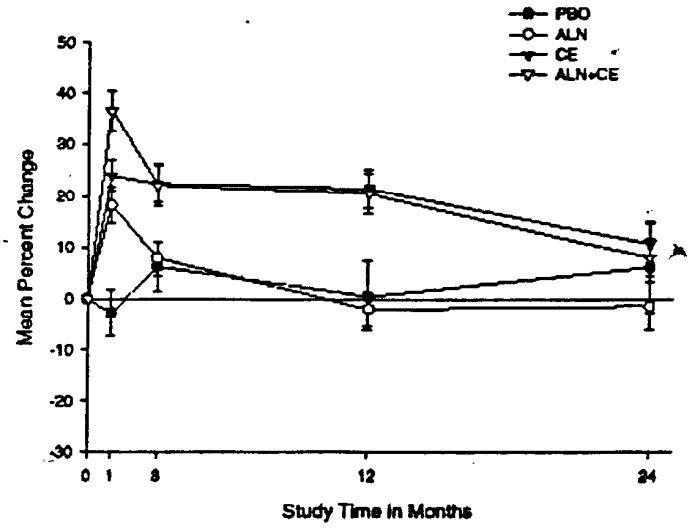
1,25-Dihydroxyvitamin D:

In PBO, there was a nonsignificant increase of 6.06% in 1,25-dihydroxyvitamin D levels from baseline at Month 24.

During the first month of treatment, levels of 1,25-dihydroxyvitamin D increased in all 3 active-treatment groups, but these levels declined thereafter. At Month 24, the levels of 1,25-dihydroxyvitamin D in ALN were decreased from baseline by 1.34% (NS), whereas CE and ALN + CE had significant increases from baseline of 10.73 and 7.98% ($p<0.010$ and $p<0.050$), respectively. Changes in 1,25-dihydroxyvitamin D are shown in the figure below:



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Correlation and subgroup analyses

Pearson correlation coefficients were computed as a measure of association between baseline lumbar spine BMD selected clinical, biochemical, and demographic parameters. Tables presenting correlation data are included in the NDA. The selected parameters were: age, number of years since menopause, estimated calcium intake, weight, height, BMI, BSAP, and NTx/Cr.

There were weak (-0.15) negative correlations between BMD and both age and the number of years since menopause (-0.15), as expected. There was also a weak negative correlation (-0.14) between BMD and baseline calcium intake. This indicates that those with higher calcium intake tended to have a lower spinal BMD. There was also a weak negative correlation (-0.14) between BMD and

baseline BSAP and NTx/Cr (-0.18 and -0.20, respectively). There were weak positive correlations between BMD and both body weight and BMI (correlations of 0.24 and 0.21, respectively).

Comments: Most of these correlations, although weak, are in the expected direction.

Subgroup analyses:

These were done according to pre-defined levels of lumber spine BMD (T-score ≤ -2.5),age, race, renal function, and prior estrogen use. Details of the results are provided in the NDA (pg. 110, ref. 3). In general results of the ITT analyses of the subgroup with lower baseline BMD were similar to those seen in the entire cohort, with a few exceptions. Some of the inter-group differences seen in the entire cohort lost statistical significance when the comparisons were made in the smaller cohort (see page 109-110, ref 3 of the NDA). In general, these discrepancies were few and of little clinical significance. They were most likely due to the small number of subjects in each treatment group in the low BMD cohort.

Within the low BMD cohort, data for BMD changes are provided in the following table:

	Lumbar Spine[†]		Total Hip[‡]		Femoral Neck[‡]		Total Body[‡]	
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
PBO	17	-1.03 (2.31)	17	0.24 (2.69)	17	-1.03 (3.16)	12	-0.82 (2.81)
ALN	41	6.66 (4.36)***	40	4.10 (2.31)***	41	2.69 (4.42)***	31	2.12 (3.64)**
CE	71	6.51 (4.99)***	71	3.55 (3.20)***	71	2.39 (4.04)***	53	3.08 (5.48)***
ALN+CE[§]	55	9.37 (4.69)***	55	4.78 (3.06)***	55	4.33 (4.29)***	43	2.19 (3.05)***

[†] Primary efficacy endpoint.
[‡] Secondary efficacy endpoint.
Within-treatment test of mean = 0 ***: p≤0.001 **: p≤0.010 *: p≤0.050.
[§] Significant difference between ALN+CE and CE at the lumbar spine, total hip, and femoral neck. Significant difference between alendronate+conjugated estrogens group, and the alendronate alone group, at the lumbar spine.

There was no significant treatment-by-age interaction (p=0.773). Summary data are provided in tabular form. The older group (age>65) tended to have a greater in crease in lumbar spine BMD across all active-treatment groups, than did the younger group. The combination ALN + CE again did better than CE alone in both age subgroups. The 95% CI's did not overlap in the comparison between ALN + CE and ALN alone in the older group, but overlapped slightly in the younger group.

The treatment-by-race (Caucasian, 89.9% of the population; non-Caucasian, 10.1%) interaction was also not significant (p=0.722).

Comment: The number of non-Caucasians was small (total 37 individuals distributed among the 4 treatment arms), and there was no significant difference in lumbar spine BMD increase from baseline among the 3 active-treatment groups in this cohort (e.g., ALN + CE was not superior to either treatment alone for this small subgroup). All 3 groups increased BMD significantly, whereas the PBO group decreased. There was no overlap between 95% CI's around the means for any of the 3 active-treatment groups and those of the PBO group.

The sponsor did not perform an analysis by renal function, because 99.5% of the patients had normal serum creatinine.

Prior estrogen use: The analysis by subgroup of patients who had used estrogen ≥30 days prior to 6 months before randomization (N=188, 44.2%, vs N=237, 55.8%, who had not used estrogen prior to the study) showed no significant treatment-by subgroup interaction (p=0.577). Results for these 2 subgroups were essentially the same (Table 38, ref.3 of the NDA submission).

8.3.2.3 Safety

Comments: The safety analysis was conducted according to routine methodology that has been described previously (see above). As in previous trials, upper GI AE's were evaluated separately. Fractures and fracture incidence in each group were reported as clinical AE's. This study did not provide adequate power to evaluate fractures as an efficacy endpoint. In addition to routine analyses this section includes a study of bone histomorphometry in a subset of individuals. The results of this study form an important part of the analysis of safety of combined estrogen and alendronate treatment.

As in previous submissions, the sponsor separately analyzes "drug-related" adverse experiences. These were, in fact, AE's that the investigator considered to be related ("possibly, probably, or definitely") to study drug. As discussed in an earlier review of alendronate, this category is scientifically meaningless. In addition, the term "drug-related" is misleading, in that it carries the implication that the relationship was objectively determined. Accordingly, this review will not separately discuss data regarding "drug-related" AE's, but will include analysis of all AE's.

Results: The % of subjects with one or more AE's did not differ among the 4 treatment groups. There was no significant difference (by pairwise comparison) between CE and ALN + CE in incidence of any AE categories listed in the sponsor's table below. There were no treatment group differences in % with a serious AE, % withdrawn due to an AE, or % withdrawn from therapy due to a serious AE.

No patients died during the trial.

	PBO (N=50)	ALN (N=92)	CE (N=143)	ALN + CE (N=140)
Number (%) of patients with one or more adverse experiences	45 (90.0)	80 (87.0)	129 (90.2)	130 (92.9)
with a drug-related* adverse experience	13 (26.0)	23 (25.0)	63 (44.1)	63 (45.0)
with a serious adverse experience	5 (10.0)	13 (14.1)	17 (11.9)	19 (13.6)
with a serious drug-related* adverse experience	2 (4.0)	1 (1.1)	1 (0.7)	1 (0.7)
withdrawn from therapy due to an adverse experience	5 (10.0)	6 (6.5)	14 (9.8)	13 (9.3)
withdrawn from therapy due to a serious adverse experience	1 (2.0)	1 (1.1)	2 (1.4)	0
withdrawn from therapy due to a drug-related* adverse experience	3 (6.0)	2 (2.2)	9 (6.3)	9 (6.4)
withdrawn from therapy due to a serious drug-related* adverse experience	1 (2.0)	0	1 (0.7)	0
Patients who died	0	0	0	0

*Determined by the investigator to be possibly, probably, or definitely drug related.
This table does not include those adverse experiences that occurred during pretreatment.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

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Adverse events are tabulated by body system (table below).

