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Month	S1 [†]	S2 [‡]	R	3 [§]	6	12 [¶]
Visit	1	2	3	N/A	4	5
CLINICAL						
Informed consent	X					
Medical history	X					
Complete physical exam (PE) with pelvic exam, pap		X				X
Dietary calcium assessment		X				
Interval PE			X		X	
Mammography [¶]		X				X
Adverse experiences			X	X	X	X
Treatment		X [§]	X [¶]	X [¶]	X [¶]	X [¶]
Tablet count			X		X	X
LABORATORY						
Laboratory tests—hematology, chemistry		X			X	X
Urine dipstick ^{¶¶}		X			X	X
TSH, PTH		X				
Urinary NTx			X		X	X
Serum BSAP			X		X	X
SPECIAL STUDY						
DXA	X				X	X

S1=screening Visit 1.
S2=screening Visit 2.
R=Randomization.
N/A=Telephone contact only—no office visit.

[†] Screening may have required more than one visit. If more than one visit was required, all procedures scheduled were completed within a 3-week period.
[‡] Telephone contact only.
[§] If a patient did not complete the study, all clinical, laboratory, and special study procedures listed for Month 12 were done at the time of discontinuation.
^{||} Interval PE included measurement of height, weight, heart rate, and blood pressure.
[¶] Baseline screening mammogram was to be performed unless a mammogram performed within the preceding 6 months was available. If available, it was considered the "baseline" study and a repeat mammogram was performed at the Month 12 visit.
^{¶¶} Single-blind placebo, usual HRT regimen, at least 1000-mg calcium daily between diet and supplement, and 400 IU vitamin D supplement during 2 week run-in period to assess compliance and tolerability.
^{¶¶¶} ALi^{††} or placebo plus usual HRT regimen, at least 1000-mg calcium daily between diet and supplement, and 400 IU vitamin D supplement.
^{¶¶¶¶} Urinary blood or protein ≥1+ by dipstick required microscopic analysis.
^{||} DXA of the PA lumbar spine and hip performed using Hologic or Lunar instrumentation.

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Visit	Visits 1 and 2 Screening	Visit 3 Randomization	Visit 4 Month 6	Visit 5 Month 12
Hematology				
Hemoglobin	X		X	X
Hematocrit	X		X	X
White blood cell count	X		X	X
Platelets	X		X	X
Blood Chemistry				
Blood urea nitrogen	X		X	X
Creatinine	X		X	X
AST	X		X	X
ALT	X		X	X
Glucose	X		X	X
Alkaline phosphatase (total)	X		X	X
Bicarbonate	X		X	X
Cholesterol	X		X	X
Triglycerides	X		X	X
Albumin	X		X	X
TSH	X			
Sodium	X		X	X
Potassium	X		X	X
Calcium	X		X	X
Phosphorus	X		X	X
PTH	X			
Protein	X		X	X
Uric acid	X		X	X
Bilirubin, total	X		X	X
LDH	X		X	X
GGT	X		X	X
Urinalysis				
Protein	X		X	X
Blood	X		X	X
WBC's	X		X	X
RBCs	X		X	X
Squamous epithelial cells	X		X	X
Renal epithelial cells	X		X	X
Casts	X		X	X
Biochemical Markers				
Bone-specific alkaline phosphatase		X	X	X
Urine N-telopeptides		X	X	X

Laboratory measurements:

As a marker of bone resorption, the sponsor used urinary N-telopeptides of type I collagen, corrected for creatinine (NTx, OSTEOMARK™). 5ml aliquots of first morning urine voids were frozen until assay.

Serum bone-specific alkaline phosphatase (BSAP) was used as a marker of bone formation. Serum samples were stored frozen until assay, using the Tandem™-R-Ostase™ (Hybritech) kit.

Bone densitometry was performed at each study site, using either Hologic or Lunar densitometers. User manuals were provided by the central quality assurance center. For each patient, measurements were taken on the same densitometer throughout the study. Quality control data were provided by each study site using hydroxyapatite phantoms. All study sites participated in a calibration program using a "gold standard" phantom. Further details on quality control are provided in the NDA submission. Densitometry of the lumbar spine and hip was performed at screening, Month 6, and Month 12. Fractured vertebrae were excluded from BMD analyses.

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8.2.1.3.2 Endpoints

Efficacy

The primary efficacy endpoint was % change in BMD of the lumbar spine (L1-4) at 1 year. The % change from baseline after 1 year of treatment in femoral neck and trochanter BMD constituted secondary endpoints. Other secondary endpoints were % change from baseline in bone formation and resorption markers.

Safety

At each visit, adverse events were determined by direct questioning, as well as physical examination. Recording and coding of all AE's were performed according to standard procedures (full details provided by sponsor in NDA submission). ~~Laboratory AE's were identified and recorded according to routine methodology (also included in submission).~~ Predefined limits of change were defined for each laboratory parameter, in order to estimate the numbers of individuals with routine laboratory results that were considered possibly adverse. These establish limits are provided in the submission.

