CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-417

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-396 and 21-417
Name of drug:	21-396: Prempro™ (conjugated estrogens and medroxyprogesterone acetate tablets)
	21-417: Premarin® (conjugated estrogens tablets)
Applicant:	Wyeth-Ayerst Laboratories
Indication:	21-396: Prevention of osteoporosis
	21-417: Prevention of osteoporosis
Documents reviewed:	21-396: \\CDSESUB1\N21396\N_000\2001-09-24\clinstat\preventionofosteoporosis\309main.pdf, 309a.pdf, 309b.pdf, 309c.pdf, 309d.pdf, 309e.pdf, 309f.pdf, 309g.pdf, 309h.pdf
	21-417: Same as the pivotal clinical study report for 21-396
Project manager:	Samuel Wu, Pharm.D. (HFD-510)
Clinical reviewer:	21-396: Bruce Schneider, M.D. (HDF-510)
	21-417: Eric Colman, M.D. (HDF-510)
Dates:	21-396: Received 09/25/01; user fee (10 months) 07/25/02
	21-417: Received 12/18/01; user fee (10 months) 10/18/02
Statistical reviewer:	Cynthia Liu, MA (HFD-715)
Statistics team leader:	Todd Sahlroot, Ph.D. (HFD-715)
Biometrics division director:	Ed Nevius, Ph.D. (HFD-715)

Keywords: NDA review, clinical studies, analysis of covariance

TABLE OF CONTENTS

1. SUMMARY OF STATISTICAL REVIEW 3

2. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE 5

2.1 Introduction and Background 5

2.2 Data Analyzed and Sources 6

2.3 Statistical Evaluation of Evidence on Efficacy 7

2.3.1 Sponsor's Results and Conclusions 7

2.3.2 Statistical Methodologies 8

2.3.3 Detailed Review of Study 0713D2-309-US (from 8/95 to 10/00) 11

Study Design and Objectives 11

Subject Disposition 12

Demographics 18

Efficacy Results and Discussion 18

2.4 Findings in Special/Subgroup Populations 25

2.5 Statistical and Technical Issues 26

2.6 Statistical Evaluation of Collective Evidence 26

2.7 Conclusions and Recommendations 27

2.8 Notes on Labeling 28

2.9 Appendix 29

1. SUMMARY OF STATISTICAL REVIEW

Wyeth-Ayerst Laboratories has conducted a Health and Osteoporosis, Progestin and Estrogen (HOPE) study to evaluate the safety and efficacy of lower doses of Premarin (conjugated estrogens, CE) and medroxyprogesterone acetate (MPA) in reducing the incidence of endometrial hyperplasia associated with the use of unopposed estrogen and in preventing postmenopausal bone loss compared with placebo. The former indication is reviewed under the Division of Reproductive and Urologic Drug Products; the latter indication is reviewed under the Division of Metabolic and Endocrine Drug Products and is the focus of this review report. The study consisted of 8 arms: 3 doses of CE mono therapy, 4 doses of CE/MPA combined therapy, and a placebo. Approvals of two new lower doses of CE (Premarin®) and CE/MPA (Prempro™) for the prevention of osteoporosis are sought under NDA 21-417 and NDA 21-396, respectively. Since the CE and CE/MPA doses are from the same clinical study, they are reviewed together here, even though they are filed under different NDA numbers.

Prevention of bone loss was assessed by measurement of bone mineral density (BMD). L2-L4 of anteroposterior lumbar spine was the primary skeletal site. BMD of femoral neck, femoral trochanter, and total body were also evaluated. This study was a Phase III, randomized, double-blind, multi-center (in USA) trial, conducted in postmenopausal women between age 40 and 65 years old, inclusive, with an intact uterus. Approximately 92% of 822 randomized subjects in the Osteoporosis and Metabolic substudy were White. The principal findings and conclusions based on Cycle 26 with last-observation-carried-forward data for the intention-to-treat population are summarized below.

- Data from the substudy demonstrate that all the CE/MPA and CE doses were highly effective in preventing postmenopausal bone loss for each of the 4 skeletal sites, when compared with the placebo, regardless of age, race, body mess index, and years since menopause. As a consequence, it supports the efficacy of lower doses of CE/MPA (0.45/1.5 and 0.3/1.5 mg) and CE (0.45 and 0.3 mg) claimed by the sponsor.

- All the CE/MPA doses consistently showed greater % increases from baseline in lumbar spine BMD when compared with the corresponding CE doses. However, no such consistency was observed in femoral neck, femoral trochanter, and total body BMD.

- Despite the difference in magnitude of treatment effects, this reviewer's conclusions generally agree with the sponsor's primary conclusions that were based on annual % changes from baseline derived from the slope estimates for the efficacy evaluable

population. In this reviewer's opinion, slope estimates were less precise (possibly biased) for subjects with missing (fewer) data points for BMD measurements over time.

2. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 Introduction and Background

The sponsor has submitted the results of 1 Phase III controlled clinical trial conducted in postmenopausal women between age 40 and 65 years old, inclusive, with an intact uterus, for the new drug applications, NDA 21-396 and NDA 21-417, for lower doses of Prempro™ (conjugated estrogens and medroxyprogesterone acetate, CE/MPA) and lower doses of Premarin® (conjugated estrogens, CE), respectively. The intended indication for both NDAs is prevention of osteoporosis.

