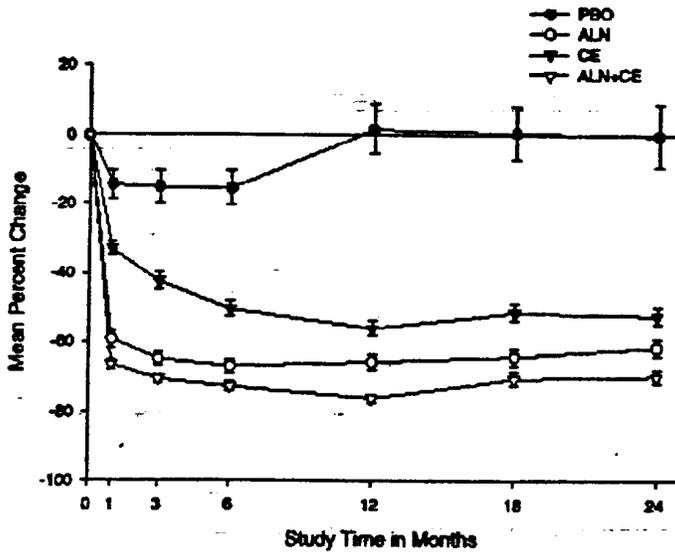
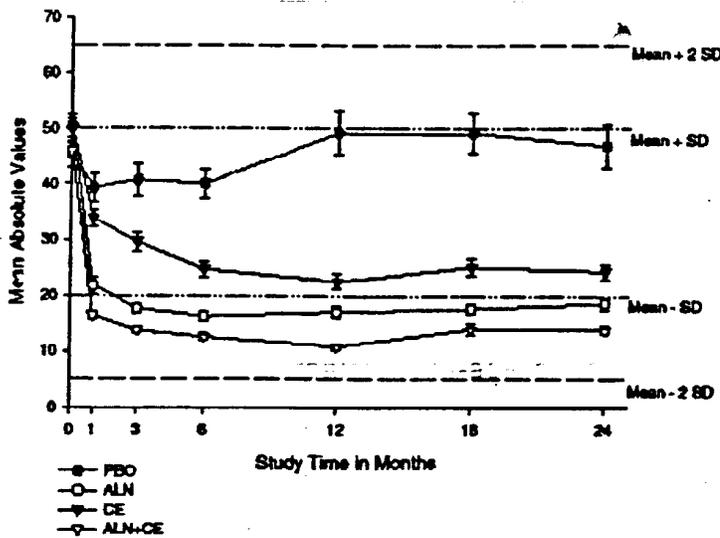


NTx?Cr



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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.

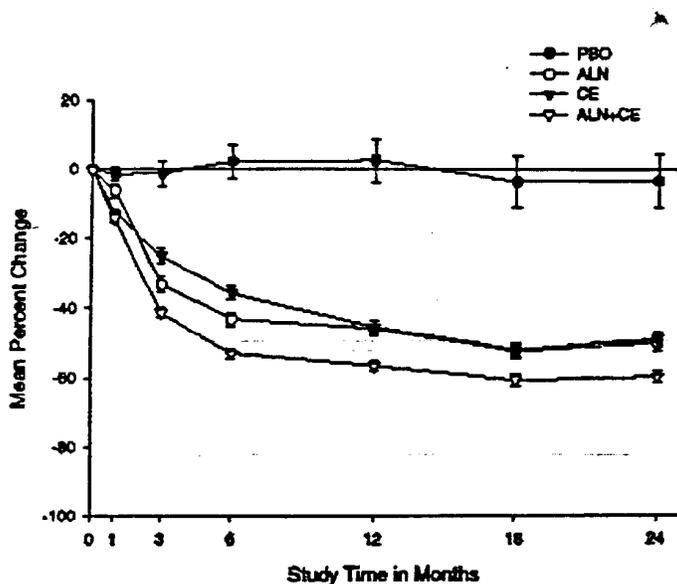
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These data are summarized in the following table:

Treatment	N	Observed Mean (nmol BCE/nmol Creatinine)		Percent Change From Baseline at Month 24			
		Baseline	Month 24	Mean ^a	Pairwise Comparison p-Value		
					ALN	CE	ALN+CE
PBO	26	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	21.44	-57.20***			<0.001
ALN+CE	94	45.70	13.89	-69.67***			

^a 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.