	PBO (N=50)	ALN (N=92)	CE (N=143)	ALN+CE (N=140)
Body as a whole/site unspecified	19 (38.0)	31 (33.7)	53 (37.1)	48 (34.3)
Cardiovascular system disorders	3 (6.0)	12 (13.0)	20 (14.0)	31 (22.1)
Digestive system disorders	18 (36.0)	36 (39.1)	62 (43.4)	64 (45.7)
Endocrine disorders	0	1 (1.1)	6 (4.2)	4 (2.9)
Hemic and lymphatic disorders	0	3 (3.3)	5 (3.5)	1 (0.7)
Metabolic, nutritional, immune disorder	3 (6.0)	8 (8.7)	16 (11.2)	15 (10.7)
Musculoskeletal disorders	30 (60.0)	45 (48.9)	74 (51.7)	75 (53.6)
Nervous system and psychiatric disorder	23 (46.0)	32 (34.8)	46 (32.2)	47 (33.6)
Respiratory system disorders	23 (46.0)	33 (35.9)	69 (48.3)	72 (51.4)
Skin and skin appendage disorders	15 (30.0)	21 (22.8)	45 (31.5)	44 (31.4)
Special sense disorders	10 (20.0)	13 (14.1)	24 (16.8)	21 (15.0)
Urogenital system disorders	16 (32.0)	26 (28.3)	69 (48.3)	69 (49.3)

This table does not include those adverse experiences that occurred during pretreatment.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

A greater proportion of subjects had cardiovascular AE's in ALN + CE (31 [22.1%]), compared with PBO (3 [6.0%]), or ALN (12 [13.0%]), or CE (20 [14.0%]). However, as reported in the sponsor's Table 41, most of these were due to increases in blood pressure. Parts of Table 41 are reproduced below:

Number (%) of Patients With Specific Clinical Adverse Experiences
by Body System and Treatment Group
(Incidence ≥2% in One or More Treatment Groups)

	PBO (N=50)	ALN (N=92)	CE (N=143)	ALN+CE (N=140)
Cardiovascular System Disorders	**3 (6.0)**	**12 (13.0)**	**20 (14.0)**	**31 (22.1)**
AV block, third degree	1 (2.0)	0	0	0
Blood pressure increased	2 (4.0)	2 (2.2)	7 (4.9)	4 (2.9)
Heart failure	1 (2.0)	0	0	1 (0.7)
Hypertension	0	4 (4.3)	3 (2.1)	5 (3.6)
Hypertension increased	0	1 (1.1)	1 (0.7)	7 (5.0)
Palpitation	0	1 (1.1)	1 (0.7)	3 (2.1)
Tachycardia	0	0	2 (1.4)	4 (2.9)
Digestive System Disorders	**18 (36.0)**	**36 (39.1)**	**62 (43.4)**	**64 (45.7)**
Acid regurgitation	2 (4.0)	4 (4.3)	8 (5.6)	8 (5.7)
Broken tooth	1 (2.0)	1 (1.1)	1 (0.7)	2 (1.4)
Constipation	1 (2.0)	5 (5.4)	8 (5.6)	6 (4.3)
Dental caries	0	2 (2.2)	4 (2.8)	4 (2.9)
Diarrhea	3 (6.0)	3 (3.3)	12 (8.4)	9 (6.4)
Diverticulitis, intestinal	1 (2.0)	2 (2.2)	1 (0.7)	1 (0.7)
Diverticulum, intestinal	1 (2.0)	0	0	2 (1.4)
Dyspepsia	3 (6.0)	7 (7.6)	9 (6.3)	8 (5.7)
Dysphagia	1 (2.0)	1 (1.1)	1 (0.7)	1 (0.7)
Esophagalgia	0	3 (3.3)	0	1 (0.7)
Esophagitis	0	1 (1.1)	2 (1.4)	3 (2.1)
Flatulence	2 (4.0)	1 (1.1)	3 (2.1)	1 (0.7)
Gastroenteritis, infectious	0	1 (1.1)	5 (3.5)	1 (0.7)
Hemorrhage, anal/rectal	1 (2.0)	0	1 (0.7)	1 (0.7)
Hemorrhoids	2 (4.0)	2 (2.2)	3 (2.1)	1 (0.7)
Infection, dental process	3 (6.0)	4 (4.3)	8 (5.6)	6 (4.3)
Infection, mouth	0	3 (3.3)	0	0
Intestinal disorder, functional	1 (2.0)	0	0	0
Nausea	4 (8.0)	12 (13.0)	20 (14.0)	19 (13.6)
Pain, dental	0	3 (3.3)	5 (3.5)	4 (2.9)
Prolapse, rectal	1 (2.0)	0	0	0
Reflux esophagitis	2 (4.0)	2 (2.2)	3 (2.1)	1 (0.7)
Vomiting	1 (2.0)	1 (1.1)	7 (4.9)	11 (7.9)

For musculoskeletal disorders,

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Musculoskeletal Disorders	30 (60.0)	45 (48.9)	74 (51.7)	75 (53.6)
Arthritis	3 (6.0)	5 (5.4)	3 (2.1)	5 (3.6)
Arthropathy, traumatic	1 (2.0)	0	0	0
Capsulitis, adhesive	1 (2.0)	0	0	0
Cramp, muscle	0	5 (5.4)	7 (4.9)	8 (5.7)
Crepitus, joint	1 (2.0)	1 (1.1)	0	1 (0.7)
Fracture, arm, right	1 (2.0)	0	0	0
Fracture, foot, left	1 (2.0)	0	1 (0.7)	0
Fracture, tibia, right	1 (2.0)	0	1 (0.7)	0
Fracture, rib	1 (2.0)	1 (1.1)	0	1 (0.7)
Fracture, rib, 5th, right	1 (2.0)	0	0	0
Fracture, vertebra, t11	1 (2.0)	1 (1.1)	1 (0.7)	0
Fracture, vertebra, t12	1 (2.0)	0	1 (0.7)	1 (0.7)
Myalgia	3 (6.0)	1 (1.1)	2 (1.4)	5 (3.6)
Osteoarthritis	4 (8.0)	2 (2.2)	2 (1.4)	4 (2.9)
Osteoarthritis, knee	1 (2.0)	1 (1.1)	1 (0.7)	0
Pain, ankle	0	3 (3.3)	2 (1.4)	5 (3.6)
Pain, arm	3 (6.0)	1 (1.1)	2 (1.4)	2 (1.4)
Pain, back	8 (16.0)	10 (10.9)	25 (17.5)	21 (15.0)
Pain, bone	0	2 (2.2)	0	2 (1.4)
Pain, elbow	1 (2.0)	1 (1.1)	0	1 (0.7)
Pain, finger	1 (2.0)	1 (1.1)	1 (0.7)	2 (1.4)
Pain, foot	4 (8.0)	3 (3.3)	3 (2.1)	4 (2.9)
Pain, hip	6 (12.0)	6 (6.5)	10 (7.0)	13 (9.3)
Pain, knee	2 (4.0)	7 (7.6)	6 (4.2)	10 (7.1)
Pain, leg	4 (8.0)	4 (4.3)	4 (2.8)	4 (2.9)
Pain, musculoskeletal	0	2 (2.2)	3 (2.1)	1 (0.7)
Pain, neck	4 (8.0)	2 (2.2)	4 (2.8)	4 (2.9)
Pain, shoulder	3 (6.0)	4 (4.3)	6 (4.2)	12 (8.6)
Pain, wrist	1 (2.0)	2 (2.2)	2 (1.4)	3 (2.1)
Stiffness	0	0	2 (1.4)	4 (2.9)
Strain, back	1 (2.0)	1 (1.1)	3 (2.1)	2 (1.4)
Swelling, joint	1 (2.0)	1 (1.1)	4 (2.8)	7 (5.0)

Serious clinical AE's:

Fifty-four subjects (approximately 13%) had at least one serious clinical AE. There were no deaths. A listing of all patients with serious clinical AE's is provided in the following table:

Study	AN	Age/Race	Drug/Total Daily Dosage at Time of AE	Relative Day of AE Onset	Adverse Experience	Duration of Adverse Experience	Intensity	Drug Relationship	Therapy Discontinuation	Outcome
PBO (N=80)										
072001	0008	71/H	P/2 tablets	595	AV block, third degree	176 days	Severe	Def not	No	SP
072002	0404	74/C	P/2 tablets	91	Neoplasm, skin, malignant	19 days	Mild	Def not	No	REC
			P/2 tablets	142	Neoplasm, skin, malignant	6 days	Mild	Def not	No	REC
072004	0055	51/C	P/2 tablets	412	Neoplasm, breast, malignant	9 days	Severe	Possibly	Yes	SP
072007	0443	66/C	Off P 1 day/2 tablets	730	Reflux esophagitis	2 days	Moderate	Possibly	No	REC
			Off P 1 day/2 tablets	730	Hernia, diaphragmatic	2 days	Moderate	Possibly	No	REC
072008	0373	76/C	Off P 32 days/2 tablets	275	Heart failure	30 days	Severe	Def not	No	REC
			Off P 32 days/2 tablets	275	Blood pressure increased	1 day	NA	Def not	No	REC
			Off P 61 day/2 tablets	304	Adverse reaction to unknown drug	30 days	Severe	Def not	No	REC
ALN (N=92)										
072001	0018	68/C	A/10 mg	371	Fracture, rib	69 days	Severe	Def not	No	REC
			A/10 mg	371	Fracture, clavicle	69 days	Severe	Def not	No	REC
072002	0028	67/C	A/10 mg	725	Neoplasm, breast, malignant	1 day	NA	Prob not	No	REC
072002	0398	67/C	A/10 mg	436	Pain, shoulder	3 days	Moderate	Def not	No	REC
			A/10 mg	436	Pain, shoulder	3 days	Moderate	Def not	No	REC
072008	0370	71/C	A/10 mg	190	Pain, chest	5 days	Severe	Def not	No	REC
			A/10 mg	195	Reaction, vasovagal	15 minutes	Severe	Def not	No	REC
			A/10 mg	353	Reaction, vasovagal	15 minutes	Moderate	Possibly	No	REC
072009	0354	58/C	Off A 1 day/10 mg	96	Pain, chest	4 days	Moderate	Prob not	No	REC
072011	0184	74/C	A/10 mg	170	Pneumonia	11 days	Severe	Def not	No	REC
072011	0194	70/C	A/10 mg	56	Neoplasm, skin, malignant	10 days	Mild	Def not	No	REC
072012	0202	58/C	A/10 mg	394	Angina pectoris	1 day	Severe	Prob not	No	REC
072012	0409	61/C	A/10 mg	276	Neoplasm, skin, malignant	64 days	Severe	Prob not	No	REC
072013	0218	75/C	A/10 mg	87	Infection, respiratory	14 days	Severe	Prob not	No	REC
			A/10 mg	87	Respiratory failure	7 days	Severe	Prob not	No	REC
072013	0225	69/C	A/10 mg	265	Neoplasm, liver, malignant	18 days	Severe	Def not	Yes	SP
			A/10 mg	265	Neoplasm, pancreas, malignant	18 days	Severe	Def not	No	SP
072013	0396	69/H	A/10 mg	358	Hernia, abdominal	24 hours	Moderate	Def not	No	REC
072019	0415	66/C	A/10 mg	158	Diverticulitis, intestinal	61 days	Severe	Prob not	No	REC
			Off A 1 day/10 mg	219	Pain, abdominal	1 day	Moderate	Def not	No	REC
			Off A 1 day/10 mg	219	Diverticulitis, intestinal	9 days	Moderate	Def not	No	REC
CE (N=143)										
072001	0012	65/C	Off E 48 days/0.625 mg	337	Fracture, calcaneus, right	136 days	Severe	Def not	No	SP
			Off E 48 days/0.625 mg	337	Fracture, malleolus, right	136 days	Severe	Def not	No	SP
072001	0479	70/C	Off E 1 day/0.625 mg	75	Thrombosis, vein	25 days	Severe	Possibly	Yes	SP
072003	0040	49/C	E/0.625 mg	84	Neoplasm, skin, malignant	1 day	Severe	Prob not	No	REC
072005	0090	62/C	E/0.625 mg	233	Pneumonia	3 days	Moderate	Def not	No	REC
072006	0094	69/C	E/0.625 mg	183	Pain, chest	19 days	Moderate	Def not	No	REC
072007	0110	62/C	E/0.625 mg	353	Neoplasm, skin, malignant	40 days	Mild	Prob not	No	REC
072007	0442	71/C	Off E 1 day/0.625 mg	464	Rectocele	23 hours	Mild	Def not	No	REC
072008	0143	77/C	E/0.625 mg	22	Pain, chest	6 hours	Moderate	Def not	No	REC
			E/0.625 mg	22	Pain, chest	6 hours	Moderate	Def not	No	REC
			Off E 1 day/0.625 mg	114	Osteoarthritis	2 days	Severe	Def not	No	REC
072008	0522	70/C	E/0.625 mg	64	Acid regurgitation	108 days	Moderate	Def not	No	REC
			E/0.625 mg	94	Reflux esophagitis	78 days	Moderate	Def not	No	REC
			E/0.625 mg	161	Pain, abdominal	11 days	Moderate	Def not	No	REC
072011	0191	56/C	E/0.625 mg	71	Melanoma	11 days	Moderate	Def not	Yes	REC
072012	0212	61/C	E/0.625 mg	195	Urolithiasis	6 days	Severe	Prob not	No	REC
072012	0346	56/C	Off E 1 day/0.625 mg	216	Pain, back	23 days	Severe	Prob not	No	REC
			E/0.625 mg	434	Pain, chest	5 days	Severe	Def not	No	REC
072012	0347	65/C	E/0.625 mg	266	Myocardial infarction	1 hour	Mild	Prob not	No	REC
			Off E 5 days/0.625 mg	273	Cerebrovascular accident	30 minutes	Mild	Prob not	No	REC
072012	0509	67/C	Off E 1 day/0.625 mg	46	Pneumonia	5 days	Moderate	Def not	No	REC
			E/0.625 mg	358	Cystocele	19 days	Severe	Def not	No	REC
072015	0452	59/C	Off E 1 day/0.625 mg	557	Drug overdose	4 days	Severe	Prob not	No	REC
			Off E 1 day/0.625 mg	557	Syncope	30 minutes	Severe	Prob not	No	REC
072017	0293	62/C	E/0.625 mg	711	Melanoma	6 days	Severe	Def not	No	REC
072019	0423	56/C	E/0.625 mg	419	Cholecystitis	24 hours	Severe	Prob not	No	REC

And for the ALN + CE group

Study	AN	Age/Race	Drug/Total Daily Dosage at Time of AE	Relative Day of AE Onset	Adverse Experience	Duration of Adverse Experience	Intensity	Drug Relationship	Therapy Discontinuation	Outcome
ALN + CE (N=140) (Cont.)										
072003 (Cont.)	0041	71/C	Off A 1 day/10 mg Off E 1 day/0.625 mg	682	Pneumonia	13 days	Severe	Def not	No	REC
072003	0042	54/C	Off A 1 day/10 mg Off E 1 day/0.625 mg	273	Appendicitis	1 day	Severe	Def not	No	REC
072005	0074	53/C	A/10 mg E/0.625 mg	87	Neoplasm, malignant	1 day	Mild	Prob not	No	REC
			A/10 mg E/0.625 mg	257	Neoplasm, skin, malignant	1 day	Mild	Prob not	No	REC
			A/10 mg E/0.625 mg	416	Neoplasm, malignant	30 minutes	Mild	Prob not	No	REC
072007	0115	69/C	A/10 mg[1]	32	Pain, chest	2 hours	Moderate	Prob not	No	REC
072008	0378	73/C	A/10 mg E/0.625 mg	548	Intervertebral disc disorder	2 days	Moderate	Def not	No	REC
072009	0161	60/C	Off A 1 day/10 mg Off E 1 day/0.625 mg	696	Ulcer, gastric w/hemorrhage	54 days	Severe	Possibly	No	SP
072010	0164	74/C	Off A 1 day/10 mg Off E 1 day/0.625 mg	697	Rectocele	1 day	Moderate	Prob not	No	REC
			Off A 1 day/10 mg Off E 1 day/0.625 mg	697	Cystocele	1 day	Moderate	Def not	No	REC
072001	0013	68/C	A/10 mg[1]	537	Anxiety	3 days	Moderate	Def not	No	REC
			A/10 mg[1]	537	Atrial fibrillation	3 days	Severe	Def not	No	REC
072002	0020	63/C	A/10 mg E/0.625 mg	418	Aneurysm, aortic	2 days	Severe	Prob not	No	REC
072002	0031	72/C	Off A 1 day/10 mg Off E 1 day/0.625 mg	260	Urinary incontinence	3 days	Moderate	Def not	No	REC
072010	0165	63/C	Off A 1 day/10 mg Off E 1 day/0.625 mg	442	Pain, abdominal	293 days	Severe	Prob not	No	SP
072012	0216	60/C	A/10 mg[1]	396	Infection, bacterial	17 days	Severe	Prob not	No	REC
072012	0343	65/C	A/10 mg E/0.625 mg	70	Nausea	16 days	Moderate	Prob not	No	REC
			A/10 mg E/0.625 mg	70	Vomiting	16 days	Moderate	Prob not	No	REC
072012	0361	68/C	A/10 mg E/0.625 mg	623	Cerebrovascular accident	30 minutes	Mild	Prob not	No	REC
072012	0510	57/C	Off A 1 day/10 mg Off E 1 day/0.625 mg	678	Tachycardia	364 days	Moderate	Def not	No	SP
072012	0512	63/C	A/10 mg[1]	737	Neoplasm, liver, malignant	1 day	Severe	Prob not	No	SP
072013	0226	63/C	A/10 mg E/0.625 mg	148	Palpitation	44 days	Mild	Def not	No	REC
			A/10 mg E/0.625 mg	178	Pain, chest	14 days	Severe	Def not	No	REC
072013 (Cont.)	0226	63/C	A/10 mg E/0.625 mg	178	Tachycardia	9 days	Severe	Def not	No	REC
			A/10 mg E/0.625 mg	178	Premature ventricular	14 days	Moderate	Def not	No	REC
			A/10 mg E/0.625 mg	186	Wolff-Parkinson-White syndrome	1 day	NA	Def not	No	REC
			A/10 mg E/0.625 mg	189	Pain, pleuritic	3 days	Moderate	Def not	No	REC
			A/10 mg E/0.625 mg	189	Pneumothorax	2 days	Moderate	Def not	No	REC
072018	0022	76/C	A/10 mg E/0.625 mg	198	Neoplasm, skin, malignant	16 days	Mild	Def not	No	REC
			A/10 mg E/0.625 mg	411	Neoplasm, skin, malignant	1 day	Mild	Def not	No	REC
			A/10 mg E/0.625 mg	666	Neoplasm, skin, malignant	1 hour	Mild	Def not	No	REC

Thirty-eight patients (8.9%) were withdrawn due to clinical AE's; 4 of these AE's were serious. A listing of all patients, by treatment group, is provided by the sponsor (Table 44 of the NDA, ref. 3). There was no obvious increase in any of the study groups.

Upper GI AE's: These were analyzed separately, because of the numerous post-marketing reports of GI AE's in patients taking alendronate. The sponsor provides a tabular summary of upper GI AE's. There were no meaningful differences in the % of subjects with upper GI AE's or serious upper GI AE's.