The trial was one of the Health and Osteoporosis, Progestin and Estrogen (HOPE) studies. Premarin 0.625 mg is approved for estrogen replacement therapy (ERT) to treat symptoms of menopause associated with estrogen deficiency and to prevent postmenopausal bone loss. However, the use of unopposed estrogen is associated with an increased risk of endometrial hyperplasia in postmenopausal women with an intact uterus. According to the sponsor, clinical evidence has demonstrated that regimens combining Premarin (CE) and medroxyprogesterone acetate (MPA) are effective in reducing the incidence of endometrial hyperplasia, and additional data have shown an increase in bone density with the addition of MPA over that seen with estrogen therapy alone. Thus, the sponsor claimed that a CE dose lower than 0.625 mg, combined with daily MPA, may be effective in reducing bone loss and the incidence of endometrial hyperplasia in postmenopausal women, while still relieving menopausal symptoms and maintaining acceptable bleeding and metabolic profiles. Note that CE/MPA 0.625/5.0- and 0.625/2.5-mg doses have been approved under NDA 20-527 for the treatment of vasomotor symptoms and vulvar and vaginal atrophy associated with menopause, and for the prevention of osteoporosis.

The study comprised two parts: a 1-year (13-cycle) basic study and a 2-year (26-cycle) Osteoporosis and Metabolic substudy. The 1-year study was mainly to evaluate the safety and efficacy of lower doses of CE/MPA in reducing the incidence of estrogen-induced endometrial hyperplasia. It is reviewed under the Division of Reproductive and Urologic Drug Products (DRUDP). The 2-year substudy, which was a continuation of the 1-year basic study, was mainly to evaluate the safety and efficacy of lower doses of CE and CE/MPA in preventing postmenopausal bone loss. It is reviewed under the Division of Metabolic and Endocrine Drug Products (DMEDP) and is the focus of this report.

NDA 21-396 seeks approval for the two new lower doses of Prempro™ continuous combined therapy (0.45/1.5 and 0.3/1.5 mg), while NDA 21-417 seeks approval for the two new lower doses of Premarin® mono therapy (0.45 and 0.3 mg). Since those CE/MPA and CE doses

are from the same study (Text Table 1), the two NDAs are therefore reviewed and evaluated simultaneously from the statistical point of view.

Text Table 1 – Summary of Key Design of Controlled Clinical Trials

Protocol No./ Report No./Location	Study Design	Dose (mg)	Evaluable Subjects	Gender Mean Age	Primary Variable
0713D2-309-US GMR-38605 (USA, Multicenter)	Interim prospective, double-blind, 1-year, randomized, phase III study of the safety and efficacy of lower doses of CE and CE/MPA in postmenopausal women	Group A: 0.625 Group B: 0.625/2.5 Group C: 0.45 Group D: 0.45/2.5 Group E: 0.45/1.5 Group F: 0.3 Group G: 0.3/1.5 Group H: Placebo	A = 348 B = 331 C = 338 D = 340 E = 331 F = 326 G = 327 H = 332	All female 53 years	Incidence of endometrial hyperplasia
0713D2-309-US CSR-41303 (USA, Multicenter)	Substudy of 2-year prospective, double-blind, randomized, phase III study; investigation of the safety and efficacy of lower doses of CE and CE/MPA in preventing osteoporosis and maintaining a favorable metabolic profile in postmenopausal women	Group A: 0.625 Group B: 0.625/2.5 Group C: 0.45 Group D: 0.45/2.5 Group E: 0.45/1.5 Group F: 0.3 Group G: 0.3/1.5 Group H: Placebo	A = 97 B = 86 C = 95 D = 96 E = 94 F = 89 G = 98 H = 94	All female 52 years	Bone mineral density

The sponsor's Clinical Data Summary and Results of Statistical Analysis Table 4.2A modified

2.2 Data Analyzed and Sources

The data files this reviewer used to do her own independent analyses are BMDADJ.XPT, DEMOG.XPT, and R11G.XPT, submitted electronically by the sponsor on 2/1/02. They are in \\CDSESUB1\N21396\N_000\2002-02-01\crt\datasets\309. In those files, intention-to-treat (ITT) or efficacy evaluable (EE) subjects were not clearly identified. No indicator was made for the last observations being carried forward (LOCF). The times of withdrawal in terms of study cycle for the dropouts were not provided. Average of the last two scans done within 60 days apart, if any, to count as the final visit value was not presented, nor were any other average values for baseline and per cycle used in the analyses. Therefore, this reviewer had to do extensive programming to maneuver the data sets.

As noted in Supplemental Volume II, section 8.1.4, there were some errors in dates and BMD values in database which were discovered during an audit after the database had been frozen and analyses completed for the final study report. In addition, according to the protocol, if one of the lumbar vertebrae (L2, L3, or L4) was abnormal, L1 was then measured in its place throughout the study. As noted in the sponsor's letter to DMEDP dated 2/1/02, substitutions were done for 14 subjects; however, 9 of them had incorrect substitutions. For

example, instead of substituting L1-L3 for L2-L4, L2-L3 was substituted for 8 subjects and L1-L2 was substituted for 1 subject. It appears to this reviewer that BMDADJ.XPT does not reflect any corrected dates, BMD values, or substitutions.

2.3 Statistical Evaluation of Evidence on Efficacy

Bone mineral density (BMD) of lumbar spine, femoral neck, femoral trochanter, and total body, measured by dual energy x-ray absorptiometry (DXA), were the main factors for determining bone metabolism in this study. Among those 4 skeletal sites, BMD of L2-L4 of the anteroposterior lumbar spine was the primary measure of bone loss. The efficacy of the combined or mono therapy doses was determined in comparison with that of the placebo.

In order to distinguish investigational sites from skeletal sites, the term centers are used for investigational sites in the following discussions.

2.3.1 Sponsor's Results and Conclusions

It was concluded by the sponsor that all doses of CE and CE/MPA produced significantly increased lumbar spine BMD, femoral neck BMD, femoral trochanter BMD, and total body BMD, when compared with the placebo based on the analyses of annual percentage changes from baseline derived from the slope estimates (primary analysis) and percentage changes from baseline at the final visit(s) for the efficacy evaluable (EE) population (Text Table 2). The same analyses based on the intention-to-treat (ITT) population, analyzed by the sponsor and verified by this reviewer, also showed similar findings (Text Table 2).