8.2.1.3.3 Statistical considerations

A complete statistics review accompanies this analysis. The primary and secondary hypotheses are indicated above. Briefly, the null hypothesis for all BMD efficacy endpoints was that the addition of alendronate to postmenopausal HRT will produce an increase in BMD that is the equivalent to that seen with HRT alone. The alternative hypothesis was that addition of alendronate will produce an increase in BMD that is greater than that seen with HRT alone. For the bone marker studies the secondary null hypothesis was that addition of alendronate to HRT regimen will produce decreases in markers of bone turnover that are equivalent to those seen on HRT alone. The alternative hypothesis is that addition of alendronate will produce decreases in markers that are greater than seen with HRT alone.

For safety/tolerability, the null hypothesis was that HRT alone will be safer and better tolerated than the combination alendronate+HRT. The alternative hypothesis was that addition of alendronate to HRT would be as safe as HRT alone.

The sponsor presents a power analysis. Based on extensive earlier experience, the standard deviation of spinal BMD measurements of the lumbar spine is estimated at about 4.0%. To detect a 1.5% difference, between treatment groups, in BMD changes from baseline, with 90% power at an alpha level of

0.05, 300 subjects would be required in a 1:1 allocation ratio. The sponsor enrolled 428 subjects in order to ensure that 300 were retained for evaluation at study end.

For the primary analysis, the sponsor employed an ANOVA model that included terms for treatment, center, stratum, and all 2-way interactions with treatment. Statistical significance for all treatment comparisons was set at the 0.05 alpha level (2-sided). This analysis was used to determine whether there was a significant difference between treatment groups in the mean % change from baseline in BMD of the lumbar spine at 1 year of treatment. The analysis used an intent-to-treat approach. The ITT population included all patients who received at least 1 dose of study drug and had at least 1 post-treatment BMD determination. For patients with only a 6-month BMD determination, the 6-month value was carried forward. An identical analysis was used for BMD changes in the femur. In addition, a per-protocol analysis of BMD data is provided.

Mean % changes in biochemical markers were analyzed (using a log-transformed data) as a fraction of baseline. Analyses of these data used a per-protocol approach, with no carrying forward of data.

Clinical and laboratory ae's were summarized separately. Between-group differences in the incidence of ae's were compared using Fisher's exact test. The sponsor conducted analyses on all reported ae's, as well as on the set of ae's considered by the investigator to be drug-related.

Subgroup analyses of BMD data were done for the following pre-defined groups: duration of HRT use (< 2 years, >2 years), age (<65 years, >65 years), baseline lumbar spine T-score (≤ 2.5 , > 2.5), and baseline calcium intake (≤ 800 mg/day, > 800 mg/day).

Further details of the statistical analyses are provided in the submission.

8.2.2 RESULTS

8.2.2.1 Populations enrolled/analyzed

The sponsor enrolled 428 women, mean age 61.7 years. With the exception of smoking history and family history of osteoporosis, there was no difference in relevant baseline characteristics. These included age (mean was about 62 years, range 40-84 years), duration of menopause (mean about 15 years, range 1.6-44 years), height, weight, duration of prior HRT (mean about 9.5 years, range 0.6-42 years), and estimated calcium intake. More than 96% were Caucasian; 56.5% had experienced a previous fracture; 60% were receiving combined estrogen/progestin therapy, the remainder taking estrogen alone.

The proportion of subjects who had a history of smoking or a family history of osteoporosis was statistically significantly greater in the alendronate + HRT group than in PBO + HRT (for + smoking history, 46.7% alendronate+HRT vs 36.5% HRT+ PBO, $p=0.039$; for family history of osteoporosis, 59.2% vs 48.6%, alendronate vs PBO, $p=0.044$). There were no other significant between-group differences at baseline. Details on baseline characteristics are provided in Tables 7 and 8 of the NDA submission.

Baseline BMD values at the spine, femoral neck, trochanter, or Ward's triangle did not differ between treatment groups (Table 10 of the NDA submission).

Baseline values for biochemical bone turnover markers, NTx and BSAP) did not differ between the two treatment groups (data in Table 11 of submission). The values for both parameters were similar to those found in normal premenopausal women.

Comment: This was presumably due to the ongoing HRT. These markers are usually elevated in osteoporotic postmenopausal women.

A complete listing of secondary diagnoses is provided in Table 12 of the NDA submission. All but one subject in each treatment group had at least one secondary diagnosis.

Comment: At baseline, the two treatment groups were evenly balanced according to specific secondary diagnoses, including GI tract disorders.

The sponsor summarizes all prior drug therapies (Table 13 of the NDA) that were taken within 14 days of baseline. Of the 428 randomized patients, 397 had at least 1 prior therapy. Of note, about 25% of all subjects were taking anti-inflammatory drugs, and approximately 27% were using GI drugs.

Concomitant therapies were listed, by treatment group, in Table 14 of the NDA. Approximately 37% of all subjects used anti-inflammatory drugs, and 28% used GI medications (excluding calcium). Use of specific concomitant therapies did not differ by treatment group.

Patient accounting:

Of the 428 patients who entered, 394 (92.1%) completed the study. The sponsor provides a complete listing of all patients who discontinued the study, along with reasons for discontinuation. The overall data are summarized in the table below:

ENTERED: Age Range (years)	Total	PBO + HRT	ALN + HRT
	428 40 to 84	214 42 to 84	214 40 to 82
	n (%)	n (%)	n (%)
COMPLETED 12 MONTHS	394 (92.1)	191 (89.3)	203 (94.9)
DISCONTINUED:	34 (7.9)	23*(10.7)	11 (5.1)
Clinical adverse experience	16 (3.7)	11 (5.1)	5 (2.3)
Laboratory adverse experience	0	0	0
Protocol deviation	1 (0.5)	1 (0.5)	0
Lost to follow-up	3 (0.7)	1 (0.5)	2 (0.9)
Patient withdrew consent	10 (2.3)	6 (2.8)	4 (1.9)
Other	4 (0.9)	4 (1.9)	0

* p=0.048.