	PBO (N=50)	ALN (N=92)	CE (N=143)	ALN+CE (N=140)
Number (%) of patients				
with one or more upper GI adverse experiences	11 (22.0)	25 (27.2)	43 (30.1)	47 (33.6)
with a drug-related* adverse experience	4 (8.0)	13 (14.1)	13 (9.1)	16 (11.4)
with a serious adverse experience	1 (2.0)	1 (1.1)	1 (0.7)	3 (2.1)
with a serious drug-related* adverse experience	1 (2.0)	0	0	1 (0.7)
withdrawn from therapy due to an adverse experience	0	1 (1.1)	3 (2.1)	2 (1.4)
withdrawn from therapy due to a serious adverse experience	0	0	0	0
withdrawn from therapy due to a drug-related* adverse experience	0	1 (1.1)	2 (1.4)	2 (1.4)
withdrawn from therapy due to a serious drug-related* adverse experience	0	0	0	0
Patients who died	0	0	0	0

* Determined by the investigator to be possible, probably, or definitely drug related.
This table does not include those adverse experiences that occurred during pretreatment.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

The most common upper GI AE's were nausea, abdominal pain, dyspepsia, and vomiting. The occurrence of these events was similar across the treatment groups, with the exception of vomiting. This AE was more common in the 2 groups receiving CE compared with the PBO and ALN groups. The numbers of subjects with esophagitis or reflux esophagitis were similar across groups. These data are shown in the sponsor's table below:

Number (%) of Patients With Specific Upper Gastrointestinal Adverse Experiences
by Body System and Treatment Group
(Incidence ≥1 Patient in One or More Treatment Groups)

	PBO (N=50)	ALN (N=92)	CE (N=143)	ALN+CE (N=140)
Number (%) of patients with one or more clinical adverse experiences	11 (22.0)	25 (27.2)	43 (30.1)	47 (33.6)
Body as a Whole/Site Unspecified				
Distention, abdominal	1 (2.0)	4 (4.3)	7 (4.9)	3 (2.1)
Hernia, diaphragmatic	1 (2.0)	0	1 (0.7)	1 (0.7)
Pain, abdominal	2 (4.0)	7 (7.6)	9 (6.3)	11 (7.9)
Digestive System Disorders				
Acid regurgitation	2 (4.0)	4 (4.3)	8 (5.6)	8 (5.7)
Anorexia	0	0	1 (0.7)	0
Duodenitis	0	0	0	1 (0.7)
Dyspepsia	3 (6.0)	7 (7.6)	9 (6.3)	8 (5.7)
Dysphagia	1 (2.0)	1 (1.1)	1 (0.7)	1 (0.7)
Eructation	0	1 (1.1)	0	0
Esophagalgia	0	3 (3.3)	0	1 (0.7)
Esophagitis	0	1 (1.1)	2 (1.4)	3 (2.1)
Gastritis	0	1 (1.1)	2 (1.4)	2 (1.4)
Gastroenteritis	0	1 (1.1)	1 (0.7)	2 (1.4)
Hemorrhage, gastrointestinal	0	0	0	1 (0.7)
Melena	0	0	0	1 (0.7)
Nausea	4 (8.0)	12 (13.0)	20 (14.0)	19 (13.6)
Reflux esophagitis	2 (4.0)	2 (2.2)	3 (2.1)	1 (0.7)
Stricture, esophageal	0	0	0	1 (0.7)
Ulcer, duodenal	0	0	0	1 (0.7)
Ulcer, gastric	0	0	0	2 (1.4)
Ulcer, gastric w/hemorrhage	0	0	0	1 (0.7)
Vomiting	1 (2.0)	1 (1.1)	7 (4.9)	11 (7.9)

Patients with more than one upper GI adverse experience are counted only once in total "Number (%) of patients with one or more upper GI adverse experiences" and once for each specific upper GI clinical adverse experience.
This table does not include those adverse experiences that occurred during pretreatment.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

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Serious Upper GI Adverse Experiences:

Six patients had a serious upper GI AE, 1 each in the PBO, ALN, and CE groups, and 3 in ALN + CE. Narratives for all serious clinical AE's are included in the NDA.

Fractures:

Fractures (vertebral and non-vertebral) were experienced by 4 (8%) of 50 subjects in PBO, 5 (5.4%) of 92 subjects in ALN, 10 (7%) of 143 in CE, and 8 (5.7%) of 140 subjects in ALN+CE. Vertebral and non-vertebral fractures were analyzed separately.

Vertebral fractures:

The number and percent of patients who had one or more vertebral fractures are given in the following table. There were no significant between-group differences in the proportion of patients who experienced such fractures during the trial.

	PBO (N=50)	ALN (N=92)	CE (N=143)	ALN+CE (N=140)
	n (%)	n (%)	n (%)	n (%)
Number (%) of patients with one or more vertebral fracture clinical adverse experiences	1 (2.0)	1 (1.1)	2 (1.4)	3 (2.1)
Fracture, vertebra, unspecified	0	0	0	2 (1.4)
Fracture, vertebra, L2	0	0	1 (0.7)	1 (0.7)
Fracture, vertebra, T8	0	0	1 (0.7)	0
Fracture, vertebra, T9	0	0	1 (0.7)	0
Fracture, vertebra, T11	1 (2.0)	1 (1.1)	1 (0.7)	0
Fracture, vertebra, T12	1 (2.0)	0	1 (0.7)	1 (0.7)

This table does not include those adverse experiences that occurred during pretreatment.
Patients with more than one vertebral fracture adverse experience are counted once in the total "Number (%) of patients with one or more vertebral fracture clinical adverse experience" and once for each specific vertebral fracture clinical adverse experience.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

There were no reports of malunion of fractures or of delayed fracture healing. malunion or delayed fracture healing.

Comments: The degree to which bone remodeling is suppressed is demonstrated in the section on histomorphometry, which follows. The possibility of malunion or delayed fracture healing remains a serious concern in a situation in which bone remodeling is as substantially suppressed as with combined ALN + CE treatment (or with treatment with ALN alone, for that matter). It is difficult to address this issue in a clinical trial, unless adequate power and monitoring features are built into the design. Given the size, duration and small number of fractures in the present trial, one cannot draw conclusions about fracture healing. This issue is discussed further in the section on histomorphometry.

Nonvertebral Fractures:

There were very few nonvertebral fractures in any treatment group. There was no difference between groups in the proportion of patients who experienced such fractures. The following table lists the number and % of subjects with one or more nonvertebral fractures.

	PBO (N=50)	ALN (N=92)	CE (N=143)	ALN+CE (N=140)
	n (%)	n (%)	n (%)	n (%)
Number (%) of patients with one or more non-vertebral fracture clinical adverse experiences	4 (8.0)*	4 (4.3)	8 (5.6)	5 (3.6)
Fracture, ankle	0	0	2 (1.4)	0
Fracture, arm	1 (2.0)	0	0	1 (0.7)
Fracture, calcaneus	0	0	1 (0.7)	0
Fracture, clavicle	0	1 (1.1)	0	1 (0.7)
Fracture, elbow	0	0	1 (0.7)	0
Fracture, foot phalanx	0	0	1 (0.7)	1 (0.7)
Fracture, foot	1 (2.0)	0	1 (0.7)	0
Fracture, knee	1 (2.0)	0	1 (0.7)	0
Fracture, malleolus	0	1 (1.1)	1 (0.7)	0
Fracture, metatarsal	0	0	0	2 (1.4)
Fracture, pelvis	0	0	1 (0.7)	0
Fracture, rib	2 (4.0)*	2 (2.2)	0	1 (0.7)
Fracture, wrist	0	1 (1.1)	1 (0.7)	0

*Following the data cutoff date for these data, the investigator reported that the rib fractures in AN 0091 (Study 006) were probably present prior to entry into the study, and were not an adverse experience; therefore, the correct n (%) for the PBO group is 3 (6.0) and for fracture, rib in PBO is 1 (2.0).
This table does not include those adverse experiences that occurred during pretreatment.
Patients with more than one nonvertebral fracture adverse experience were counted once in the total "Number (%) of patients with one or more nonvertebral fracture clinical adverse experiences" and once for each specific nonvertebral fracture clinical adverse experience.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

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Morphometric vertebral fractures:

Morphometric vertebral fractures are diagnosed radiographically according to pre-specified criteria. They are identified as part of a radiographic screening program and are usually not clinically apparent or symptomatic.

Lateral thoracolumbar spine radiographs were obtained at baseline and Month 24. These were digitized and read at a central facility, according to a standardized protocol and algorithm. An incident morphometric vertebral fracture was defined as a decrease from baseline of ≥ 20%, together with a decrease of ≥4 mm in height of any vertebra.

Two hundred seventy subjects had digitized spine radiographs at baseline and Month 24. Four individuals were found to have incident morphometric vertebral fractures: one in CE, one in PBO, and 2 in CE + ALN.

COMMENTS: The number of incident morphometric vertebral fractures in this group of 270 women, over 2 years, is lower than in previous trials of alendronate. Perhaps the younger mean age of this cohort explains the lower fracture rate. Results of stature changes during the trial are discussed below.

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Laboratory adverse experiences:

Included in this safety population were all subjects with at least one laboratory test after the start of treatment. As shown in the following table, this comprised nearly all of the subjects in each of the 4 groups. The proportion of patients with laboratory AE's ranged from 12% in the ALN group to 22% in CE. Only one patient had a serious laboratory AE and one patient was withdrawn from therapy due to a laboratory AE. No subjects were withdrawn due to a serious laboratory AE.

	PBO (N=50)	ALN (N=92)	CE (N=143)	ALN + CE (N=140)
Number of patients with at least one laboratory test after start of treatment	50	90	139	138
Number (%) of patients with one or more adverse experiences	9 (18.0)	11 (12.2)	31 (22.3)	21 (15.2)
with a drug-related* adverse experience	1 (2.0)	0	3 (2.2)	3 (2.2)
with a serious adverse experience	0	0	0	1 (0.7)
with a serious drug-related* adverse experience	0	0	0	1 (0.7)
withdrawn from therapy due to an adverse experience	0	0	1 (0.7)	0
withdrawn from therapy due to a serious adverse experience	0	0	0	0
withdrawn from therapy due to a drug-related* adverse experience	0	0	1 (0.7)	0
withdrawn from therapy due to a serious drug-related* adverse experience	0	0	0	0

*Determined by the investigator to be possibly, probably, or definitely drug related.
This table does not include those adverse experiences that occurred during pretreatment.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

Specific Laboratory Adverse Experiences:

These are presented in tabular form in the NDA submission (Table 55).
As the sponsor observes, the listed incidences of AE's in this category is not entirely reliable because the tests wre not performed on either all patients or a random sample of each group. Seventy-two subjects (16.9% of all participants) had at least one laboratory AE. There were no between-group differences in incidences of specific AE's.