It appears to this reviewer that the mean % changes for the EE population using either annual or final visit calculation were generally greater than those for the ITT population. This is foreseeable because the analysis on the ITT population generally yields more conservative results than the EE population. In addition, the estimated biannual mean % changes from baseline derived from the slopes were generally larger than the mean % changes from baseline at the final visit(s) in either EE or ITT population. Note that the biannual mean % changes (estimated 2-year change, 2 × annual) were calculated by this reviewer to compare with the mean % changes at the final visit(s) since this was a 2-year study and the majority of the subjects were in the study for at least 1 year.

According to the sponsor, analyses were redone after the database was corrected for the erroneous dates, BMD values, and substitutions mentioned above. It was stated that the changes in the results were insignificant and no impact on the overall conclusions was observed. This reviewer could not verify the statement since no corrected data file was submitted.

Text Table 2 – Substudy: Adjusted Mean % Change from Baseline in BMD

		EE Population[a]			ITT Population[b]		
Skeletal Site	Regimen	Annual	Biannual[c]	Final Visit	Annual	Biannual[c]	Final Visit
L2-L4	A (0.625)	1.68	3.36	2.83	1.4980	2.9961	2.3195
	B (0.625/2.5)	2.03	4.06	3.77	1.8064	3.6128	3.3908
	C (0.45)	1.28	2.56	2.28	1.2701	2.5402	2.0826
	D (0.45/2.5)	1.51	3.02	3.10	1.5901	3.1803	2.9142
	E (0.45/1.5)	1.14	2.28	2.45	1.1281	2.2562	2.2112
	F (0.3)	0.76	1.52	1.51	0.5439	1.0878	1.2391
	G (0.3/1.5)	0.92	1.84	1.77	0.9933	1.9865	1.6705
	H (Placebo)	-1.49	-2.98	-2.63	-1.3714	-2.7427	-2.4561
F. Neck	A (0.625)	1.11	2.22	2.13	0.8003	1.6007	1.7393
	B (0.625/2.5)	0.86	1.72	1.67	1.0189	2.0377	1.7725
	C (0.45)	1.16	2.32	1.98	1.6858	3.3715	1.9517
	D (0.45/2.5)	0.99	1.98	1.76	0.9354	1.8708	1.6694
	E (0.45/1.5)	0.80	1.60	1.43	1.1075	2.2150	1.3953
	F (0.3)	0.28	0.56	0.80	-0.1801	-0.3603	0.5687
	G (0.3/1.5)	0.77	1.54	1.51	0.7587	1.5174	1.4351
	H (Placebo)	-1.30	-2.60	-1.97	-1.2620	-2.5240	-1.8085
F. Trochanter	A (0.625)	2.30	4.60	4.17	2.2449	4.4897	3.7785
	B (0.625/2.5)	2.20	4.40	4.05	1.8145	3.6290	3.7769
	C (0.45)	2.04	4.08	3.79	2.4623	4.9246	3.4608
	D (0.45/2.5)	2.60	5.20	5.08	2.3035	4.6070	4.6681
	E (0.45/1.5)	1.87	3.74	3.60	1.6301	3.2603	3.0401
	F (0.3)	1.67	3.34	3.58	1.5623	3.1245	3.1922
	G (0.3/1.5)	2.23	4.46	4.66	1.8687	3.7373	4.1796
	H (Placebo)	0.31	0.62	0.82	0.3514	0.7027	0.9262
Total Body	A (0.625)	0.42	0.84	0.78	0.5039	1.0077	0.6615
	B (0.625/2.5)	0.58	1.16	0.96	0.5642	1.1284	0.9078
	C (0.45)	0.47	0.94	0.85	0.4836	0.9673	0.7089
	D (0.45/2.5)	0.51	1.02	1.07	0.5228	1.0455	0.9909
	E (0.45/1.5)	0.25	0.50	0.56	0.3604	0.7207	0.5714
	F (0.3)	0.24	0.48	0.48	0.1536	0.3073	0.3673
	G (0.3/1.5)	0.30	0.60	0.55	0.3434	0.6869	0.5088
	H (Placebo)	-0.85	-1.70	-1.56	-0.9115	-1.8229	-1.5215

[a] BMD values under EE population are from the sponsor's Supportive Tables ST9-4 and ST9-6.
[b] BMD values under ITT population are this reviewer's results. They match the sponsor's numbers shown in the Supportive Tables ST9-10 and ST9-12.
[c] BMD values under Biannual are simply 2 × Annual.

2.3.2 Statistical Methodologies

For the primary efficacy variable BMD, the sponsor conducted at least 8 types of statistical analyses, as described below, for each of the 4 skeletal sites.

1. Compare annual percentage changes from baseline, based on analysis of slopes, unweighted, efficacy evaluable population.

2. Compare annual percentage changes from baseline, based on analysis of slopes, weighted, efficacy evaluable population.
3. Compare percentage changes by cycle, efficacy evaluable population.
4. Compare percentage changes at final visit(s) from baseline, efficacy evaluable population.
5. Compare annual percentage changes from baseline, based on analysis of slopes, unweighted, intention-to-treat population.
6. Compare percentage changes by cycle, intention-to-treat population.
7. Compare percentage changes at final visit(s) from baseline, intention-to-treat population.
8. Compare percentage changes by cycle with last-observation-carried-forward, intention-to-treat population.

The first 7 types of analyses were pre-specified in the statistical analysis plan; the last one was added in the clinical study report (CSR-41303).

As defined by the sponsor, the intention-to-treat (ITT) population consisted of all the randomized subjects who had at least 1 baseline and at least 1 post-baseline BMD reading, while the efficacy evaluable (EE) population consisted of the randomized subjects who met the following criteria:

- Must have taken at least 80% of study medication during the interval between any two consecutive BMD evaluations. As soon as one interval failed to meet the criterion, the BMD value collected at the end of that interval as well as all the subsequent BMD values were excluded.
- Had no chronic use of non-study medication that may affect bone calcium metabolism.
- Scans done more than 60 days after the termination of study medications were excluded.
- Must have at least 1 baseline and at least 2 post-baseline BMD readings with no more than one of these being the termination scan.