For the BMD analysis, the number of patients included in the ITT and per-protocol analyses are given in the table below:

	PBO + HRT (N=214)	ALN + HRT (N=214)	Total (N=428)
Total Included In			
Intention-to-Treat Analysis	202	206	408
Per-Protocol Analysis	178	192	370
Total Excluded From			
Intention-to-Treat Analysis	12	8	20
Per-Protocol Analysis	36	22	58

To be included in the ITT analysis at a given time point, patients must have had a baseline measurement and at least one post-treatment measurement prior to or at that time point. Patients were excluded from per-protocol analyses for any of the following reasons: study drug non-compliance, postmenopausal <4.5 years, prior HRT <1 year, BMD exclusion criteria.

Specific estrogen use: Data on specific estrogen preparations and doses are provided by the sponsor. The majority of patients (approximately 65%) were taking CEE, 0.625 mg/day, with the remainder receiving higher doses of CEE, or transdermal estradiol, micronized estradiol, estropipate, or esterified estrogen. One patient took ethinyl estradiol. There were no significant differences between treatment groups in the type or dose of estrogen. The sponsor has summarized estrogen use in the table below:

Preparation	Daily Dosage	PBO + HRT (N=214)	ALN + HRT (N=214)
Conjugated Equine Estrogens	0.625 mg	136 (63.6)	147 (68.7)
	0.9 mg	9 (4.2)	10 (4.7)
	1.25 mg	10 (4.7)	9 (4.2)
Transdermal Estradiol	0.05 mg	8 (3.7)	15 (7.0)
	0.075 mg	1 (0.5)	0
	0.1 mg	7 (3.3)	4 (1.9)
Micronized Estradiol	0.5 mg	4 (1.9)	4 (1.9)
	0.75 mg	1 (0.5)	0
	1.0 mg	13 (6.1)	11 (5.1)
	1.5 mg	1 (0.5)	1 (0.5)
	2.0 mg	8 (3.7)	0
Estropipate	0.625 mg	4 (1.9)	4 (1.9)
	0.75 mg	1 (0.5)	0
	0.937 mg	0	1 (0.5)
	1.25 mg	5 (1.9)	4 (1.9)
Esterified Estrogen	0.625 mg	7 (3.3)	3 (1.4)
Ethinyl Estradiol	0.02 mg	0	1 (0.5)

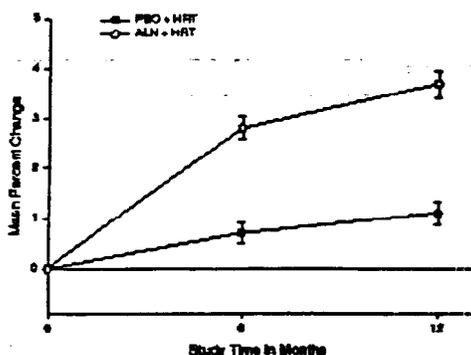
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8.2.2.2 Efficacy outcomes

For bone mineral density, the mean % change from baseline constituted the primary outcome, using an ITT approach. In addition, a per-protocol analysis, which yielded comparable results, is included in the submission. The treatment-by-stratum (see above for definitions of strata) interaction analysis demonstrated no qualitative interactions. Thus each stratum showed the same differences between treatments. This analysis was done for each BMD outcome variable, with the same results.

Lumbar spine BMD:

Over the 12-month period, BMD increased in both treatment groups at this site, as shown by the sponsor in the figure below:



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The mean % change from baseline was significant ($p < 0.001$) for both treatment groups at both the 6-month and 12-month time points. The % change from baseline was significantly greater ($p < 0.001$) in the alendronate + HRT group than in the HRT+PBO group at both time points.

The sponsor provides a summary of these data in the table below:

Treatment	N	Observed Mean (pctgs)		Percent Change From Baseline at Month 6				Pairwise Comparison P Value ALN + HRT vs. PBO + HRT
		Baseline	Month 6	Mean	SD	Adjusted Mean	95% C.I.	
PBO + HRT	213	0.853	0.858	0.7***	3.0	0.6	(0.1, 1.0)	<0.001
ALN + HRT	214	0.859	0.884	2.8***	3.4	2.7	(2.2, 3.2)	
Within-treatment test of mean: ***p<0.001. p-Value for consistency of treatment across centers: 0.994. p-Value for consistency of treatment across strata based on prior estrogen use: 0.715. Pooled SD: 3.25.								
Treatment	N	Observed Mean (pctgs)		Percent Change From Baseline at Month 12				Pairwise Comparison P Value ALN + HRT vs. PBO + HRT
		Baseline	Month 12	Mean	SD	Adjusted Mean	95% C.I.	
PBO + HRT	213	0.853	0.862	1.1***	3.5	1.0	(0.4, 1.5)	<0.001
ALN + HRT	214	0.859	0.892	3.7***	3.9	2.6	(2.0, 3.1)	
Within-treatment test of mean: ***p<0.001. p-Value for consistency of treatment across centers: 0.354. p-Value for consistency of treatment across strata based on prior estrogen use: 0.568. Pooled SD: 3.65.								