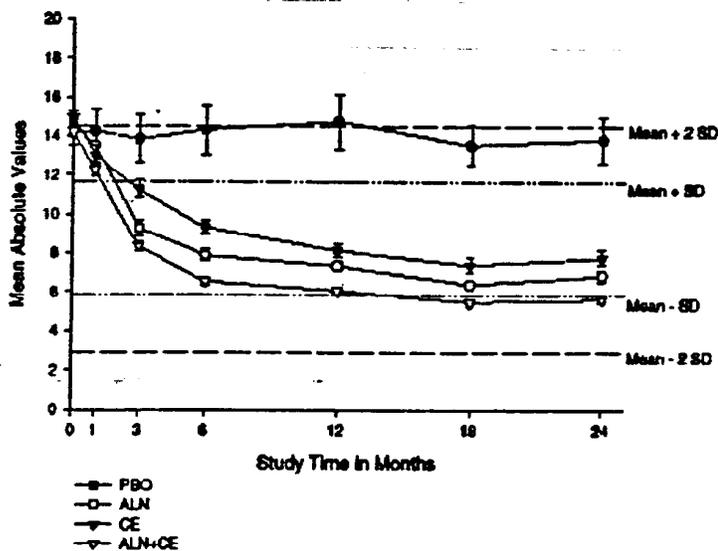
For BSAP, the 3 active treatment groups significantly decreased levels of this bone formation marker (relative to both baseline and to PBO, $p \leq 0.001$) throughout the 24 months. The PBO group showed a nonsignificant decrease of 3.27% during this period. For the 3 active-treatment groups, ALN, CE, 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			
		Baseline	Month 24	Mean*	Pairwise Comparison p-Value		
					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.

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.

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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			
		Baseline	Month 24	Mean ^a	Pairwise Comparison p-Value		
					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***			

^a 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.

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Serum Phosphate:

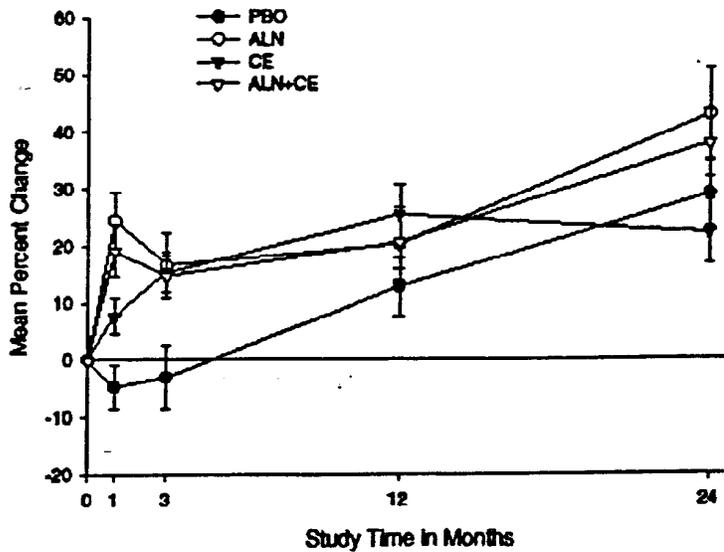
The PBO group had a significant ($p < 0.010$) decrease in phosphate of 7.88% by Month 24. ALN, CE, and ALN + CE also had significant ($p < 0.001$) decreases of 7.31, 8.11, and 9.73%, respectively, during this period. The serum phosphate fell more rapidly in the 3 active-treatment groups than in PBO, 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:



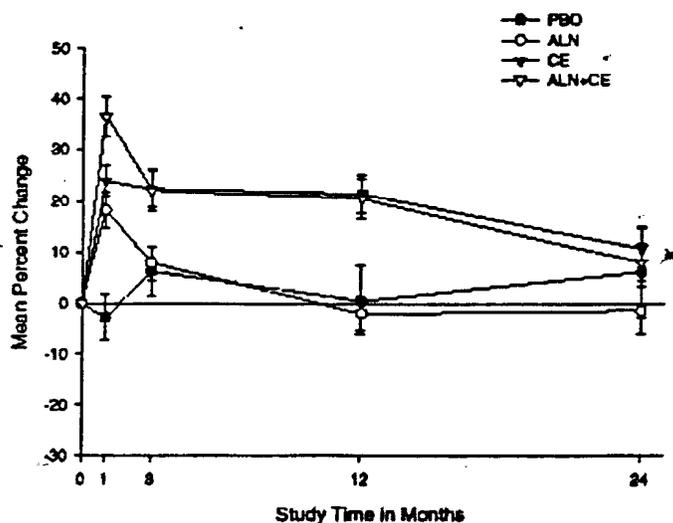
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1,25-Dihydroxyvitamin D:

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

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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 lumbar 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:

Treatment	Lumbar Spine ¹		Total Hip ¹		Femoral Neck ¹		Total Body ¹	
	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 ²	55	9.37 (4.69)***	55	4.78 (3.06)***	55	4.33 (4.29)***	43	2.19 (3.05)***

¹ Primary efficacy endpoint.
² Secondary efficacy endpoint.
 Within-treatment test of mean = 0 ***: p \leq 0.001 **: p \leq 0.010 *: p \leq 0.050.
³ 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 increase 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).