All scans were included in the ITT population, even though they were done 60 days after the termination of study medications. In the ITT and EE populations, the last two scans performed within 60 days of each other were both treated as the termination scans; otherwise, only the last one was used.

The annual percentage change from baseline for each individual was derived by first fitting a linear regression line to their BMD values over time in days, then estimating the slope (BMD change per day), and multiplying it by 365 (days) to obtain the annual change in BMD. The annual percentage change from baseline was then calculated as

(annual change in BMD / baseline) × 100%.

Among those 8 types of analyses, comparing annual % changes from baseline derived from the regression slopes of the EE subjects was the primary analysis proposed by the sponsor. However, this reviewer had a concern about the accuracy of treatment effects assessed by this type of analysis due to the following reasons. The annual % change from baseline was actually an estimate, rather than an observed value as % change from baseline at the final visit(s) or at Cycle 26 with last-observation-carried-forward (LOCF). From the medical officer's past experience, bone mineral density was not always increased or decreased linearly over time. Therefore, fitting a linear regression line to this type of data could yield a biased estimate and result in incorrect inferences. For example, the annual changes in BMD derived from the slopes might be overestimated for the early withdrawn subjects. Furthermore, analysis on EE population could also increase bias caused by exclusion of some randomized subjects representing part of the target population. As a consequence, this reviewer felt that the % change from baseline at the final visit(s) or at Cycle 26 with LOCF based on the ITT population was a better measure for efficacy assessment.

The % changes from baseline at the final visit(s) were basically the same as the % changes from baseline at Cycle 26 with LOCF, except for the cases where the subjects made their final visit(s) after Cycle 26, at which time the study medications had been stopped (see Supplemental Volume II, 6.2.1). After consultation with the medical officer, the percentage change from baseline at Cycle 26 with LOCF based on the ITT population was chosen to be the focus of the review.

This reviewer basically employed the same statistical model and testing techniques as the sponsor did to analyze the % change from baseline in BMD of lumbar spine at Cycle 26 with LOCF from the ITT population. The initial analysis of covariance (ANCOVA) model included treatment, center, treatment-by-center interaction, and two covariates (years since menopause and body weight at baseline). The two covariates, as stated in the study protocol, were used to improve the precision of the tests. Since there was no significant treatment-by-center interaction at $p < 0.10$ suggesting similar response patterns across centers, the model consisting of only treatment, center, and the two covariates was then used as the main statistical model for all the 4 skeletal sites in this review.

Linear contrast techniques were implemented for least significant difference (LSD) test to compare the efficacy of CE/MPA combined therapy (main study interest of NDA 21-396) or CE mono therapy (main study interest of NDA 21-417) with that of placebo. In order to control the false positive error rate caused by multiple group comparisons, the sponsor proposed a sequential testing approach so that the tests of lower doses of CE/MPA versus

placebo were conditioned on the significance ($p \leq 0.05$) of higher doses of CE/MPA versus placebo. Also, the tests of CE mono doses versus placebo were conditioned on the significance ($p \leq 0.05$) of the corresponding CE/MPA combined doses versus placebo. This reviewer did an additional set of group comparisons by using Dunnett-Hsu t-test (modified Dunnett's t-test or many-on-one test) to compare the 7 active treatment groups with placebo simultaneously while controlling the overall false positive error rate at 5%.

The % changes from baseline at the final visit(s) and the annual % changes from baseline derived from the slopes, using the ITT population, were also analyzed by this reviewer. Their results are summarized and compared along with the sponsor's results based on the EE population (see Text Table 2).

The average of the two pre-treatment BMD values, if any, was calculated and used as the baseline for all the analyses. For the subjects who had more than one on-therapy BMD value within one cycle or had two termination scans from the final visits, the average was used in the calculation of percentage change from baseline. However, all the individual post-baseline data points were used in the regression analysis for slope estimation for the ITT population.

The sponsor analyzed the 4 skeletal sites separately without any p-value adjustment over the sites. Since L2-L4 of the anteroposterior lumbar spine was the only primary site claimed by the sponsor, this reviewer did not strongly feel the necessity of the adjustment either.

2.3.3 Detailed Review of Study 0713D2-309-US (from 8/95 to 10/00)

Study Design and Objectives

Study 309 was a prospective, 2-year, randomized, double-blind, placebo- and active-controlled, 8-parallel-group, multicenter (in USA) trial, conducted in generally healthy postmenopausal women between age 40 and 65 years old, inclusive, with an intact uterus.

The study comprised two parts: a 1-year (13-cycle) basic study and a 2-year (26-cycle) Osteoporosis and Metabolic substudy. Each cycle lasted for 28 days. The substudy subjects were from the centers not only participating in the basic study but also being designated for the substudy. The on-therapy study visits were scheduled at Cycles 3, 6, 9, 13, 16, 19, 22, and 26 for the substudy subjects.

The 8 treatment arms consisted of 3 doses of CE mono therapy, 4 doses of CE/MPA combined therapy, and a placebo. A double-dummy design was implemented so that the randomized subjects in the active treatment groups would take either one CE tablet along with one CE/MPA appearance of placebo tablet or one CE appearance of placebo tablet

along with one CE/MPA tablet (see the dosing regimens below). In addition, all patients were asked to take Caltrate, elemental calcium, 600 mg once daily throughout the study.

Regimen	CE (mg)	CE/MPA (mg)	Days of Use per Cycle
A	0.625	Placebo	28
B	Placebo	0.625/2.5	28
C	0.45	Placebo	28
D	Placebo	0.45/2.5	28
E	Placebo	0.45/1.5	28
F	0.3	Placebo	28
G	Placebo	0.3/1.5	28
H	Placebo	Placebo	28

As stated in the clinical study report (CSR-41303), the substudy subjects were assigned to the treatment regimens that were randomized in blocks of 16 available at her study center.