Comments: The data clearly show an enhancement in BMD accrual at the lumbar spine in association with alendronate + HRT, compared to HRT

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alone. The between-group differences were 2-2.6%; most of the difference was achieved by 6 months.

Femoral neck BMD:

Result: Both treatment groups demonstrated an increase in BMD at the femoral neck over the 12 months of the study. For both groups at both time points, the increases over baseline were significant at $p \leq 0.05$. There was a numerical difference between groups at both time points, with alendronate > PBO, but the differences were not statistically significant ($p=0.318$ at 6 months; $p=0.072$ at 12 months).

The data are summarized in the table below:

Treatment	N	Observed Mean (g/cm ²)		Percent Change From Baseline at Month 6				Pairwise Comparison P Value ALN + HRT vs. PBO + HRT
		Baseline	Month 6	Mean	SD	Adjusted Mean	95% C.I.	
PBO + HRT	213	0.681	0.688	1.0*	5.2	0.9	(0.2, 1.7)	0.318
ALN + HRT	214	0.684	0.694	1.5***	4.4	1.5	(0.7, 2.2)	
Within-treatment test of mean = 0: ** $p \leq 0.05$; *** $p \leq 0.001$. p-Value for consistency of treatment across centers: 0.450. p-Value for consistency of treatment across strata based on prior estrogen use: 0.908. Pooled SD: 4.75.								
Treatment	N	Observed Mean (g/cm ²)		Percent Change From Baseline at Month 12				Pairwise Comparison P Value ALN + HRT vs. PBO + HRT
		Baseline	Month 12	Mean	SD	Adjusted Mean	95% C.I.	
PBO + HRT	213	0.681	0.687	0.8*	4.9	0.8	(0.0, 1.5)	0.072
ALN + HRT	214	0.684	0.695	1.6***	5.1	1.7	(1.0, 2.5)	
Within-treatment test of mean = 0: * $p \leq 0.05$; *** $p \leq 0.001$. p-Value for consistency of treatment across centers: 0.838. p-Value for consistency of treatment across strata based on prior estrogen use: 0.938. Pooled SD: 5.06.								

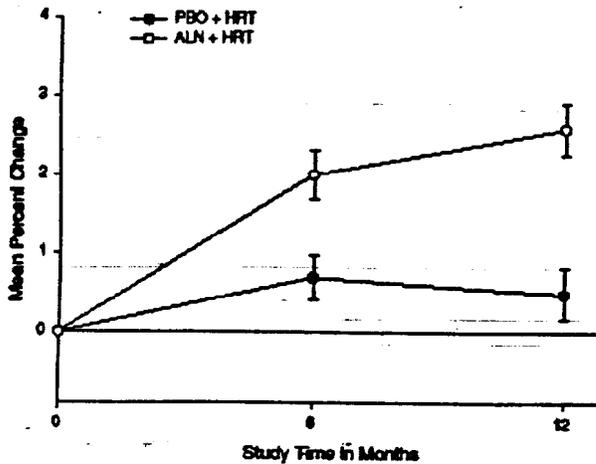
Trochanter BMD:

Result: For the alendronate + HRT group, trochanter BMD increased significantly ($p \leq 0.001$) from baseline at both (6- and 12-month) time points. For the HRT + PBO group, the increase was significant at 6 months ($p \leq 0.05$), but not at 12 months. At the trochanter, the increases in BMD in the alendronate + HRT group were significantly greater than those in the HRT + PBO group at both time points ($p=0.003$ at 6 months and $p \leq 0.001$ at 12 months). The differences between groups were 1.3-2.0%. The results are given in the sponsor's figure below:

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TROCHANTER BMD



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Summary data with statistics are provided by the sponsor in the table below:

Treatment	N	Observed Mean (g/cm ³)		Percent Change From Baseline at Month 6				Pairwise Comparison P Value ALN + HRT vs. PBO + HRT
		Baseline	Month 6	Mean	SD	Adjusted Mean	95% C.I.	
PBO + HRT	213	0.592	0.595	0.7*	4.2	0.8	(0.2, 1.5)	0.003
ALN + HRT	214	0.588	0.602	2.0***	4.7	2.3	(1.6, 2.9)	

Within-treatment test of mean: *p<0.05; ***p<0.001.
 p-Value for consistency of treatment across centers: 0.889.
 p-Value for consistency of treatment across strata based on prior estrogen use: 0.294.
 Pooled SD: 4.41.

Treatment	N	Observed Mean (g/cm ³)		Percent Change From Baseline at Month 12				Pairwise Comparison P Value ALN + HRT vs. PBO + HRT
		Baseline	Month 12	Mean	SD	Adjusted Mean	95% C.I.	
PBO + HRT	213	0.592	0.596	0.5	4.8	0.5	(-0.2, 1.2)	<0.001
ALN + HRT	214	0.588	0.604	2.6***	4.9	2.7	(1.2, 3.4)	

Within-treatment test of mean: *p<0.05; ***p<0.001.
 p-Value for consistency of treatment across centers: 0.763.
 p-Value for consistency of treatment across strata based on prior estrogen use: 0.428.
 Pooled SD: 4.71.

