

8.3 Reviewer's Trial #3, Sponsor's Trial #072

"A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate and Compare the Safety and Efficacy of Oral Alendronate Sodium, Conjugated Estrogens, and Combination Conjugated Estrogens With Alendronate Sodium for the Treatment of Postmenopausal Osteoporosis"

8.3.1.1 Objectives

As stated by the sponsor, the primary objectives of this trial were:

- 1) To evaluate and compare the effects over time of treatment with concomitant daily oral ALN (10 mg) and CE (0.625 mg), to CE (0.625 mg) alone, on BMD of the lumbar spine in hysterectomized, osteoporotic, postmenopausal women treated for 2 years*
- 2) To evaluate and compare the safety and tolerability of daily oral administration of 10 mg ALN, 0.625 mg CE, both agents administered concomitantly, and PBO in hysterectomized, osteoporotic, postmenopausal women treated for 2 years, by comparing relevant safety parameters and by analyzing the incidence of adverse experiences and patient dropouts due to adverse experiences*

The secondary objectives were:

- 1) To evaluate and compare the effects over time of daily oral administration of 10 mg ALN, 0.625 mg of CE, both agents administered concomitantly, and PBO on BMD of the lumbar spine, hip (total and region-specific) and total body in hysterectomized, osteoporotic, postmenopausal women treated for 2 years*
- 2) To evaluate and compare the effects over time of daily oral administration of ALN (10 mg), CE (0.625 mg), both agents administered concomitantly, and placebo on biochemical markers of bone turnover (urinary N-telopeptides of type 1 collagen corrected for creatinine [NTx/Cr], serum bone-specific alkaline phosphatase [BSAP]), mineral metabolism (serum parathyroid hormone, 1,25-dihydroxyvitamin D, serum calcium, serum phosphate), and serum lipids (total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and triglycerides) in hysterectomized, osteoporotic, postmenopausal women treated for 2 years*
- 3) To evaluate and compare the effects of daily oral ALN (10 mg), CE (0.625 mg), both agents administered concomitantly, and PBO on indices of bone turnover, bone mineralization, and bone architecture assessed by*

histomorphometric analysis of bone biopsy samples in a subset of hysterectomized, osteoporotic, postmenopausal women treated for 18 months

The stated hypotheses were:

Primary

- 1) *Treatment of hysterectomized, osteoporotic, postmenopausal women with concomitant daily oral ALN (10 mg) and CE (0.625 mg) will produce a mean increase in lumbar spine BMD at 2 years, which is significantly greater than that observed with treatment with CE (0.625 mg) alone.*
- 2) *Daily concomitant oral administration of ALN (10 mg) and CE (0.625 mg) will be sufficiently safe and well tolerated to be used in women with postmenopausal bone loss.*

Secondary

- 1) *Daily oral administration of ALN (10 mg) alone, CE (0.625 mg) alone, and both agents administered concomitantly to hysterectomized, osteoporotic, postmenopausal women for 2 years will each result in mean increases in lumbar spine and total hip BMD, relative to both baseline and to placebo.*
- 2) *Treatment of hysterectomized, osteoporotic, postmenopausal women with concomitant daily oral ALN (10 mg) and CE (0.625 mg) will produce a mean increase in total hip BMD at 2 years which is greater than that observed with treatment with CE (0.625 mg) alone.*
- 3) *Treatment of hysterectomized, osteoporotic, postmenopausal women with daily oral ALN (10 mg) alone will produce greater mean increases in lumbar spine and total hip BMD at 2 years than treatment with CE (0.625 mg) alone.*
- 4) *Treatment of hysterectomized, osteoporotic, postmenopausal women with concomitant daily oral ALN (10 mg) and CE (0.625 mg) will produce mean increases in lumbar spine and total hip BMD at 2 years equal to or greater than those observed in patients treated with ALN (10 mg) alone.*

8.3.1.2 Study Design

This was a randomized, double-blind, placebo-controlled, multicenter, two-year study of 425 hysterectomized postmenopausal women with low spinal bone mineral density. The purpose of the study was to compare the safety, tolerability, and effects on BMD and bone turnover markers of daily oral alendronate (ALN) 10 mg, daily oral conjugated estrogens (CE) 0.625 mg, and the combination of

the two. The study consisted of 4 arms: placebo, CE, alendronate, and combination CE plus alendronate (1:2:3:3). The study was conducted at 19 sites in 16 states in the US.