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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 ¹ 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 ¹ 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 ¹ adverse experience	3 (6.0)	2 (2.2)	9 (6.3)	9 (6.4)
withdrawn from therapy due to a serious drug-related ¹ adverse experience	1 (2.0)	0	1 (0.7)	0
Patients who died	0	0	0	0

¹ 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)	53 (57.6)	89 (62.3)	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=30)	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)	3 (3.6)
Hypertension increased	0	1 (1.1)	1 (0.7)	2 (1.4)
Palpitation	0	1 (1.1)	1 (0.7)	2 (1.4)
Tachycardia	0	0	2 (1.4)	2 (1.4)
Digestive System Disorders	18 (36.0)	26 (29.1)	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, ileocecal	1 (2.0)	2 (2.2)	1 (0.7)	1 (0.7)
Diverticulum, ileocecal	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)
Protrusion, 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)

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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)	3 (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, knee, 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, (11)	1 (2.0)	1 (1.1)	1 (0.7)	0
Fracture, vertebra, 112	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)

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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:

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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	71A1	P/2 tablets	395	AV block, third degree	176 days	Severe	Def not	No	SP
072002	0404	74C	P/2 tablets	31	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	51C	P/2 tablets	412	Neoplasm, breast, malignant	9 days	Severe	Possibly	Yes	SP
072007	0443	66C	OAT P 1 day/2 tablets	730	Reflex esophagitis	2 days	Moderate	Possibly	No	REC
			OAT P 1 day/2 tablets	730	Hernia, diaphragmatic	2 days	Moderate	Possibly	No	REC
072008	0373	76C	OAT P 32 days/2 tablets	275	Heart failure	30 days	Severe	Def not	No	REC
			OAT P 32 days/2 tablets	275	Blood pressure increased	1 day	NA	Def not	No	REC
			OAT P 61 days/2 tablets	304	Adverse reaction to unknown drug	30 days	Severe	Def not	No	REC
ALN (N=92)										
072001	0018	68C	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	67C	A/10 mg	725	Neoplasm, breast, malignant	1 day	NA	Prob not	No	REC
072002	0398	67C	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

072006	0370	71C	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	0254	58C	OAT A 1 day/10 mg	96	Pain, chest	4 days	Moderate	Prob not	No	REC
072011	0184	74C	A/10 mg	170	Pneumonia	11 days	Severe	Def not	No	REC
072011	0194	70C	A/10 mg	56	Neoplasm, skin, malignant	10 days	Mild	Def not	No	REC
072012	0202	58C	A/10 mg	394	Angina pectoris	1 day	Severe	Prob not	No	REC
072012	0409	61C	A/10 mg	276	Neoplasm, skin, malignant	64 days	Severe	Prob not	No	REC
072013	0218	75C	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	69C	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	69H1	A/10 mg	358	Hernia, abdominal	24 hours	Moderate	Def not	No	REC
072019	0415	66C	A/10 mg	158	Divericulitis, intestinal	61 days	Severe	Prob not	No	REC
			OAT A 1 day/10 mg	219	Pain, abdominal	1 day	Moderate	Def not	No	REC
			OAT A 1 day/10 mg	219	Divericulitis, intestinal	9 days	Moderate	Def not	No	REC