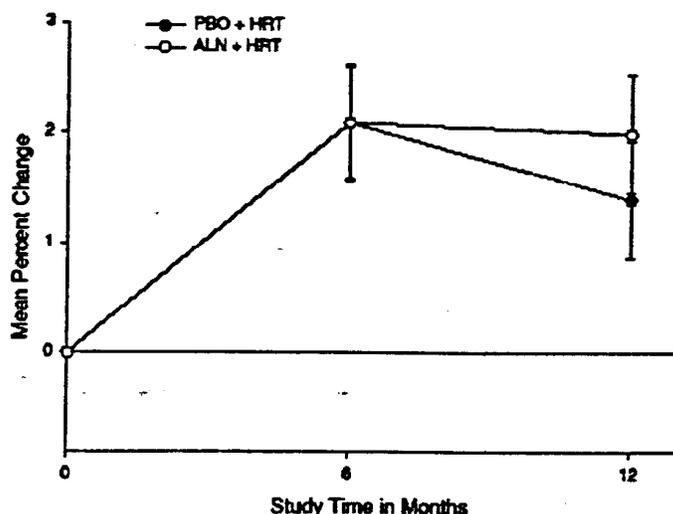
Ward's triangle:

Result: At Ward's triangle, both treatment groups had significant increases in BMD at 6 and 12 months (p<0.05); however, there was no difference between the groups at either time point (sponsor's figure below).

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WARD'S TRIANGLE BMD



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For the BMD studies, there was no significant treatment-by-center interaction, at any skeletal site. As mentioned above, the per-protocol analysis, presented as part of the submission, yielded essentially the same results.

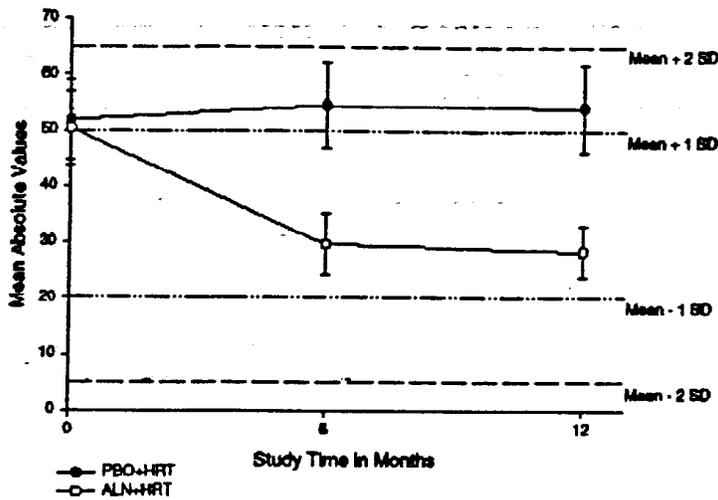
The subgroup analyses, described above, were based on age, HRT duration, lumbar spine BMD, and baseline calcium intake. The analyses showed no significant changes or responses by subgroup, suggesting that subjects in all the pre-defined subgroups responded similarly to treatment. Complete data from the subgroup analyses are provided with the submission.

Biochemical Efficacy

Biochemical marker endpoints were analyzed using a per-protocol approach, in which data were analyzed up to and including the last time point that subjects received study drug. No data were carried forward in this analysis.

For urine NTx, the mean values for both treatment groups (mean absolute values \pm SE, NTx/Cr, in nmol/mmol) are presented in the sponsor's figure below. The figure includes the normal premenopausal mean NTx \pm 2 SD. The reason for the slight elevation in baseline mean NTx was the inclusion of a few patients with very high values in both treatment groups. The median NTx values for both groups were within the normal premenopausal range.

NTx/Cr



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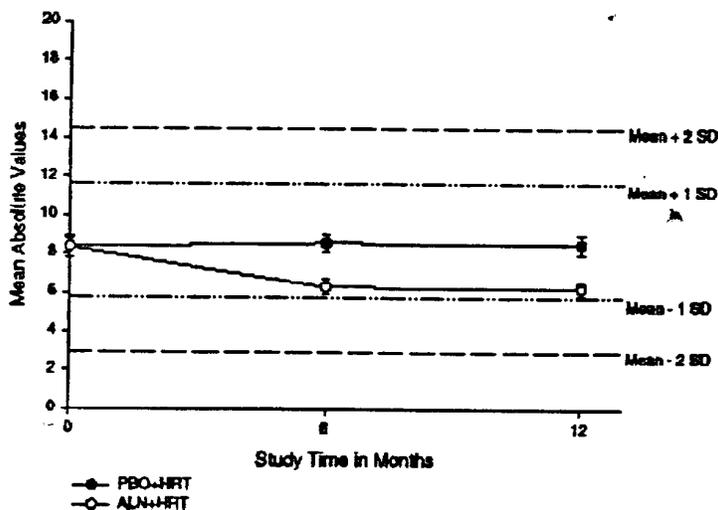
As shown in this figure, and in the table below, there was no significant change in urine NTx in the HRT + PBO group over the 12 months, whereas the NTx decreased significantly ($p < 0.001$) from baseline in the alendronate + HRT group at both 6 months (-41.7%) and 12 months (-45.5%). The differences between the two treatment groups were significant ($p < 0.001$) at both time points. The changes from baseline were similar, using either mean or median values.