Target enrollment was 360 women at 19 centers in the US, with the goal of at least 240 completing 2 years of treatment.

Randomized subjects were stratified according to prior estrogen use, which was defined as >1 month of oral or transdermal estrogen taken during the peri- or postmenopausal period, with or without a progestin. Patients who had taken estrogens were placed into Stratum I; patients with no prior estrogen use were assigned to Stratum II.

This trial began with a 2-week single-blind placebo run-in period, in which all subjects were given placebos for both ALN and CE. The purpose of this run-in was to assess compliance with dosing, and also to determine any adverse experiences in patients who were given calcium supplementation. Any patient who was < 85% compliant with placebo tablets was excluded from further participation.

The trial used a "double-dummy" design, in which each patient received both ALN or placebo for ALN, and CE or placebo for CE, as shown below. PREMARIN™ (Wyeth Ayerst) was used as CE.

Group	Treatment	N
PBO	Placebo for ALN + Placebo for CE	40
ALN	ALN 10 mg + Placebo for CE	80
CE	CE 0.625 mg + Placebo for ALN	120
ALN+CE	ALN 10 mg + CE 0.625 mg	120
Total		360

PBO: Placebo.
 ALN: Alendronate.
 CE: Conjugated estrogens (PREMARIN™).

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8.3.1.3 Protocol

8.3.1.3.1 Populations, Procedures, and Concurrent Medications

A complete listing of inclusion/exclusion criteria is given in the NDA submission. Of particular importance to this study, the inclusion criteria were:

"The patient was a woman, 45 to 75 years of age, who had undergone hysterectomy (with or without removal of the ovaries) at least 3 months prior to entry and had experienced menopause (either surgical or natural) at least 3 years prior to entry. Patients were considered to have met the latter criterion if they fell into one or more of the following categories:

- (a) age >60, (b) a surgical/pathology report was available documenting

oophorectomy at least 3 years prior to entry, (c) absent menses for ≥ 6 months prior to hysterectomy, beginning ≥ 3 years prior to entry, or (d) onset of typical climacteric symptoms ≥ 3 years prior to entry in a woman who underwent hysterectomy without confirmed oophorectomy. If the patient gave no history of climacteric symptoms, an FSH level was obtained through the central laboratory and must have exceeded the lower end of the reference range for postmenopausal women for the patient to be eligible.”

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Other important inclusion criteria were that the patient had a lumbar spine BMD $< 0.86\text{g/cm}^2$ by Hologic QDR measurement. Patients also agreed not to take systemic estrogens, except as prescribed, throughout the study.

A complete list of exclusion criteria is reproduced here:

“1) The patient had received treatment with estrogens within 6 months prior to randomization (other than topical estrogen-containing vaginal creams, which were acceptable if used up to twice weekly).

2) The patient was, in the opinion of the investigator, mentally or legally incapacitated such that informed consent could not be obtained.

3) The patient had participated in another therapeutic trial within 30 days of randomization.

4) The patient intended to move within 2 years of entry into the study, rendering per-protocol follow-up impractical.

5) The patient had a history of any illness or had significant abnormalities on prestudy clinical or laboratory evaluation that, in the opinion of the investigator, might have posed an unacceptable risk to the patient from participation in this study or complicated the interpretation of study data.

6) The patient was, at the time of the study, a current user of any illicit drugs or had a history of drug or alcohol abuse within the past 5 years.

7) The patient consumed more than 2 glasses of wine, 2 beers, or 2 standard alcoholic drinks on average per day.