The primary objective of the Osteoporosis and Metabolic substudy was to evaluate the safety and efficacy of lower doses of Premarin (CE) and medroxyprogesterone acetate (MPA) in preventing postmenopausal bone loss compared with placebo and in improving bone metabolism profiles. The associated primary efficacy variable was bone mineral density (BMD) which was measured at least twice prior to treatment, once at Cycles 6, 13, and 19, and twice at Cycle 26, for L2-L4 of anteroposterior lumbar spine (primary skeletal site), femoral neck and trochanter of the hip, and total body. The secondary efficacy variables were biochemical indices of bone metabolism such as serum osteocalcin, urine calcium, urine creatinine, and N-telopeptide.

The secondary objective of interest in this substudy was to evaluate the efficacy of lower doses of CE and MPA in maintaining an acceptable metabolic profile. The associated variables for the safety evaluation were coagulation, carbohydrate, and lipid parameters.

Based on consultation with the medical officer, those biochemical indices and metabolic parameters would not be the focus of the review.

Subject Disposition

A total of 822 outpatients from 20 designated sites of the 1-year basic study participated in the 2-year Osteoporosis and Metabolic substudy (Text Table 3). All 51 subjects from Center 30952 were excluded from all the analyses due to site termination caused by issues related to non-compliance with Good Clinical Practice (GCP), as noted in the clinical study report (CSR-41303), section 8.1. However, no specific issues were given in the study report. A summary of disposition for those 51 subjects is shown in Text Table 4. An additional 22

subjects were also excluded from all the analyses since no diary cards were returned and therefore no medications, if any, were recorded. As a result, only 749 randomized subjects were considered as "evaluable subjects" (the sponsor's terminology). Note that efficacy evaluable population or intention-to-treat population was derived from those 749 evaluable subjects.

The overall withdrawal rate with respect to the total evaluable subjects during the randomized treatment period was 31% (= 230/749), which was within the sponsor's prediction during the determination of sample size for the substudy. The number of subjects completing the 2-year substudy per group, except for CE 0.625 mg, was close to the sample size that the trial was powered on (64 per group based on femoral neck and 50 per group based on lumbar spine for 80% power). The withdrawal rates in each of the CE/MPA groups were smaller than that in any of the CE groups, where CE 0.625 mg showed the highest rate (53.6%) and CE/MPA 0.3/1.5 mg showed the smallest rate (21.4%). The most common reason leading to withdrawal in this substudy was adverse events (Text Table 5), particularly in the CE 0.625-mg group, where 31% of 97 evaluable subjects withdrew for this reason. The withdrawal rate in the placebo group was about 34%, where 14% of 94 subjects withdrew because of unsatisfactory efficacy response. Except adverse events and unsatisfactory efficacy response, the various reasons listed in Text Table 5 for withdrawal were similar across the treatment groups.

Text Table 3 – Substudy Subject Disposition during Randomized Treatment Phase

Regimen	A		B		C		D		E		F		G		H		Total	
Dose (mg)	0.625		0.625/2.5		0.45		0.45/2.5		0.45/1.5		0.3		0.3/1.5		Placebo			
Randomized	**103**		**98**		**104**		**108**		**103**		**96**		**107**		**103**		**822**	
Termination of Site 30952	(6)		(7)		(6)		(8)		(5)		(5)		(7)		(7)		(51)	
No medications recorded	(0)		(5)		(3)		(4)		(4)		(2)		(2)		(2)		(22)	
Evaluable	**97**		**86**		**95**		**96**		**94**		**89**		**98**		**94**		**749**	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Cycle 1	97	14	86	5	95	5	96	9	94	6	89	5	98	8	94	9	749	61
Cycle 6	83	16	81	4	90	13	87	5	88	10	84	7	90	8	85	9	688	72
Cycle 13	67	13	77	11	77	9	82	9	78	5	77	11	82	4	76	12	616	74
Cycle 19	54	9	66	1	68	5	73	2	73	2	66	1	78	1	64	1	542	22
Cycle 25	45	0	65	0	63[a]	0	71	0	71	0	65	0	77	0	63	1	520	1
Completers	45 (46.4%)		65 (75.6%)[a]		63 (66.3%)[a]		71 (74.0%)[a]		71 (75.5%)		65 (73.0%)		77 (78.6%)		62 (66.0%)		519 (69.3%)	
Withdrawals	52 (53.6%)		21 (24.4%)		32 (33.7%)		25 (26.0%)		23 (24.5%)		24 (27.0%)		21 (21.4%)		32 (34.0%)		230 (30.7%)	

A = Number of subjects beginning the treatment cycle (from the sponsor's Supportive Table ST10-1)

B = Number of subjects discontinuing during or after the treatment cycle (from the sponsor's Supportive Table 8-1)

Number of completers and withdrawals are from CSR Figure 8.1A, and their percentages were calculated with respect to the number of evaluable subjects.

[a] This reviewer noted some discrepancies among Supportive Table ST8-1, Supportive Table ST10-1, and CSR Figure 8.1A with regard to the numbers of completers and withdrawals in Regimens B, C, and D. For example, numbers of patients beginning Cycle 26 were 64 (B), 60 (C), and 70 (D) in ST10-1, while Figure 8.1A listed 65, 63, and 71, respectively. Also, for Regimen C, no dropout was noted during or after Cycle 22 in ST8-1; however, there was 1 withdrawal indicated between Cycles 22 and 23 in ST10-1.