Treatment	N	Observed Mean		Observed Median		Percent Change From Baseline at Month 6	
		Baseline	Month 6	Baseline	Month 6	Geometric Mean	Pairwise Comparison p-Value ALN + HRT vs. PBO + HRT
PBO + HRT	170	51.8	54.5	33	34	3.5	<0.001
ALN + HRT	184	50.4	29.7	34	18	-41.7***	
Within-treatment test of mean = 0: ***p<0.001. p-Value for consistency of treatment across centers: 0.938. p-Value for consistency of treatment across strata based on prior estrogen use: 0.164. Transformed from ln (fraction of baseline) Pooled SD: 0.65.							
Treatment	N	Observed Mean		Observed Median		Percent Change From Baseline at Month 12	
		Baseline	Month 12	Baseline	Month 12	Geometric Mean	Pairwise Comparison p-Value ALN + HRT vs. PBO + HRT
PBO + HRT	170	51.8	54.1	33	36	0.7	<0.001
ALN + HRT	184	50.4	28.4	34	18	-45.5***	
Within-treatment test of mean = 0: ***p<0.001. p-Value for consistency of treatment across centers: 0.909. p-Value for consistency of treatment across strata based on prior estrogen use: 0.403. Transformed from ln (fraction of baseline) Pooled SD: 0.70. Values greater than 3 SD from the overall mean were considered outliers and were removed from the estimation of means. All patients were included in the analysis of the ranked data which provides the comparison of treatments							

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BSAP Results: For BSAP, a marker of bone formation, the HRT + PBO group had a small, but nonsignificant increase during the study. In contrast, the HRT + alendronate group showed a decrease at Month 6 that was maintained through Month 12. The decrease, which was about 21% from baseline, was statistically significant ($p < 0.001$). These decreases in the alendronate group were statistically significantly greater than those seen in the placebo group at both time points ($p < 0.001$).

The changes in BSAP over time are shown in the sponsor's figure below, which plots serum BSAP, in ng/ml, over time. Again, the normal premenopausal mean \pm 2SD is included in the figure. As shown in the figure, and in the following table, the baseline mean and median values for BSAP in both treatment groups were essentially the same as those found in normal premenopausal women (premenopausal mean BSAP is 8.7 ng/mL, according to assay reference data).



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Summary data, with statistics, for changes in BSAP are shown in the sponsor's table below:

BSAP SUMMARY DATA

Treatment	N	Observed Mean		Observed Median		Percent Change From Baseline at Month 6	
		Baseline	Month 6	Baseline	Month 6	Geometric Mean	Pairwise Comparison p-Value ALN + HRT vs. PBO + HRT
PBO + HRT	188	8.4	8.6	8.2	8.7	5.5	
ALN + HRT	193	8.3	6.9	7.8	6.1	-21.7***	<0.001
Within-treatment test of mean = 0: ***p<0.001. p-Value for consistency of treatment across centers: 0.424. p-Value for consistency of treatment across sites based on prior estrogen use: 0.762. *Transformed from ln (fraction of baseline) Pooled SD: 0.44.							
Treatment	N	Observed Mean		Observed Median		Percent Change From Baseline at Month 12	
		Baseline	Month 12	Baseline	Month 12	Geometric Mean	Pairwise Comparison p-Value ALN + HRT vs. PBO + HRT
PBO + HRT	188	8.4	8.5	8.2	8.4	4.1	
ALN + HRT	193	8.3	6.2	7.8	6.1	-20.4***	<0.001
Within-treatment test of mean = 0: ***p<0.001. p-Value for consistency of treatment across centers: 0.978. p-Value for consistency of treatment across sites based on prior estrogen use: 0.702. *Transformed from ln (fraction of baseline) Pooled SD: 0.45. Values greater than 5 SD from the overall mean were considered outliers and were removed from the estimation of means. All patients were included in the analysis of the ranked data which provides the comparison of treatments.							

Comments: The results of these studies show that the baseline biochemical markers of bone formation and resorption were, on average, essentially the same as in premenopausal women. This is most likely due to the estrogen replacement therapy (although this study lacked a control group of patients who were not taking HRT). These results suggest that these subjects were generally compliant with the HRT.

The addition of alendronate to the ongoing HRT produced additional, statistically significant, decreases in markers of bone turnover (formation and resorption) over those found in subjects taking HRT alone. These differences were seen at both the 6- and 12-month time points. In subjects receiving alendronate + HRT, the markers remained within the lower normal range of values found in premenopausal women.

8.2.2.3 Safety

This safety analysis compared the frequency of adverse events, as well as the % of patients with specific adverse events, between the two treatment groups. In the analysis, 214 alendronate and 214 placebo patients were evaluated. Upper GI AE's and fracture AE's were evaluated separately, because of concerns related specifically to alendronate.