8) The patient had any of the following: any severe malabsorption syndrome; moderate or severe hypertension that was uncontrolled; new onset angina or myocardial infarction within 6 months of entry into the study; evidence for impaired renal function defined as a serum creatinine greater than 1.6 mg/dL; endogenous hypercortisolism within 1 year of entry into the study; known symptomatic gallbladder disease not treated with prior cholecystectomy; history of porphyria; or other significant end organ diseases (genitourinary, cardiovascular, hepatic, psychiatric, renal, hematologic, or pulmonary) that, in the opinion of the investigator, posed an added risk to the patient or impaired her ability to complete the trial.

9) The patient had a history of major upper gastrointestinal (GI) (esophagus, stomach, duodenum) mucosal erosive disease as defined by:

(1) significant upper GI bleeding within the last 5 years resulting in hospitalization and/or transfusion; (2) recurrent ulcer disease documented by radiographic or endoscopic means (two episodes in the last 5 years); (3) dyspepsia treated on a daily basis, or (4) esophageal or gastric variceal disease.

10) The patient had a history of cancer. However, patients with the following cancers were considered eligible for the study: (a) superficial basal or squamous cell carcinoma of the skin that had been completely resected, or (b) other malignancies (with the exceptions indicated below) successfully treated > 10 years prior to screening, where in the judgment of both the investigator and a consulting oncologist, appropriate follow-up had

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revealed no evidence of recurrence from the time of treatment through the time of screening. However, patients with a history of leukemia, lymphoma, myeloproliferative disease, endometrial cancer, breast cancer (including histologic diagnosis of lobular carcinoma in situ), or known or suspected estrogen-sensitive neoplasia were excluded regardless of the time since treatment or disease status.

11) The patient had a history of, or evidence for, metabolic bone disease (other than postmenopausal bone loss) including but not limited to hyper- or hypoparathyroidism, Paget's disease of bone, osteomalacia, and osteogenesis imperfecta. Patients with surgically cured hyperparathyroidism due to parathyroid adenoma at least 1 year prior to randomization were eligible for the study.

12) If the screening 25-OH vitamin D level was below 50% of the lower limit of normal (central laboratory), the patient was excluded. If the screening 25-OH vitamin D level was below the normal range but $\geq 50\%$ of the lower limit of normal, the patient was excluded if there was any other evidence for osteomalacia (e.g., clinical manifestations or abnormalities in calcium, phosphorus, or alkaline phosphatase). If the screening 25-OH vitamin D level was below the normal range but $\geq 50\%$ of the lower limit of normal and there was no other evidence to suggest osteomalacia, the patient could be treated with oral vitamin D, 800 IU daily for a minimum of 2 months (preferably 3 to 4 months if time permitted), and subsequently entered if repeat 25-OH vitamin D level was normal.

13) The patient had received treatment (other than estrogens) prior to randomization which might have influenced bone turnover, including:

- (a) within 6 months: anabolic steroids, calcitonin, or progestins;
- (b) thyroid hormone, unless on a stable dose for at least 6 weeks before randomization with serum thyroxine and thyroid stimulating hormone (TSH) within the normal range;
- (c) fluoride treatment at a dose greater than 1 mg/day for more than 1 month at any time; given for a shorter time than 1 month it must have been greater than 1 year before randomization;
- (d) glucocorticoid treatment for more than 1 month with >7.5 mg of oral prednisone (or the equivalent) per day within 6 months prior to randomization; patients who received therapeutic glucocorticoids in the past must have been considered highly unlikely to require retreatment (with >7.5 mg of oral prednisone or the equivalent) during the course of the study; and (e) any previous treatment with a bisphosphonate for more than 2 weeks; if given for 2 weeks or less, it must have occurred more than 1 year before randomization.

14) The patient was receiving any medication that might alter bone or calcium metabolism, including vitamin A in excess of 10,000 IU per day or vitamin D in excess of 800 IU per day, anticonvulsants, or regular use of phosphate-binding antacids.

15) The patient had active rheumatoid arthritis.

16) The patient had active thrombophlebitis or a history of prior thromboembolic disease.

17) The patient's baseline mammogram (performed within 1 year of entry) raised any suspicion of malignancy requiring follow-up (e.g., repeat mammogram) within a 9-month period, unless proven benign by biopsy.