Serious laboratory AE's: One patient had a serious laboratory AE: low WBC in a 76-year-old woman taking CE + ALN: persistent WBC of 3000-3500/mm^3 from days 179-529. Thereafter, the WBC fell to 2600, then to 2200 at the completion of the study. About 5 months after completion, a follow-up WBC was 1900. A bone marrow biopsy showed adequate myelopoiesis and no other pathology. This suggested some defect in neutrophil production rate or increased neutrophil utilization, such as in an infectious or immune-mediated process. There was no evidence for maturation arrest. There was some reduction in plasma cells. A specific diagnosis was not made, and the patient was ambulatory, with a low WBC for over 1 year.

Clinical safety measurements:

There were no meaningful changes in weight in any of the 4 groups over the 2 years of the study.

Height: The mean height decreased significantly by 2.6 and 2.1 mm in CE and ALN + CE ($p \leq 0.010$), respectively. For PBO and ALN, there was a nonsignificant increase of 1.4 mm and a decrease of 0.9 mm, respectively.

Comments: Although this was a small study, there is no evidence for a beneficial treatment effect on loss of height. As discussed in earlier reviews of alendronate, the inexorable loss of height found in postmenopausal women is multifactorial. However, loss of height is a recognized, clinically important consequence of severe spinal osteoporosis. If there is no (or only marginal) prevention of height loss, how effective is treatment? What is the meaning of increased spinal BMD as a result of ALN + CE treatment if height loss is not retarded?

Blood pressure: All treatment groups had nonsignificant changes in systolic blood pressure, except for ALN + CE, in which there was an increase of 2.68mm Hg ($p \leq 0.050$). All 4 treatment groups experienced small, nonsignificant decreases from baseline in mean diastolic blood pressure.

Pulse rate: There were no significant changes from baseline in this parameter in any of the treatment groups.

There were no clinically meaningful between-group differences in occurrence of laboratory values that exceeded pre-defined limits of change. In addition, there were no statistically significant differences in these occurrences between CE and CE + ALN.

Bone Histomorphometry

Ninety-eight individuals consented to have bone histomorphometry studies, which were done after 18 months of treatment. Histomorphometry was primarily evaluated as a safety parameter (this involved bone quality results). However, the sponsor anticipated that bone turnover would be decreased in ALN + CE, compared to ALN or CE alone, and evaluated this decrease as an efficacy parameter. The sponsor states that histomorphometry provides only "a very imprecise estimate" of the rate of bone turnover for individual patients. This, according to the sponsor, is more accurately reflected by the biochemical markers.

Of the 98 biopsies, 6 could not be quantitatively studied because of damaged trabecular bone.

Assessment of mineralization was performed by analyzing osteoid thickness, osteoid volume (OV/BV, the % of bone volume that is unmineralized osteoid) and mineral apposition rate (MAR).

OTh=mean thickness of osteoid seams
MAR=mineral apposition rate, which = distance between the 2 tetracycline labels/time interval between administration of the tetracycline labels
OV/BV= osteoid volume/bone volume = fraction (or %) of bone volume that is unmineralized osteoid
MS/BS=mineralizing surface, or the fraction (or %) of total bone surface that takes up the tetracycline label

Bone turnover was assessed by mineralizing surface (% of total bone surface that takes up tetracycline).

For convenience, the definitions of histomorphometric parameters are summarized as:

OTh=mean thickness of osteoid seams

MAR=mineral apposition rate, which = distance between the 2 tetracycline labels/time interval between administration of the tetracycline labels

OV/BV= osteoid volume/bone volume = fraction (or %) of bone volume that is unmineralized osteoid

MS/BS=mineralizing surface, or the fraction (or %) of total bone surface that takes up the tetracycline label

Results:

Osteoid thickness: As shown in the table below, at Month 18, OTh in ALN + CE was significantly different from PBO (p=0.002), ALN (p=0.012), and CE (p<0.001).

Nonparametric Analysis of Osteoid Thickness
(Unit: Micrometers)

Treatment	N	Observed Median	SE (Median)	Range	Comparison Between Treatments		
					ALN	CE	ALN+CE
PBO	8	6.30**	0.43	(4.60, 8.70)	0.192	0.419	0.002
ALN	23	5.20**	0.29	(4.30, 7.50)		0.453	0.012
CE	27	5.60**	0.32	(3.90, 9.00)			<0.001
ALN+CE	34	4.90**	0.16	(3.80, 6.90)			

Within-treatment test of median=0 ***: p≤0.001 **: p≤0.010 *: p≤0.050.
Overall treatment effect p-value: 0.001.
Pooled SD: 0.92.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

The sponsor states that the decrease found in ALN + CE is most likely due to suppression of bone turnover. The reduced Oth suggests that there was no defect in mineralization.

Comment: It is not clear why suppression of bone turnover should result in a diminution in the thickness of osteoid seams. However, the reductions in Oth in the treatment groups are in keeping with the order of reduction in markers of bone turnover. The data certainly suggest that there was no defect in mineralization of osteoid in association with active treatment and especially with ALN + CE.

Mineral apposition rate (MAR):

As shown in the following table, there was no between-group difference in MAR.

Analysis of Mineral Apposition Rate
(Unit: Micrometers/Day)

Treatment	N	Observed Mean	SD	Adjusted Mean	95% CI	Comparison Between Treatments		
						PBO	ALN	CE
PBO	8	0.55**	0.10	0.52	(0.42, 0.63)	–	–	–
ALN	17	0.54**	0.17	0.51	(0.44, 0.59)		–	–
CE	25	0.52**	0.15	0.49	(0.41, 0.57)			–
ALN+CE	12	0.46**	0.21	0.44	(0.36, 0.51)			

Within-treatment test of mean=0 ***: p≤0.001 **: p≤0.010 *: p≤0.050.
Overall treatment-effect p-value: 0.566.
Pooled SD: 0.16.
Note: Pairwise comparisons were not performed since the overall treatment effect was not significant.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

Comments: Note that patients who had no detectable mineralizing surface (i.e., no tetracycline labeling in the specimen) could not be included in the analysis of MAR. The following (reviewer's) table lists the numbers of patients included in each analysis, by treatment group. The greatest number of patients excluded from the MAR analysis were in the ALN + CE group.

TREATMENT GROUP	# IN OTh ANALYSIS	# IN MAR ANALYSIS
PBO	8	8
ALN	23	17
CE	27	25
ALN + CE	34	12

Osteoid Volume (OV/BV, osteoid volume as a fraction or % of bone volume):

OV/BV differed significantly among the 4 groups, as shown in the following table:

Nonparametric Analysis of Osteoid Volume/Bone Volume
(Unit: Percent)

Treatment	N	Observed Median	SE (Median)	Range	Comparison Between Treatments		
					ALN	CE	ALN+CE
PBO	8	2.11**	0.39	(0.69, 4.17)	0.002	0.023	<0.001
ALN	23	0.58**	0.13	(0.01, 4.03)		0.175	0.057
CE	27	0.62**	0.20	(0.06, 4.34)			<0.001
ALN+CE	34	0.24**	0.08	(0.01, 1.80)			

Within-treatment test of median=0 ***: p≤0.001 **: p≤0.010 *: p≤0.050.
Overall treatment effect p-value: <0.001.
Pooled SD: 0.87.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

The data show a decrease in OV/BV in all active-treatment groups, relative to PBO, and are consistent with suppression of bone turnover in these groups, most prominently in ALN + CE. Again, there is no indication of impaired mineralization.

Mineralizing Surface:

At Month 18, MS differed significantly among the 4 treatment groups, as shown in the table below. Based on the values for MS, ALN + CE had the lowest rate of bone turnover of all 4 treatment groups.

Nonparametric Analysis of Mineralizing Surface
(Unit: Percent)

Treatment	N	Observed Median	SE (Median)	Range	Comparison Between Treatments		
					ALN	CE	ALN+CE
PBO	8	5.14**	1.04	(2.70, 7.17)	<0.001	0.007	<0.001
ALN	23	0.30**	0.14	(0.00, 3.59)	–	<0.001	0.040
CE	27	1.24**	0.49	(0.00, 9.57)	–	–	<0.001
ALN+CE	34	0.09**	0.09	(0.00, 1.02)	–	–	–

Within-treatment test of median=0 ***: p≤0.001 **: p≤0.010 *: p≤0.050.
Overall treatment effect p-value: <0.001.
Pooled SD: 0.69.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

Taking the mean values (mean data presented elsewhere in NDA), the reductions seen in ALN alone, about 88% lower than PBO, are consistent with earlier data on alendronate. Of note, ALN + CE suppressed the mean values even further, to 95% of PBO.

Comments: Relative to PBO, the median values were suppressed by about 96 and 98% in the ALN and ALN + CE, respectively. The PBO group is postmenopausal and not on HRT. The CE group presumably is estrogen-

sufficient, as judged by degree of suppression of biochemical turnover markers. Relative to this group, the MS/BS in ALN was suppressed by about 75%, and in ALN + CE, the MS/BS was suppressed by about 93%. According to the sponsor, the data show that, in ALN + CE, bone turnover was not "completely" suppressed. However, the level of suppression found in ALN + CE, relative to PBO and even in relation to CE, was nearly 100%. According to the sponsor, 19 individuals had a MS of 0. Fourteen of these were in the ALN + CE group, 4 in ALN, and 1 in CE.[4] In addition, CE+ALN was represented by 22 fewer individuals in the MAR analysis than in the osteoid thickness analysis. Presumably, this was due to the lack of tetracycline labeling in these individuals. The reason for the discrepancy in the number of patients missing from these analyses is not given.