No patients withdrew from this study because of a serious AE, and there were no deaths. A summary of clinical adverse experience, by treatment group, is provided by the sponsor in the following table:

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	PBO + HRT (N=214)	ALN + HRT (N=214)
	n (%)	n (%)
Number of patients evaluated	214	214
Number (%) of patients:		
with one or more adverse experience	178 (83.2)	186 (86.9)
with a drug-related [†] adverse experiences	44 (20.6)	46 (21.5)
with a serious adverse experience	17 (7.9)	12 (5.6)
with serious drug-related [†] adverse experiences	0	0
withdrawn from therapy due to an adverse experience [‡]	14 (6.5)	8 (3.7)
deaths	0	0
withdrawn due to a drug-related adverse experience ^{†,‡}	11 (5.1)	4 (1.9)
withdrawn due to a serious adverse experience [‡]	2 (0.9)	1 (0.5)
withdrawn due to a serious drug-related adverse experience ^{†,‡}	0	0

† Determined by the investigator to be possibly, probably, or definitely drug related.
‡ Includes those patients who discontinued study drug therapy but completed the study on HRT alone (3 alendronate + HRT, 3 placebo + HRT).
This table does not include those adverse experiences that occurred during pretreatment, prior to randomization.

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The number of patients with clinical AE's, by body system, did not differ between groups, as shown below:

	PBO + HRT (N=214)	ALN + HRT (N=214)
	n (%)	n (%)
Body as a whole/site unspecified	40 (18.7)	39 (18.2)
Cardiovascular system disorders	26 (12.1)	18 (8.4)
Digestive system disorders	70 (32.7)	74 (34.6)
Endocrine disorders	2 (0.9)	3 (1.4)
Hematologic and lymphatic disorders	4 (1.9)	0
Metabolic, nutritional, immune disorders	12 (5.6)	13 (6.1)
Musculoskeletal disorders	63 (29.4)	78 (36.4)
Nervous system and psychiatric disorders	31 (14.5)	46 (21.5)
Respiratory system disorders	91 (42.5)	82 (38.3)
Skin or skin appendage	35 (16.4)	39 (18.2)
Eye, ear, nose	10 (4.7)	14 (6.5)
Urogenital system disorders	68 (31.8)	64 (29.9)

This table does not include those adverse experiences that occurred during pretreatment. Although a patient may have had two or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

The sponsor provides a table of all clinical AE's occurring in at least 2% of patients in either treatment group. The most common of these were URI's, sinusitis, headache, back pain, and abdominal pain. Back pain was reported in a significantly greater proportion patients in the HRT + alendronate group than in the HRT + PBO group: 9.8% vs 3.3% (p<0.01). Full details are provided in Table 26 of the submission.

Upper GI AE's: A separate analysis is presented for upper GI AE's. The following table summarizes the number and percent of patients with upper GI AE's. There were no significant between-group differences in any of these parameters. The sponsor provides narratives for all upper GI AE's that resulted in discontinuation from the study.

	FBO + HRT (N=214)	ALN + HRT (N=214)
	n (%)	n (%)
Number of patients evaluated	214	214
Number (%) of patients		
with one or more upper GI adverse experiences	49 (22.9)	52 (24.3)
with a drug-related† adverse experience	23 (10.7)	23 (10.7)
with a serious adverse experience	1 (0.5)	2 (0.9)
with a serious drug-related† adverse experience	0	0
withdrawn from therapy due to a adverse experience	7 (3.3)	3 (1.4)
withdrawn from therapy due to a serious adverse experience	0	0
withdrawn from therapy due to a drug-related† adverse experience	7 (3.3)	2 (0.9)
withdrawn from therapy due to a serious drug-related† adverse experience	0	0
Patients who died	0	0

† Determined by the investigator to be possibly, probably, or definitely related to treatment with study drug.

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The number and % of patients with specific upper GI AE's is provided in the table below. There were no significant between-group differences.

	PBO + HRT (N=214) n (%)	ALN + HRT (N=214) n (%)
Patients with one or more upper GI adverse experiences	49 (22.9)	52 (24.3)
Abdominal distention	3 (1.4)	7 (3.3)
Abdominal pain	14 (6.5)	13 (6.1)
Acid regurgitation	8 (3.7)	9 (4.2)
Cholelithiasis	1 (0.5)	1 (0.5)
Dyspepsia	6 (2.8)	12 (5.6)
Eructation	2 (0.9)	0 (0.0)
Gastritis	2 (0.9)	2 (0.9)
Nausea	12 (5.6)	6 (2.8)
Reflux esophagitis	3 (1.4)	2 (0.9)
Vomiting	7 (3.3)	2 (0.9)

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Serious Clinical AE's

A serious AE is defined by the sponsor as one that "resulted in death, permanent or substantial disability, new or prolonged hospitalization, was immediately life threatening, cancer, congenital anomaly, or the result of an accidental or intentional overdose with the study medication."

During this study, 29 individuals (7%) experienced at least one serious AE. There were no deaths during the study. A listing of all patients with serious AE's is provided in table 28 of the NDA. There were 2 lung neoplasms, one in the placebo group and one in the alendronate group. Cardiac AE's were slightly more frequent in the alendronate group, with one myocardial infarction, 2 cases of unstable angina, and one conduction disorder reported in the alendronate group and none in the placebo group. There was one deep vein thrombosis in the placebo (HRT alone) group and none in the alendronate+HRT group.

According to the sponsor, 22 patients discontinued due to clinical AE's: 8 in the alendronate group and 14 among placebo subjects. Three of these AE's were serious. There was no obvious difference in the nature or number of these AE's, according to treatment group. Complete narratives for all cases are provided in the NDA.

Non-vertebral fractures:

Twenty-four patients experienced a non-vertebral fracture: 9 PBO and 15 ALN. According to the sponsor, X-ray reports or other documentation of these fractures were available in only 4 of the PBO group and 12 in the ALN group. However, a fracture was not seen in one of these. There was no correlation between

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baseline lumbar spine BMD, or biochemical bone resorption/formation markers, and incidence of fracture.