Text Table 4 – Summary of Disposition for All Randomized Subjects in Center 30952

Regimen Dose (mg)	A 0.625	B 0.625/2.5	C 0.45	D 0.45/2.5	E 0.45/1.5	F 0.3	G 0.3/1.5	H Placebo	Total
Number of randomized subjects	6	7	6	8	5	5	7	7	51
Number of completers	2	1	1	2	0	2	2	1	11
Number of withdrawals	4	6	5	6	5	3	5	6	40
Other non-medical event	2	2	2	5	0	3	2	1	17
Protocol violation	0	1	3	1	0	0	1	2	8
Failed to return	0	0	0	0	3	0	2	1	6
Adverse reaction	1	1	0	0	0	0	0	0	2
Patient/subject request	0	0	0	0	1	0	0	1	2
Other medical event	0	1	0	0	0	0	0	0	1
Unsatisfactory response – efficacy	0	0	0	0	0	0	0	1	1
No medication recorded	1	1	0	0	1	0	0	0	3

The sponsor's Attachment 1 (Report 3-5) modified. Almost all other non-medical events were study site closeout.

Text Table 5 – Number (%) of Substudy Subjects Withdrawn due to Primary Reason during Randomized Treatment Phase

Regimen Dose (mg)	A 0.625	B 0.625/2.5	C 0.45	D 0.45/2.5	E 0.45/1.5	F 0.3	G 0.3/1.5	H Placebo
Number of evaluable subjects	97	86	95	96	94	89	98	94
Adverse events	30 (30.9)	11 (12.8)	11 (11.6)	9 (9.4)	10 (10.6)	7 (7.9)	4 (4.1)	4 (4.3)
Failed to return	9 (9.3)	2 (2.3)	1 (1.1)	3 (3.1)	2 (2.1)	5 (5.6)	6 (6.1)	6 (6.4)
Other medical event	5 (5.2)	0	2 (2.1)	2 (2.1)	3 (3.2)	2 (2.2)	3 (3.1)	3 (3.2)
Other non-medical event	1 (1.0)	4 (4.7)	7 (7.4)	1 (1.0)	2 (2.1)	3 (3.4)	1 (1.0)	1 (1.1)
Patient request	4 (4.1)	4 (4.7)	4 (4.2)	4 (4.2)	6 (6.4)	5 (5.6)	2 (2.0)	3 (3.2)
Protocol violation	2 (2.1)	0	1 (1.1)	4 (4.2)	0	1 (1.1)	3 (3.1)	2 (2.1)
Unsatisfactory response – efficacy	1 (1.0)	0	6 (6.3)	2 (2.1)	0	1 (1.1)	2 (2.0)	13 (13.8)
Total	**52 (53.6)**	**21 (24.4)**	**32 (33.7)**	**25 (26.0)**	**23 (24.5)**	**24 (27.0)**	**21 (21.4)**	**32 (34.0)**

The sponsor's Table 8.1.1A modified. The percentages were calculated with respect to the number of evaluable subjects.
Unsatisfactory response – efficacy refers to development of endometrial hyperplasia, increased vasomotor symptoms, or annualized loss >7.5% in lumbar spine bone mineral density.

Text Table 6 – Substudy: Demographic Characteristics of **All Randomized Subjects**

Regimen	A	B	C	D	E	F	G	H	
Dose (mg)	0.625	0.625/2.5	0.45	0.45/2.5	0.45/1.5	0.3	0.3/1.5	Placebo	Total
No. of all randomized subjects	103	98	104	108	103	96	107	103	822
Age (years): Mean ± SD	51.9 ± 3.2	51.6 ± 4.1	51.8 ± 3.8	51.3 ± 3.8	51.0 ± 3.4	52.1 ± 3.9	51.4 ± 3.4	51.2 ± 4.0	51.5 ± 3.7
Range	45 – 61	41 – 61	43 – 62	41 – 65	40 – 59	42 – 61	42 – 59	41 – 60	40 – 65
<50 (%)	21 (20)	29 (30)	24 (23)	27 (25)	33 (32)	26 (27)	28 (26)	33 (32)	221 (27)
50 – 54 (%)	61 (59)	45 (46)	59 (57)	62 (57)	57 (55)	41 (43)	58 (54)	51 (50)	434 (53)
≥55 (%)	21 (20)	24 (24)	21 (20)	19 (18)	13 (13)	29 (30)	21 (20)	19 (18)	167 (20)
Race: White (%)	95 (92)	89 (91)	92 (88)	105 (97)	96 (93)	87 (91)	95 (89)	97 (94)	756 (92)
Black (%)	4 (4)	3 (3)	5 (5)	3 (3)	2 (2)	5 (5)	7 (7)	3 (3)	32 (4)
Hispanic (%)	2 (2)	4 (4)	4 (4)	0	3 (3)	3 (3)	3 (3)	2 (2)	21 (3)
Asian (%)	1 (1)	1 (1)	2 (2)	0	2 (2)	1 (1)	2 (2)	0	9 (1)
Native American (%)	1 (1)	0	1 (1)	0	0	0	0	0	2 (<1)
Other (%)	0	1 (1)	0	0	0	0	0	1 (1)	2 (<1)
Weight (kg): Mean ± SD	67.0 ± 9.0	66.1 ± 9.2	65.8 ± 8.3	65.0 ± 8.7	68.0 ± 9.4	64.7 ± 8.1	65.2 ± 8.3	64.6 ± 8.8	65.8 ± 8.8
Height (cm): Mean ± SD	164.4 ± 5.3	164.5 ± 6.7	164.4 ± 6.5	164.0 ± 6.3	165.3 ± 6.1	162.9 ± 6.2	163.8 ± 6.0	163.7 ± 5.6	164.1 ± 6.1
BMI (kg/m^2): Mean ± SD	24.7 ± 2.7	24.4 ± 2.9	24.4 ± 2.6	24.1 ± 2.6	24.9 ± 2.9	24.4 ± 2.7	24.3 ± 2.8	24.1 ± 3.0	24.4 ± 2.8
<20 (%)	4 (4)	8 (8)	5 (5)	6 (6)	11 (11)	4 (4)	3 (3)	9 (9)	50 (6)
20 – 30 (%)	98 (95)	90 (92)	99 (95)	102 (94)	92 (89)	91 (95)	102 (95)	94 (91)	768 (93)
≥30 (%)	1 (1)	0	0	0	0	1 (1)	2 (2)	0	4 (<1)
Age at menopause (years):									
Mean ± SD	50.0 ± 3.0	49.4 ± 4.1	49.2 ± 3.5	48.9 ± 3.6	48.7 ± 3.2	49.8 ± 3.6	49.1 ± 3.3	48.9 ± 3.7	49.2 ± 3.5
Range	42 – 57	39 – 59	40 – 58	40 – 62	39 – 56	40 – 59	38 – 56	39 – 57	38 – 62
Years since menopause:									
Mean ± SD	2.3 ± 0.9	2.3 ± 0.9	2.4 ± 1.0	2.4 ± 1.0	2.3 ± 1.0	2.3 ± 1.0	2.2 ± 1.0	2.4 ± 1.0	2.3 ± 1.0
<2 (%)	45 (44)	42 (43)	38 (37)	42 (39)	45 (44)	45 (47)	48 (45)	42 (41)	347 (42)
2 – 3 (%)	34 (33)	31 (32)	34 (33)	34 (31)	31 (30)	24 (25)	35 (33)	30 (29)	253 (31)
≥3 (%)	24 (23)	25 (26)	32 (31)	32 (30)	27 (26)	27 (28)	24 (22)	31 (30)	222 (27)