This extreme level of suppression of bone turnover found in ALN + CE is of concern, particularly if this regimen is to be used for extended periods (as it most probably will be). The overall effects of long-term local suppression of bone remodeling are not known. However, it is possible that inhibition of bone remodeling may delay fracture healing or even cause malunion. The safety data base provided by this study (400 women over 2 years) is inadequate to address these concerns.

Bone Architecture

According to the sponsor, overall bone architecture was normal. There was no evidence of woven bone, marrow fibrosis, or other structural abnormalities.

Drug-Demographic Interactions

There were no drug-demographic interactions for safety issues. The analysis considered age, race, and renal function (serum creatinine).

[4] Specimens from these individuals were re-examined using a search within multiple additional sections; evidence for tetracycline labeling of cancellous bone was subsequently found in 16 of these individuals.

8.3.3 Summary of efficacy and safety of Trial 072

This was a 2-year study of 425 hysterectomized postmenopausal women with lumbar spine BMD ≤ -2. Subjects were randomized to placebo, CE alone, ALN alone, and ALN + CE. The study demonstrated that, at the lumbar spine and femoral neck, the BMD increases relative to baseline seen in ALN + CE were greater than in ALN or CE alone.

At these sites, the increases from baseline were:

INCREASES FROM BASELINE (%)

TREATMENT GROUP	LUMBAR SPINE	FEMORAL NECK
ALN	6.0	2.9
CE	6.0	2.6
ALN + CE	8.3*	4.2*

* significantly greater than in either treatment group ($p<0.001$ for both comparisons at the lumbar spine and $p=0.022$ vs ALN and $p=0.003$ vs CE at the femoral neck)

Very small changes from baseline were seen in PBO at either site over the 2 years. All 3 active-treatment groups experienced greater BMD increases than were found in PBO.

Other changes:

Total hip and trochanter: ALN + CE had greater increases than CE alone, but not greater than ALN alone. The differences between CE and ALN + CE were about 2%.

Total body BMD: all 3 active-treatment groups produced significant increases from baseline in total body BMD of about 1.33 to 2.5 %. However, there were no significant differences between treatment groups.

ALN did not differ significantly from CE at any site except the trochanter, where the increases were 5.9% CI: [5.3, 6.6]) for ALN vs 4.3%, CI: [3.8, 4.8] for CE.

The differences in mean % BMD increases from baseline, at 5 anatomic sites, associated with 2 years of treatment with combined [ALN + CE] vs CE alone or ALN alone are summarized in the following (reviewer's) table:

SKELETAL SITE	[ALN+CE] vs CE	[ALN+CE] vs ALN
SPINE	2.27%	2.26%
FEMORAL NECK	1.55%	1.3 %
TROCHANTER	2%	0.6%
TOTAL HIP	1.21%	0.67%
TOTAL BODY	NO DIFFERENCE	NO DIFFERENCE

In an analysis of treatment-by-demographic interactions, the sponsor found that the BMD results were all independent of age, race, or prior estrogen usage. The effects on were also independent of baseline BMD and were similar in the subgroup of individuals with a baseline lumbar spine BMD T-score $\leq$ -2.5 SD.

Biochemical markers of bone resorption and formation were also suppressed more with combined ALN + CE treatment, compared to ALN or CE alone. All 3 active treatment groups experienced statistically significant and quite substantial reductions in NTx/Cr and BSAP during the treatment period. In general, treatment with either ALN or CE alone reduced resorption markers from typically elevated post-menopausal levels to those found in premenopausal women. With combined ALN + CE, the levels declined even further, to between –1 and –2 SD of the mean for premenopausal women. For NTx/Cr , these declines were of the order of 60-70% (from PBO). For BSAP, the reductions were of the order of 50-60% of PBO. ALN produced about the same (for BSAP), or slightly greater (NTx), reductions than were found in CE.

Although ALN + CE substantially reduced BSAP and NTx, the means for both parameters were not less than 2 SD below the reference means for premenopausal women. The sponsor's conclusion is that bone turnover was not completely suppressed. While this is true for the entire skeleton, it may not apply to all sites, particularly sites rich in cancellous bone. The discordance between the histomorphometric parameters and the biochemical parameters, discussed below, is suggestive of this.

Height:

Height was reported as a safety parameter. Of interest, the mean height decreased significantly by 2.6 and 2.1 mm in CE and ALN + CE ($p \leq 0.010$), respectively. For PBO and ALN, there was a nonsignificant increase of 1.4 mm and a decrease of 0.9 mm, respectively.

Comments on this issue appear above. There was clearly no beneficial treatment effect on loss of height.

Safety:

Overall, the safety profile of combined ALN + CE was similar to that of either treatment alone, or to placebo. There were no deaths and very few serious AE's. In this study, there was no evidence for an increase in upper GI AE's in alendronate-treated groups.

It should be noted that the absence of measurable increases in upper GI AE's in this and previous controlled alendronate trials is inconsistent with the numerous reports of upper GI AE's, some very serious, found during the post-marketing period. The cause of this discrepancy has not been elucidated, but poor representation of the intended population by the trial population is a likely possibility. This issue has been discussed in detail previously (see review of the 4-year FIT trial, earlier this year).

Treatment with CE alone or in combination with ALN was not unexpectedly associated with weight gain or breast pain.

Fractures: There were very few incident fractures in the trial: 5 (5.4%) of 92 ALN; 8 (5.7%) of 140 ALN + CE; 4 (8%) of 50 PBO and 10 (7%) of 143 CE. Most of these were non-vertebral fractures, mainly foot, ankle, and rib. There were no laboratory safety issues that were associated with the use of ALN + CE for the 2-year period.

Thus, from the standpoint of routine safety monitoring and tolerability, the use of the combination of the two agents had a favorable profile.

Histomorphometry:

In contrast to the overall safety/tolerability results of this trial, portions of the histomorphometry data were not as reassuring and raised questions about the long-term safety of combined therapy.

From the standpoint of normality of the bone, there was no evidence of impairment in mineralization, nor were there any changes in bone

architecture that would raise any concerns. This is similar to earlier results with alendronate alone.

The problem is not with the architecture or with any lack of mineralization, but with the extreme degree to which bone turnover is suppressed in the combined therapy group. According to the sponsor, this suppression is entirely consistent with the known action of the two agents and with the degree of suppression of the biochemical markers. As noted above, the fact that the marker values remained above –2SD of the premenopausal mean, was interpreted by the sponsor as an indication that bone turnover was not completely shut down by treatment.

In further explaining the nearly complete suppression of turnover seen in the histomorphometry, the sponsor states that ALN "decreases the rate of iliac trabecular (cancellous) bone turnover to a greater extent than in the skeleton as a whole. This is due to the fact that ALN localizes preferentially at sites of active bone turnover, especially highly vascularized ones, such as the ilium. Thus, histomorphometric measurements overestimate the effects of ALN on overall bone turnover. Specific biochemical markers, such as NTx, provide better indices for the effects of ALN on overall skeletal turnover than bone biopsies."

To explain the lack of tetracycline label that was seen in 19 individuals (14 of these on combined ALN + CE, 4 on ALN, and 1 on CE), the sponsor states that active, labeled sites may be missed normally and that one would expect an even greater proportion of individuals to lack tetracycline labeling when taking anti-resorptive agents. This is true, but it still fails to address the fact that none of the 8 PBO and only 1 of 27 CE lacked tetraclycline labeling (as opposed to 4 of the 23 ALN and 14 of the 34 ALN + CE).

Comparison of the histomorphometry data with the changes in biochemical markers shows that the relationship between the two is not simple. For the biochemical markers, the order of suppression potency was [ALN + CE] > ALN > CE. However, the differences between the 3 active-treatment groups were not large (e.g., for NTx, about –70%, -61%, and –52%, respectively; for BSAP, -60%, -50%, and –49%). Despite the fact that this hierarchy was maintained in the histomorphometry results, the differences between the groups was much more substantial in this study. For MS/BS (expressed as %), the results were 0.09, 0.30, 1.24, and 5.14% ([ALN + CE], ALN, CE, PBO, respectively). This means that the bone turnover rate in ALN was 25% that of CE; more striking, the turnover rate of [ALN + CE] was 30% that of ALN and 7% that of CE. Thus, the thirteen-fold difference in bone turnover rate in [ALN + CE], relative to CE, that was seen on histomorphometry was accompanied by only a 45% difference in absolute mean NTx and a 25% difference in BSAP. In other words, there was a 4- to 6-fold disproportion

between the two methods, when the methods were used to compare degrees of suppression of bone turnover among treatment groups. The histomorphometry study was performed at 18 months, and there is no indication whether the suppression of local bone turnover will increase or abate with further treatment.

Assuming that the systemic bone turnover markers represent resorption and formation activity of the entire skeleton, then it is quite probable that the iliac crest (the site of the biopsies), composed mainly of cancellous bone, is not representative of the entire skeleton. It is also significant that, in CE+ALN, BMD continued to increase at nearly all measured skeletal sites at 2 years, with no sign of a plateau. According to the sponsor, this selectivity is a likely explanation for the differences in the turnover results, as well as for the severe degree of suppression found in the biopsy specimens. However, there remains the concern that if this degree of suppression can occur at one site, what evidence is there that it cannot occur at another? Why is the iliac crest a valid indicator site for bone architecture, but not for bone turnover?

One can only speculate about the mechanism of synergy between ALN and CE in suppressing bone turnover, at least at selected sites. However, the extreme degree of suppression raises serious concerns about long term safety, concerns that are not allayed by the sponsor's emphasis on the continued presence of biochemical markers.