Comments: Therefore, documented non-vertebral fractures occurred in 4 PBO and 11 ALN subjects. However, a listing of specific non-vertebral fractures is provided in tabular form (Table 34). According to this table, there were only 3 undocumented or falsely + X-rays in the 9 PBO patients. In addition, there were 13 documented patients with non-vertebral fractures in the ALN group. The reason for this discrepancy is not clear.

I have summarized the data, in the table below, for the documented fractures in the 13 ALN subjects and for the 6 subjects in the PBO group for whom there was no specific exclusion on the basis of non-documentation. Each row indicates a separate individual.

HRT + PBO	HRT + ALENDRONATE
arm	rib (multiple)
foot	rib
radius	foot
ankle	metatarsal (foot)
metatarsal (foot)	wrist
radius	patella
tibia	hand
	ankle
	metatarsal (foot)
	foot
	foot
	foot
	foot

There are twice as many patients with documented non-vertebral fractures in the ALN group. The difference is accounted for by a large increase in the number of foot fractures (7 vs 2). The reason for the discrepancy between the narrative and the data in the table is unclear. Of note, this was not replicated in the next trial, 072, which was two years' duration (see below).

Laboratory AE's:

The sponsor summarizes the laboratory AE experience during this study in the table below. There were no unexpected changes in laboratory parameters during this study, in either treatment group.

	PBO + HRT (N=214) n (%)	ALN + HRT (N=214) n (%)
Number of patients with at least one laboratory test postbaseline	212	211
Number (%) of patients:		
with one or more adverse experiences	25 (11.8)	29 (13.7)
with drug-related ¹ adverse experiences	8 (3.8)	7 (3.3)
with serious adverse experiences	0 (0.0)	0 (0.0)
with serious drug-related ¹ adverse experiences	0 (0.0)	0 (0.0)
withdrawn from therapy due to an adverse experiences	0 (0.0)	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.		

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Data for specific laboratory AE's, by test category and treatment group are given in Table 37 of the NDA and will not be reproduced here. The number and % of patients with specific laboratory AE's (incidence ≥ 1 patient in 1 or more treatment groups) did not differ between treatment groups.

There were no serious laboratory AE's in either treatment group. No patients discontinued due to a laboratory AE.

Clinical safety measurements:

There were no significant changes from baseline in body weight, in either treatment group. Both treatment groups showed a statistically significant change in diastolic blood pressure from baseline at month 12 (mean increases of about 2 mm Hg). There was no difference between the groups. There were no changes in systolic blood pressure from baseline in either treatment group. Similarly, there were no changes from baseline in pulse rates in either group at any time.

Laboratory Safety Measurements

The mean percent changes in serum alkaline phosphatase, total serum calcium, and serum phosphorus are presented in tabular form in the NDA. In both treatment groups, the (total) serum alkaline phosphatase level decreased significantly from baseline at 6 and 12 months. The decline from baseline was significantly greater in the ALN group at 12 months (-14.3% vs -1.9%, $p \leq 0.001$).

Serum phosphorus decreased significantly, by 3.5% in PBO and 3.0% in ALN, at 6 and 12 months (between group differences NS at both time points).

At 6 and 12 months, the mean serum calcium level decreased significantly from baseline, by 1.2 and 0.8%, respectively, in the ALN group. In the PBO group, there was a non-significant increase from baseline after 12 months (1.0%). At Month 6, the between-group differences were significant ($p=0.026$), but not at Month 12.

Comments: These changes are not likely to be of clinical significance. In no patient was the calcium level $< 8.5\text{mg/dl}$ (Table 42).

Pre-defined limits of change:

As shown in Table 42 of the NDA, there were no significant between-group differences in any laboratory parameter except serum AST and monocyte count. The ALN group had 6 patients with increases in AST above the predefined limits compared with none in the PBO group ($p=0.015$). There were 12 subjects with a decrease in monocytes $>$ predefined limits in the ALN group, vs 2 PBO subjects ($p=0.012$).

8.2.2.4 Assessment of efficacy and safety for Trial 097

This study enrolled 428 postmenopausal women (96% Caucasian, average age 61.7 years, average of 15.3 years post-menopause) who had taken HRT for an average of 9.6 years. 56.5% of the trial population had experienced previous fractures. No BMD data prior to onset of HRT are available, and it is therefore not possible to determine the subjects' BMD responses to the HRT. However, the average time between onset of menopause and initiation of HRT in these subjects was 5 years, and it is likely that many experienced a period of rapid bone loss that accompanies estrogen withdrawal. This possibility, together with the fact that the BMD responses to HRT begin to reach a plateau at around 3 years, most likely explain the presence of osteopenia and osteoporosis at baseline. That the baseline biochemical markers of bone turnover were within the premenopausal range suggests that subjects were compliant with HRT regimens during the period prior to study start, and that the HRT doses were adequate.

Efficacy:

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 group were statistically significantly greater than those in the PBO group at the lumbar spine and hip trochanter at 6 and 12 months. The differences were a little over 2%. 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.

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

For the 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 has 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: The addition of alendronate, 10mg, to an ongoing regimen of HRT was generally safe and well tolerated over the course of a one-year study. 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.