Text Table 7 – Substudy: Demographic Characteristics of **All Evaluable Subjects**

Regimen Dose (mg)	A 0.625	B 0.625/2.5	C 0.45	D 0.45/2.5	E 0.45/1.5	F 0.3	G 0.3/1.5	H Placebo	Total
No. of evaluable subjects	97	86	95	96	94	89	98	94	749
Age (years): Mean ± SD	51.9 ± 3.3	51.5 ± 4.1	52.0 ± 3.7	51.5 ± 3.8	51.1 ± 3.5	52.3 ± 3.9	51.3 ± 3.5	51.3 ± 4.1	51.6 ± 3.7
Range	45 – 61	41 – 61	44 – 62	41 – 65	40 – 59	42 – 61	42 – 59	41 – 60	40 – 65
<50 (%)	21 (22)	26 (30)	20 (21)	22 (23)	29 (31)	23 (26)	27 (28)	30 (32)	198 (26)
50 – 54 (%)	55 (57)	41 (48)	55 (58)	55 (57)	52 (55)	38 (43)	51 (52)	45 (48)	392 (52)
≥55 (%)	21 (22)	19 (22)	20 (21)	19 (20)	13 (14)	28 (31)	20 (20)	19 (20)	159 (21)
Race: White (%)	90 (93)	78 (91)	85 (89)	94 (98)	91 (97)	80 (90)	87 (89)	88 (94)	693 (93)
Black (%)	3 (3)	2 (2)	5 (5)	2 (2)	1 (1)	5 (6)	6 (6)	3 (3)	27 (4)
Hispanic (%)	2 (2)	4 (5)	3 (3)	0	1 (1)	3 (3)	3 (3)	2 (2)	18 (2)
Asian (%)	1 (1)	1 (1)	1 (1)	0	1 (1)	1 (1)	2 (2)	0	7 (1)
Native American (%)	1 (1)	0	1 (1)	0	0	0	0	0	2 (<1)
Other (%)	0	1 (1)	0	0	0	0	0	1 (1)	2 (<1)
Weight (kg): Mean ± SD	67.1 ± 8.9	65.7 ± 8.9	65.7 ± 8.5	65.4 ± 8.9	67.7 ± 9.4	64.7 ± 8.0	65.3 ± 8.5	64.9 ± 8.9	65.8 ± 8.8
Height (cm): Mean ± SD	164.5 ± 5.2	164.2 ± 6.2	164.3 ± 6.5	164.1 ± 6.4	165.3 ± 6.1	162.7 ± 5.9	163.6 ± 6.1	163.5 ± 5.6	164.0 ± 6.0
BMI (kg/m^2): Mean ± SD	24.8 ± 2.8	24.3 ± 2.8	24.3 ± 2.6	24.3 ± 2.7	24.7 ± 2.9	24.4 ± 2.7	24.4 ± 2.8	24.3 ± 3.0	24.4 ± 2.8
<20 (%)	4 (4)	7 (8)	5 (5)	5 (5)	10 (11)	3 (3)	3 (3)	7 (7)	44 (6)
20 – 30 (%)	92 (95)	79 (92)	90 (95)	91 (95)	84 (89)	85 (96)	93 (95)	87 (93)	701 (94)
≥30 (%)	1 (1)	0	0	0	0	1 (1)	2 (2)	0	4 (1)
Age at menopause (years):									
Mean ± SD	49.6 ± 3.1	49.2 ± 4.2	49.4 ± 3.4	49.0 ± 3.7	48.8 ± 3.3	49.9 ± 3.6	49.0 ± 3.4	48.9 ± 3.8	49.2 ± 3.6
Range	42 – 57	39 – 59	41 – 58	40 – 62	39 – 56	40 – 59	38 – 56	39 – 57	38 – 62
Years since menopause:									
Mean ± SD	2.2 ± 0.9	2.2 ± 0.9	2.5 ± 1.0	2.5 ± 0.9	2.3 ± 0.9	2.3 ± 1.0	2.3 ± 1.0	2.4 ± 0.9	2.3 ± 0.9
<2 (%)	43 (44)	38 (44)	32 (34)	37 (39)	41 (44)	41 (46)	42 (43)	40 (43)	314 (42)
2 – 3 (%)	33 (34)	28 (33)	32 (34)	30 (31)	28 (30)	22 (25)	33 (34)	26 (28)	232 (31)
≥3 (%)	21 (22)	20 (23)	31 (33)	29 (30)	25 (27)	26 (29)	23 (23)	28 (30)	203 (27)

Demographics

Based on this reviewer's analyses, demographic characteristics of the 822 randomized substudy subjects, such as age, race, weight, height, body mess index (BMI), age at menopause, and years since menopause, were generally homogeneous across the treatment groups (Text Table 6). The mean age at entry was 51.5 years old, ranging from 40 to 65. All the subjects were female who started menopause naturally at age between 38 and 62, with mean age 49.2 years old. In other words, the average number of years since menopause was about 2 years. Almost 92% of 822 subjects were White; 4% and 3% were Black and Hispanic, respectively. The weight and height at baseline in average were 65.8 kg and 164.1 cm, respectively. The mean body mess index was around 24 kg/m^2.