In the overall summary, the sponsor concludes that *"there is no evidence that the decrease in bone turnover induced by ALN (alone or in combination with CE) is excessive. The decrease in MS seen in ALN-treated patients in this study is consistent with previous studies, in which ALN was shown to decrease fracture risk."*

I cannot agree with this assessment. There is striking evidence that combined therapy can suppress bone turnover very severely at selected sites. This suppression may not be generalized throughout the entire skeleton, as suggested by the persistence of biochemical markers and the rise in BMD at several sites. Nonetheless, complete local inhibition of bone remodeling may result in microfractures or delayed healing of fractures. Although a decreased rate of fractures was observed in the earlier alendronate trials, and although estrogen alone may prevent fractures, this does not mean that the combination of the two agents (with demonstrably additive effects) will have the same bone safety and efficacy. Further investigation will certainly be required to define the relationship of the iliac crest histomorphometry data with bone metabolism at other skeletal sites.

9 and 10 sNDA 20560-018: Overall assessment of efficacy and safety

This submission consisted of three trials. The first (Protocol 080) was a small, 4-month clinical pharmacology study that compared the effects of estrogen + progestin to estrogen alone on biochemical markers of bone turnover. This study essentially reconfirmed earlier observations that addition of MPA to estrogen did not reduce the bone-sparing effects of estrogen alone.

The second trial, Protocol 097, was a one-year study of the effects of adding alendronate to ongoing HRT in osteopenic women (BMD t-score ≤-2.0). The cause of the osteopenia was thought by the sponsor to be a delay prior to initiation of HRT, combined with a plateau in efficacy of HRT. This assumption is reasonable. Efficacy endpoints were BMD and biochemical markers of bone turnover. The study enrolled 428 postmenopausal women (average age 61 years, average time from menopause onset 15 years) who had taken HRT for an average of 9.6 years. The subjects were randomized 1:1 into HRT alone (continued regimen) or HRT + ALN. Patients continued their individual HRT regimens.

Results:

1) BMD: At the 4 skeletal sites (lumbar spine, femoral neck, trochanter, and Ward's triangle) both treatment groups, HRT alone (PBO) and alendronate (10 mg) plus ongoing HRT (ALN), experienced statistically significant increases above baseline in BMD after 6 and 12 months. The single exception to this was trochanter BMD at 12 months in the PBO group. The increases were generally of the order of about 0.5-1% in the PBO group and 1.6-3.7% in the ALN group. A plausible explanation for the increases in BMD over baseline in the PBO group is increased calcium and vitamin D intake.

Comparisons between groups: The BMD increases found in the ALN + HRT group were statistically significantly greater than those in the HRT + PBO group at the lumbar spine and hip trochanter at 6 and 12 months. However, the differences between groups were not significant at the femoral neck and Ward's triangle.

2) Biochemical markers of bone turnover:

For both groups, the baseline median values for BSAP and NTx were similar to values found in premenopausal women, indicating long term effects of HRT, as well as compliance with HRT regimens.

For the HRT alone group, there was no significant change in BSAP or NTx during the 12 months of the study.

For the ALN (HRT + ALN) group, there were statistically significant decreases from baseline in BSAP (by about 21%) and NTx (by about 42%) at 6 and 12 months. At both 6 and 12 months, the means both markers were slightly below the premenopausal means, but were within 1 SD and remained within the normal premenopausal range.

The between-group (ALN vs PBO) differences in levels of both markers were statistically significant at both 6- and 12-month time points.

Thus, the sponsor demonstrated that, over the course of 12 months, the addition of alendronate, 10mg, to an ongoing regimen of HRT, further suppresses biochemical markers of bone turnover and further increases BMD at the spine and trochanter, but not at the femoral neck and Ward's triangle (where the differences between treatment groups were not significant).

Safety: There were no safety issues as a result of this trial. There was no increase in adverse events in general, or in adverse events usually associated with either treatment alone. There appeared to be an increase in foot fractures in the alendronate-treated patients, but the level of documentation for all fractures remains unclear, based on the data presentation. In any case, there was no increase in fractures in the third trial, which was two-years' duration.

The third trial, Protocol 072, was a two-year study of 425 hysterectomized postmenopausal women with lumbar spine BMD T-score $\leq$ -2. Subjects were randomized to PBO, ALN, CE, and CE + ALN. Efficacy was change from baseline BMD at several anatomic sites, and changes biochemical markers of bone turnover. An additional histomorphometry study was performed on a subset of 96 subjects at 18 months of treatment.

This study demonstrated that the combination of ALN + CE produced increases in BMD at the lumber spine and femoral neck that were greater (by about 2%) than those found in CE or ALN alone. At the total hip and trochanter, ALN + CE produced BMD changes that were about 2% greater than with CE alone, but were not significantly greater than with ALN alone. There were no significant differences between the 3 active treatment groups in total body BMD at 24 months.

Biochemical markers of bone formation and resorption were suppressed into the premenopausal range by all 3 active treatments. The suppression was greater with ALN + CE than with either agent alone.

Curiously, subjects in the ALN + CE and CE alone groups lost about 2.5 mm over the two years; both within-group changes were statistically significant from baseline. Neither the PBO nor the ALN alone group had a statistically significant change in mean height over the two years.

There were no safety issues in the study. There was no increase in specific AE's in ALN + CE over those found in any of the other 3 arms.

There was no significant difference in fracture incidence (vertebral, morphometric vertebral, or non-vertebral) among the 4 arms during the course of the study.

The bone histomorphometry study showed profound inhibition of bone turnover in the ALN + CE group. The MS/BS ratio found in this group was about 30% of that seen in the ALN only group and about 7% of that found in CE. Other histomorphometric parameters indicated no mineralization defect in any treatment group. The bone architecture was normal in all treatment groups. The relationships among systemic markers, local histomorphometric changes, and clinically important outcomes are still unclear and remain to be elucidated.

In summary, there were several overall problems with this submission. From the standpoint of physiology, the combination of ALN and CE may have effects on bone that are not entirely predictable on the basis of knowledge of the action of either agent alone. The synergistic effect of the two agents on suppression of bone turnover is a prime example of this. Given the complexity of the entire system and the large size of the population that will inevitably be exposed to ALN + CE, a larger trial, of size and duration sufficient to examine fracture efficacy, would certainly have been more appropriate. In addition, an approach to the potential problems of delayed fracture healing and malunion of fractures would be very helpful.

In this regard, the emphasis placed on surrogate markers, BMD and biochemical turnover indicators, has hindered our ability to determine the true efficacy and safety of a novel drug combination. When surrogates for a disease are allowed to become the disease itself, the analysis of a complicated issue becomes scientifically simplistic and potentially hazardous. The assumption that an increase in BMD is always beneficial, or that an increase in BMD caused by drug A is physiologically the same as an equivalent increase caused by drug B, is scientifically unsound.

In this sNDA submission, the reliance on BMD as a surrogate for a disease, as well as an indicator for an incompletely understood change in bone physiology, has resulted in a study with uncertain conclusions regarding either clinical efficacy or long term bone safety. A few hundred women

have been exposed to a novel drug combination for one to two years. We know that surrogate markers have changed in the anticipated directions and that these changes have been shown to be associated with beneficial effects in previous studies of alendronate alone. We also know that, overall, there were no obvious safety problems, in terms of adverse experiences. However, we know nothing about meaningful clinical benefits associated with combination therapy. The study lacked sufficient statistical power to detect treatment-associated differences in fracture rates, and, in fact, there was not even a meaningful trend in either direction. If anything, combination therapy had an adverse effect on stature: the ALN + CE group lost height, while the placebo group increased stature non-significantly. In addition, a serious safety concern was raised by the histomorphometric data, a concern that was not allayed by the sponsor's explanation of the bone suppression.

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CONCLUSIONS

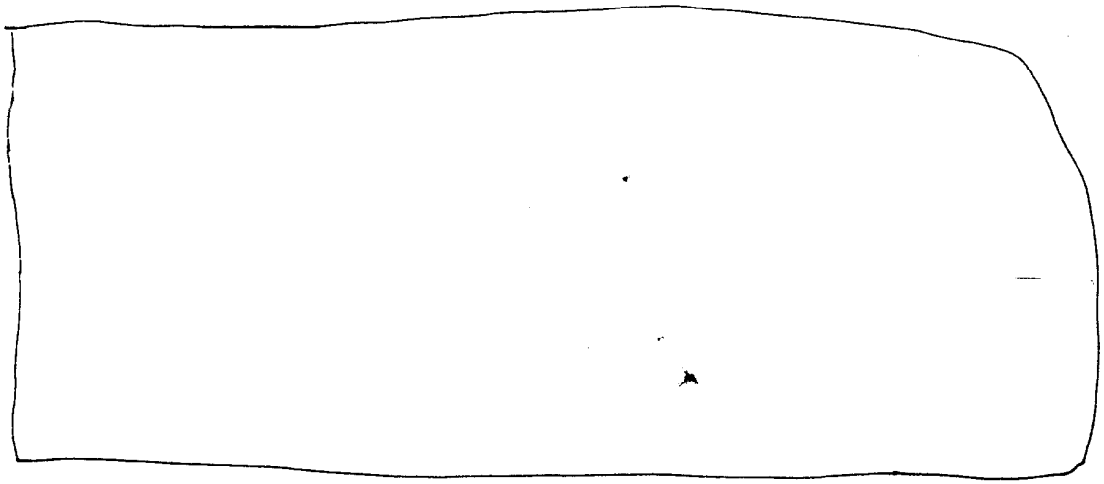
These studies demonstrated that:

1) Over 1 year, alendronate, 10mg/day, added to ongoing HRT, produced greater increases in BMD at selected skeletal sites than were achieved with continuation of HRT alone.
2) In a 2-year study, alendronate plus CE produced greater increases in BMD at selected sites than were achieved with either drug alone.
3) Changes in systemic levels of bone turnover markers were parallel to the BMD changes. The combination ALN + CE produced greater suppression of bone turnover markers than was achieved with either therapy alone.
4) The combination ALN + CE was well tolerated and had an overall safety profile that was essentially the same as that found with either drug alone or with placebo treatment.
5) Histomorphometry data confirmed that bone quality at the iliac crest is architecturally normal following 18 months of treatment with combination therapy. However, at the iliac crest, combined therapy inhibited bone resorption by almost 98%, relative to placebo, and by 70%, relative to alendronate alone. These data raise concerns regarding long-term safety of combination therapy.
6) Fracture efficacy was not part of the study; of some concern, patients on combination therapy lost more height over two years than patients on placebo, with trends towards greater height loss compared to either

group alone. Thus the clinical benefit of combination therapy is not clear, despite changes in surrogate markers.