18) The patient was at increased risk for breast cancer to the degree that, in the judgment of the investigator or patient, the risks of possible estrogen therapy outweighed the benefits.

19) The patient had a history of genital bleeding within the preceding year for which a cause had not been identified or that, in the judgment of the investigator, placed the patient at increased risk from estrogen therapy.

20) The patient had fasting serum triglycerides >400 mg/dL.

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- 21) The patient had any clinical condition (including climacteric symptoms) which she or the investigator believed could require systemic estrogen therapy within 2 years following enrollment.
- 22) The patient had a history of allergy, hypersensitivity, or intolerance to any bisphosphonate (including agents used for diagnostic testing) or any conjugated estrogen or other estrogen preparation.
- 23) The patient was a regular user (more than once per day) of any medication (including over-the-counter analgesics such as nonenteric coated aspirin, ibuprofen, or other nonsteroidal anti-inflammatory drugs) having the potential for GI irritation, unless taken at an unchanged dosage for >2 months without occurrence of symptoms referable to the upper GI tract.
- 24) The patient demonstrated noncompliance with taking study medication during the placebo run-in phase (consumption of <85% of all prescribed tablets) or anticipated significant difficulty in taking study medications precisely as directed."

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Comments: The sponsor's definition of "osteoporosis" is based solely on BMD. This definition is now widely but not universally accepted. Many authorities insist on evidence of bone fragility in addition to osteopenia.

The sponsor gives no description of methodology for recruitment of participants. There is no indication of the method of initial patient contact, number of patients initially contacted, number screened, number excluded at each level of selection prior to final randomization, and the reasons for exclusion at each step. As discussed in earlier alendronate reviews, the careful selection and screening of participants helps ensure a high level of compliance, as well as a remarkable retention rate during trials. For example, in the FIT trial (reviewed earlier this year), 96% of subjects originally randomized completed the study, with over 80% still on study drug. In this trial, the additional feature of a placebo run-in period further ensures enrichment of the trial population with compliant individuals. This approach increases the technical quality of a controlled trial and allows questions to be answered in a scientifically rigorous manner. The trade-off is that the trial population may not be representative of the population of patients who will receive the drug. Thus, a trial may show that treatment A is superior to treatment B, but in a population that inadequately represents the market population. One indication of inadequacy of representation of the trial populations is the discordance between the frequency of GI adverse events reported in all alendronate clinical trials and the number of GI adverse events that have marked post-marketing experience with alendronate.

Concomitant medications:

If dietary calcium intake was assessed to be <1000 mg/day, subjects were advised to take 500 mg of supplemental calcium. The calcium was provided by

the investigator (OSCAL 250 + D™). If the estimated daily dietary calcium was >1000 mg, subjects were advised to continue current intake and were not given supplemental calcium.

Supplemental vitamin D was prescribed only if judged to be indicated by the investigator, in which case no more than 400 IU daily supplement was given.

Comments: This will probably be inadequate supplementation for many of the subjects in the trial. Postmenopausal women require 1500 mg elemental calcium per day and should also be given 400 IU of vitamin D per day.

Drugs that affect mineral metabolism were not permitted (see above for complete listing).

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Procedures (clinical observations and laboratory measurements):

The sponsor provides a schedule of clinical and laboratory assessments during the screening and randomization periods and throughout the 24 months of the trial:

Month	Screening		Randomization	1	3	6	9	12	18	24
	1	2								
Informed consent	X			X ¹					X ²	
Mammography		X ³						X ⁴		X ⁵
Dietary calcium assessment	X							X ⁶		X ⁷
History/adverse experiences	X		X ⁸	X ⁹	X ¹⁰	X ¹¹	X ¹²	X ¹³	X ¹⁴	X ¹⁵
Physical examination	X		X ¹⁶	X ¹⁷	X ¹⁸	X ¹⁹	X ²⁰	X ²¹	X ²²	X ²³
Height/weight	X		X	X	X	X	X	X	X	X
Electrocardiogram		X								
Routine hematology and chemistry	X		X		X	X	X	X	X	X
Screening chemistry	X									
Serum lipids	X							X		X
Bone-specific alkaline phosphatase	X		X	X	X	X		X	X	X
Parathyroid hormone: 1,25-OH vitamin D			X	X	X	X		X	X	X
Routine urinalysis		X		X	X	X	X	X	X	X
Special urine chemistry (creatinine and NTx)		X		X	X	X	X	X	X	X
Archival serum samples	X		X	X	X	X	X	X	X	X
Dual-energy X-ray absorptiometry (DXA)	X ¹⁶	X ¹⁷	X ¹⁸	X ¹⁹	X ²⁰	X ²¹		X ²²	X ²³	X ²⁴
Thoracolumbar spine X-rays	X									X