CE (N=143)										
072001	0012	65C	OAT E 48 days/0.625 mg	337	Fracture, calcaneus, right	136 days	Severe	Def not	No	SP
			OAT E 48 days/0.625 mg	337	Fracture, malloleus, right	136 days	Severe	Def not	No	SP
072001	0479	70C	OAT E 1 day/0.625 mg	75	Thrombosis, vein	25 days	Severe	Possibly	Yes	SP
072003	0040	49C	E/0.625 mg	84	Neoplasm, skin, malignant	1 day	Severe	Prob not	No	REC
072005	0090	62C	E/0.625 mg	233	Pneumonia	3 days	Moderate	Def not	No	REC
072006	0094	69C	E/0.625 mg	183	Pain, chest	19 days	Moderate	Def not	No	REC
072007	0110	62C	E/0.625 mg	353	Neoplasm, skin, malignant	40 days	Mild	Prob not	No	REC
072007	0442	71C	OAT E 1 day/0.625 mg	464	Reticule	23 hours	Mild	Def not	No	REC
072008	0143	77C	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
			OAT E 1 day/0.625 mg	114	Osteoarthritis	2 days	Severe	Def not	No	REC
072008	0522	70C	E/0.625 mg	64	Acid regurgitation	108 days	Moderate	Def not	No	REC
			E/0.625 mg	94	Reflex esophagitis	78 days	Moderate	Def not	No	REC
			E/0.625 mg	161	Pain, abdominal	11 days	Moderate	Def not	No	REC
072011	0191	56C	E/0.625 mg	71	Melanoma	11 days	Moderate	Def not	Yes	REC
072012	0212	61C	E/0.625 mg	195	Urotheliasis	6 days	Severe	Prob not	No	REC
072012	0346	56C	OAT 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	65C	E/0.625 mg	266	Myocardial infarction	1 hour	Mild	Prob not	No	REC
			OAT E 5 days/0.625 mg	273	Cardiovascular accident	30 minutes	Mild	Prob not	No	REC
072012	0509	67C	OAT E 1 day/0.625 mg	46	Pneumonia	3 days	Moderate	Def not	No	REC
			E/0.625 mg	358	Cysticerc	19 days	Severe	Def not	No	REC
072015	0452	59C	OAT E 1 day/0.625 mg	357	Drug overdose	4 days	Severe	Prob not	No	REC
			OAT E 1 day/0.625 mg	357	Syncope	30 minutes	Severe	Prob not	No	REC
072017	0293	62C	E/0.625 mg	711	Melanoma	6 days	Severe	Def not	No	REC
072019	0423	56C	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=149) (Cont.)										
072003	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	87	Neoplasm, malignant	1 day	Mild	Prob not	No	REC
			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	096	Ulcer, gastric/whorlulcerage	54 days	Severe	Positivity	No	SP
072010	0164	74/C	Off A 1 day/10 mg	097	Retrovire	1 day	Moderate	Prob not	No	REC
			Off E 1 day/0.625 mg	697	Cystocole	1 day	Moderate	Def not	No	REC
			Off A 1 day/10 mg Off E 1 day/0.625 mg	697	Cystocole	1 day	Moderate	Def not	No	REC

072001	0013	64/C	A/10 mg ¹	537	Anxiety	3 days	Moderate	Def not	No	REC
072002	0020	63/C	A/10 mg ¹	537	Atrial fibrillation	3 days	Severe	Def not	No	REC
			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	70	Nausea	16 days	Moderate	Prob not	No	REC
			E/0.625 mg	70	Vomiting	16 days	Moderate	Prob not	No	REC
072012	0361	64/C	A/10 mg	623	Cerebrovascular accident	30 minutes	Mild	Prob not	No	REC
			E/0.625 mg	623	Tachycardia	30 days	Moderate	Def not	No	SP
072012	0510	57/C	Off A 1 day/10 mg Off E 1 day/0.625 mg	678	Tachycardia	30 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	148	Palpitation	44 days	Mild	Def not	No	REC
			E/0.625 mg	178	Pain, chest	14 days	Severe	Def not	No	REC

072013 (Cont.)	0226	63/C	A/10 mg	178	Tachycardia	9 days	Severe	Def not	No	REC
			E/0.625 mg	178	Premature ventricular	14 days	Moderate	Def not	No	REC
			A/10 mg	186	Wolff-Parkinson-White syndrome	1 day	NA	Def not	No	REC
			E/0.625 mg	189	Pain, pleuritic	3 days	Moderate	Def not	No	REC
			A/10 mg	189	Pneumothorax	2 days	Moderate	Def not	No	REC
			E/0.625 mg	198	Neoplasm, skin, malignant	16 days	Mild	Def not	No	REC
			072018	0322	76/C	A/10 mg	411	Neoplasm, skin, malignant	1 day	Mild
			E/0.625 mg	666	Neoplasm, skin, malignant	1 hour	Mild	Def not	No	REC

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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.

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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 \geq 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.

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	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 0001 (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 $\geq 20\%$, 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 ¹ 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 ¹ 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 ¹ adverse experience	0	0	1 (0.7)	0
withdrawn from therapy due to a serious drug-related ¹ adverse experience	0	0	0	0

¹ 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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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 were 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/mm³ 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