11 Labeling review

Proposed changes to the current label are presented below. Other, extensive, changes to the Fosamax® label have been negotiated with the sponsor, on the basis of the results of the FIT trial.



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2 pages

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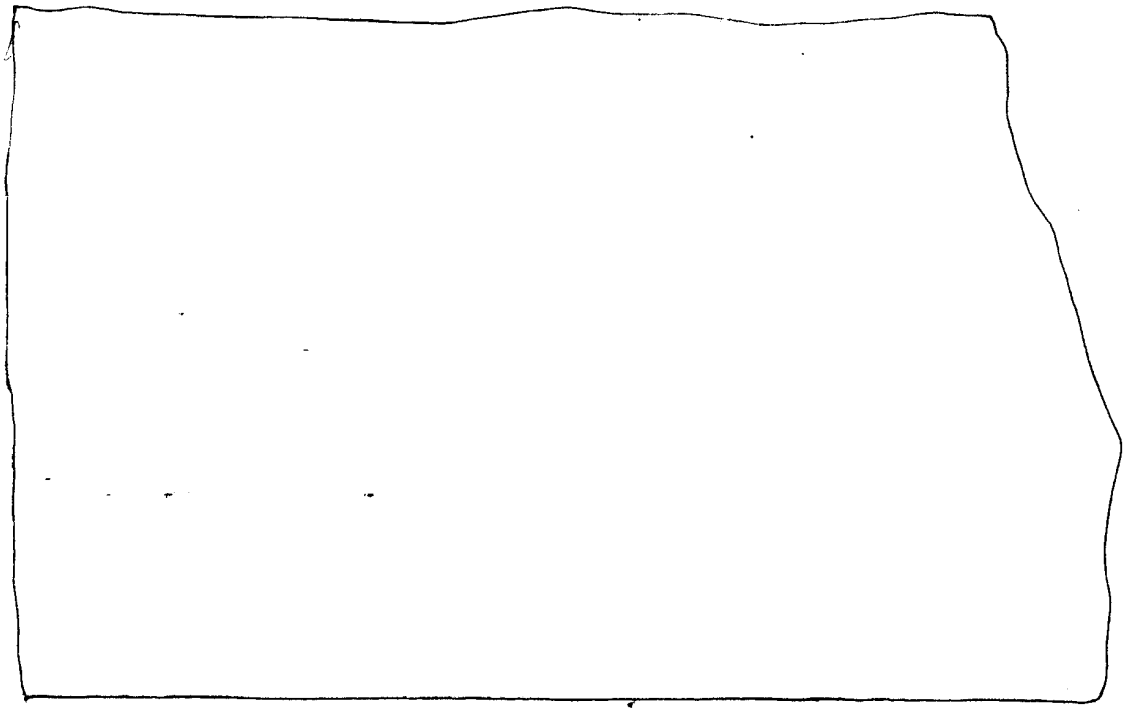
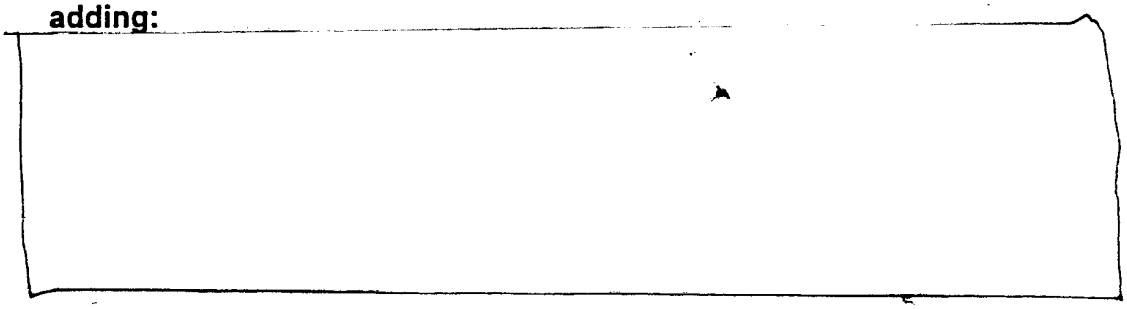
LABELING



In the Clinical Pharmacology and Drug Interaction sections, I recommend adding:



RECOMMENDATIONS:

APPROVAL, WITH INDICATED LABELING CHANGES. IT SHOULD ALSO BE MADE CLEAR THAT ALL PROMOTIONAL MATERIAL REGARDING ALENDRONATE WITH HRT MUST CARRY THE ABOVE STATEMENT.

/S/

BRUCE S. SCHNEIDER, MD

/S/ 11/19/99

MEDICAL OFFICER, DMEDP, HFD-510
CC DRS. SOBEL, TROENDLE, MR. HEDIN, HFD-510 FILE

20560n832 November 19, 1999

NDA 20560/S-018
Merck
Alendronate (Fosamax)

Team Leader's Comments on Combined Fosamax and HRT

Safety and efficacy data from 2 trials constitute the principal basis for this NDA supplement.

Another study 080 was a 4-month study of the effect on biochemical markers (Urinary N-Telopeptide/creatinine excretion) of adding progesterone (Medroxyprogesterone acetate, MPA) on days 1-12 of each month to continuous conjugated estrogen (CE). This study in 41 (38 completed) healthy, hysterectomized postmenopausal women, 40-75 yr of age & on HRT at least 1 yr, satisfactorily demonstrated that addition of MPA to ERT did not significantly alter bone markers.

Both Studies 097 and 072 were randomized and placebo-controlled, used 10 mg Alendronate, 0.625 mg CE and compared lumbar spine BMD as the primary endpoint.

Study 097 is a 1 year comparison of effects on BMD induced by Alendronate plus placebo and ALN plus HRT in women who are $\geq$40 years of age, postmenopausal $\geq$5 years (or at least age 25 more and surgically menopausal at least 5 years) with BMD $\leq$2 SD below peak bone mass at the lumbar spine or the femoral neck. 428 participants were enrolled, and 394 completed this study. LS BMD increased more in the ALN plus HRT group than in the placebo plus HRT patients by 2-2.6%.

Study 072 is a 2-year comparison of the effects on BMD of ALN alone compared to CE alone, the combination of ALN and CE, and placebo in 45-75 year old hysterectomized (at least 3 years prior to entry) women who had LS BMD <0.86 g/cm^2. 425 paarticipants were enrolled and 395 completed this study. Results were highly significant increases in BMD (6, 5.99, and 8.265 at the lumbar spine for ALN, CE, and ALN+CE, respectively) with no increase in the placebo patients. This difference is 2.266% more BMD with CE + ALN than with CE alone.

Histomorphometry was done on 92 biopsies on patients in Study 072. This was an important substudy, because the principal concern in combining ALN and HRT in an individual patient has been that we are thus combining two drugs, both of which inhibit bone remodeling. Dr. Schneider's very excellent review addresses the findings in these specimens. Osteoid thickness, mineral apposition rate, osteoid volume, and mineralizing surface were evaluated for signs of bone remodeling or lack of it. In each of the parameters, reduction in patients on CE + ALN exceeded reduction in those on CE alone. Significance of this finding for median OTh, OV/BV, and MS/BS were $P<0.001$, 0.001, and 0.001. For MAR, no significance was found, and observed means were 0.52 and 0.46 for CE and CE + ALN. That is what was intended and expected in combining two agents that both act by inhibiting osteoclasts. The observed median was 0.09 (placebo mean was 5.14), and the range was 0.00 to 1.02 (placebo range was 2.70 to 7.17). This almost total lack of mineralizing surface is frightening.

What happens when bone remodeling is halted completely? Because of the absence of information on this issue, I find it impossible to evaluate this submission as adequate to support the addition of this information to the package insert for Alendronate. If it is to be mentioned in the insert under Clinical Pharmacology, the risks must be stated in language that can be understood by the average or even the below-average physician. The benefits have not been shown to outweigh the risks. I support the wording that was proposed by Dr. Schneider in his review. The designation of histomorphometry results as 98% submission is less acceptable, but may convey the sense we have that further information is necessary. If the sponsor is unable to propose a satisfactory phase study, the application should not be approved.

Recommendations: Approvable if sponsor agrees to do an adequate study post marketing.

/S/ 11/19/99

Gloria Troendle

Cc:HFD-510/NDA 20560

Div File/GTroendle/BSchneider/RHedin/SSobel

November 16, 1999

MEMORANDUM

TO: NDA 20560-S018 FILE

RE: SAFETY UPDATE

A separate safety update has not been included with this submission. However, complete safety data on all patients in the trial were included with the submission, and in my opinion a separate safety update is not needed.

/S/

Bruce S. Schneider, MD

Medical Officer, DMEDP

/S/ 11/16/99

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