Month	Screening		Randomization	1	3	6	9	12	18	24
	1	2								
Bone biopsy (with consent)										
Study drugs		X ²⁵	X ²⁶	X ²⁷	X ²⁸	X ²⁹	X ³⁰	X ³¹	X ³²	
Tablet counts			X	X	X	X	X	X	X	X
Randomization			X							

¹ Baseline screening mammogram was performed unless a mammogram performed within the preceding year was available. In the latter case, it was considered the "baseline" study and repeat mammograms were performed at 1-year intervals from the date of that mammogram for the duration of the study.

² Intra-visit medical history to identify changes in symptoms, adverse experiences and changes in medication usage.

³ Limited physical examination was performed only if indicated by the occurrence of symptoms or for any other reason.

⁴ DXA of the lumbar spine only.

⁵ DXA of the hip and total body only.

⁶ DXA of the lumbar spine, hip, and total body.

⁷ DXA of the lumbar spine and hip only.

⁸ Transected bone biopsy on a subgroup of approximately 100 consenting subjects.

⁹ Placebo run-in (2 weeks).

¹⁰ Study medications.

¹¹ For those patients who had a bone biopsy performed.

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Methodology: A complete description of the methodologies employed for all laboratory assessments is provided in the NDA. Blood and urine specimens were collected according to the schedule presented in the table above.

In addition, a subgroup of 98 individuals consented to have transiliac bone biopsies after approximately 18 months of treatment. Complete details of the methodology for bone histomorphometry are provided in the NDA. Standard techniques, including tetracycline labeling, were employed.

Subjects received demeclocycline (DECLOMYCIN™, Lederle) 300 mg b.i.d. for 2 days, followed by 12 days without demeclocycline, followed by an additional 2 days of demeclocycline 300 mg b.i.d. The bone biopsy was performed 4 to 6 days after the last demeclocycline dose. On the last day of demeclocycline administration, all subjects provided a urine specimen, which was stored frozen for future assay in the event that no tetracycline was detected in the bone biopsy. After local anesthesia, a bicortical transiliac biopsy, using a 7-mm trephine needle, was performed. Biopsy specimens, protected from UV light, were processed and stored according to routine, standard procedures. Following shipment to the central histomorphometry laboratory [REDACTED]

[REDACTED] specific histomorphometric parameters of bone turnover and mineralization were assessed on undecalcified sections.

The mineralization and turnover parameters measured were:

- 1) trabecular osteoid volume
- 2) combined trabecular and endocortical: a) osteoid thickness, b) mineral apposition rate
- 3) extent of surface undergoing mineralization

In addition, qualitative assessments of bone architecture were performed using polarized light microscopy (collagen fibrils) and study of the appearance of cellular components. Marrow fibrosis was also noted, if present.

Bone densitometry was assessed with [REDACTED] according to routine procedures (details in NDA). At each study site, the same densitometer was used for each subject throughout the study. Strict procedures were used for QA. Cross-calibration data, and phantom data were archived and analyzed by a central data management facility. BMD of spine and hip were assessed at 3, 6, 12, 18, and 24 months and total body BMD at 12 and 24 months. BMD data were not included for vertebrae that fractured during the study.

All patients had a baseline mammogram, unless results of mammography conducted during the previous year were available. Patients then had yearly mammograms for the remainder of the study.

At baseline, lateral thoracolumbar spine X-rays were obtained to determine the presence of fracture(s). These were repeated at Month 24. The X-rays were sent to Dr. Michael Nevitt, Ph.D, at the University of California at San Francisco (UCSF) for digitization and determination of fractures. As with the FIT trial, the readings were blinded to treatment but not to sequence, based on agreement with the FDA.

8.3.1.3.2 Endpoints

Efficacy

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Clinical efficacy:

The primary efficacy endpoint was mean percent change in lumbar spine (L1 to L4) BMD from baseline to Month 24.

Secondary efficacy endpoints: mean percent changes in BMD (baseline to Month 24) of the total hip, femoral neck, trochanter, intertrochanteric, Ward's triangle hip and total body.

Biochemical Efficacy

Changes in biochemical markers of bone turnover (urine NTx and serum BSAP and total alkaline phosphatase) were secondary endpoints. The endpoint for this analysis was the log-transformed fraction of baseline at Month 24.

Changes in indices of mineral homeostasis (serum calcium and phosphate) were also analyzed as the log-transformed fraction of baseline at Month 24.

Safety

A comprehensive clinical and laboratory safety assessment and analysis was performed.

Clinical adverse experiences (obtained via history taken at each visit, plus spontaneous reporting to the investigator) were recorded on the Adverse Experience Case Report Form. These were rated as to severity (mild to severe).

Physical examinations were performed according to the schedule, provided above:

Laboratory safety tests were performed (by the central laboratory) according to the schedule provided in the table above. Specific tests and methodologies are provided in the NDA. The tests included a complete hematology profile and battery of serum chemistries, serum lipids, and urinalyses. Additionally, at visit 1, the sponsor determined levels of 25-hydroxyvitamin D, total thyroxine, and TSH.

In addition, the sponsor determined levels of total alkaline phosphatase, BSAP, PTH, and 1,25-dihydroxyvitamin D.

Predefined limits of change were established for laboratory safety parameters.

Bone histomorphometry (described above) was analyzed as a safety outcome.

8.3.1.3.3 Statistical Considerations

The primary efficacy parameter was change from baseline in BMD of the lumbar spine. BMD at other sites (total body, femoral neck, trochanter, intertrochanteric, and Ward's triangle) were secondary efficacy parameters.

For each of the 4 treatment groups, at the 3-, 6-, 12-, 18-, and 24-month time points, summary statistics for % change were calculated. Mean % change in BMD (with 95% CI's) was compared between treatment groups at the 2-year time point.

The safety/tolerability of each of the 4 regimens was assessed by clinical review of all relevant parameters. Proportions of subjects with AE's, with changes in laboratory variables outside of predefined limits, and with new vertebral fractures (X-ray) were compared among the 4 treatment groups. For continuous variables, (e.g., blood pressure) summary statistics of changes over the 24 months were employed.

For biochemical indices of mineral metabolism, the sponsor used the log-transformed fraction of baseline in each treatment group to compare changes among groups.

A correlation analysis of the relationship between baseline BMD and percent changes in BMD from baseline was performed. In addition, the sponsor performed an analysis of correlations between changes in BMD, and biochemical parameters (both baseline and changes from baseline). Other, exploratory (i.e., hypothesis-generating) correlations were determined.

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

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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 lumbar spine BMD (Table 17 of the NDA)

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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.

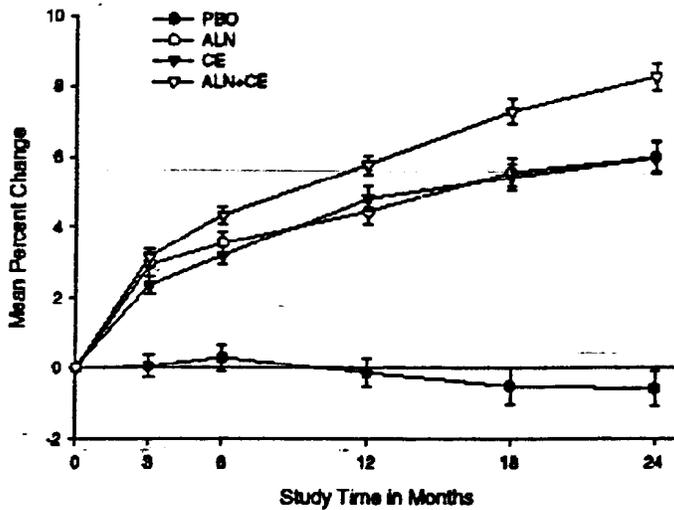
Main Result: The PBO group experienced a nonsignificant (0.6%) decrease in BMD at this site. All 3 other treatment groups had an increase in BMD, relative to baseline and PBO ($p \leq 0.001$ and $p < 0.001$, respectively). The mean increase in the ALN + CE group was statistically significantly ($p < 0.001$) 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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Data for changes in lumbar spine BMD are summarized in the table below:

Treatment	N	Observed Mean (g/cm^3)		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	0.77	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)			<0.001

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:

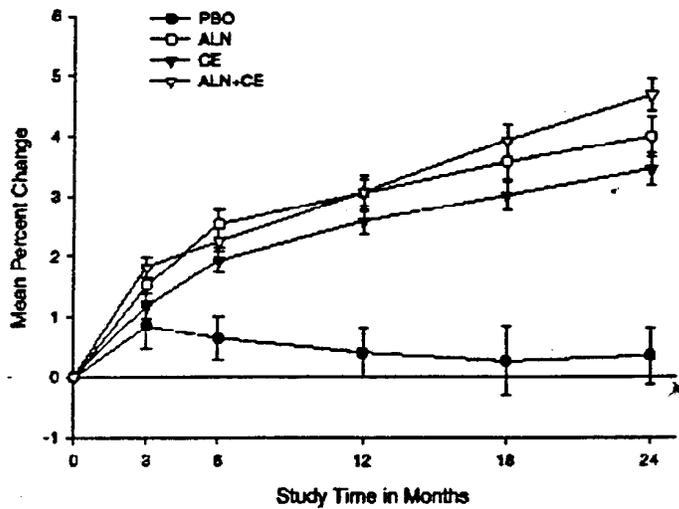
All groups except the PBO had a significant increase in total hip BMD from baseline over the 24 months. The ALN + CE group had a significantly ($p=0.001$) greater increase in total hip BMD, compared with the CE group. There was no

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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/cm^2)		Percent Change From Baseline at Month 24				Pairwise Comparison p-Value		
		Baseline	Month 24	Mean	SD	Adjusted Mean	95% CI	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.

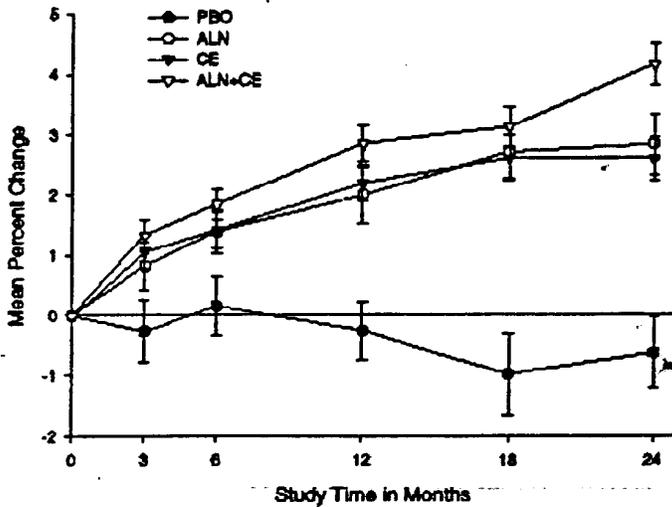
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Femoral Neck BMD:

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/cm ²)		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 ***: $p < 0.001$ **; $p < 0.010$ *; $p < 0.050$.
 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.

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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/cm ²)		Percent Change From Baseline at Month 24				Pairwise Comparison p-Value		
		Baseline	Month 24	Mean	SD	Adjusted Mean	95% CI	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)			<0.001

WUms-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).

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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/cm^2)		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)			<0.001

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 ($p \leq 0.006$). There were no significant differences in BMD changes among the 3 active-treatment groups ($p \geq 0.219$). 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/cm ²)		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:

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