Similar demographic characteristics were also observed when only the 749 evaluable subjects were analyzed (Text Table 7).

Efficacy Results and Discussion

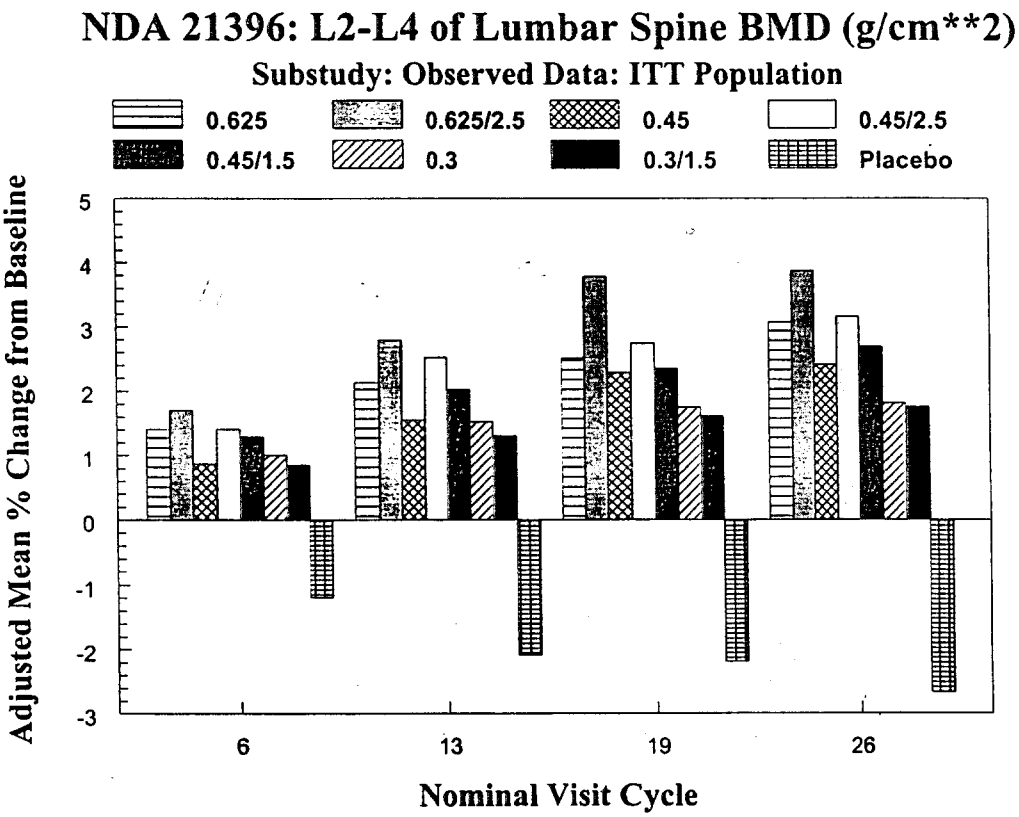
Among the 749 evaluable subjects, 54 of them did not have post-baseline bone scans done for any of the 4 skeletal sites and 2 additional subjects did not have any scan done for lumbar spine, but had scans for the other 3 sites. They were excluded from the ITT population accordingly. As a result, the ITT population for lumbar spine consisted of 693 subjects, while 695 subjects were evaluated for the other sites. The raw mean BMD values at pre-treatment, Cycles 6, 13, 19, and 26, using the observed data from the ITT population are depicted in Figures 1-4 in Appendix for lumbar spine, femoral neck, femoral trochanter, and total body, respectively. Based on this reviewer's analyses, the baseline BMD values were comparable among the 8 study groups for each of the 4 skeletal sites.

BMD of Anteroposterior Lumbar Spine (L2-L4). All the active treatment groups showed an increased mean BMD of lumbar spine from baseline at Cycle 26 using the LOCF data, while the placebo group showed a decrease, -2.51% (Text Table 8). The mean % increases from baseline in the CE/MPA groups were generally larger than that of the corresponding CE groups. The % increases from baseline among the CE/MPA groups were in a dose-dependent fashion (1.69%, 2.20%, 2.98%, and 3.48% for 0.3/1.5, 0.45/1.5, 0.45/2.5, and 0.625/2.5 mg, respectively), so were the % increases among the CE groups (1.33%, 2.11%, and 2.37% for 0.3, 0.45, and 0.625 mg, respectively). Both LSD and Dunnett-Hsu tests showed that all the CE/MPA and CE groups were highly significantly better than the placebo group in preventing bone loss based on the measurements of lumbar spine BMD at Cycle 26 (Text Table 9). For example, in the lowest CE/MPA and CE dose groups, 4.21% and 3.84% increases, respectively, over the placebo group were observed after two years of treatment. Note that the substudy was designed to show 80% power to declare a 2.25% difference

between the placebo and treated groups in annual percentage change from baseline (approximately 4.5% biannual) in lumbar spine BMD based on 50 completers per group.

The 7 active treatment groups also showed significantly increased mean % changes from baseline in lumbar spine BMD when compared with the placebo at Cycles 6, 13, 19, and 26 based on the observed data (Text Figure 1). The response patterns of CE/MPA groups and CE groups at each intermediate cycle were qualitatively similar to the ones at Cycle 26. The quantitative responses in each group were also similar between Cycles 19 and 26.

Text Figure 1



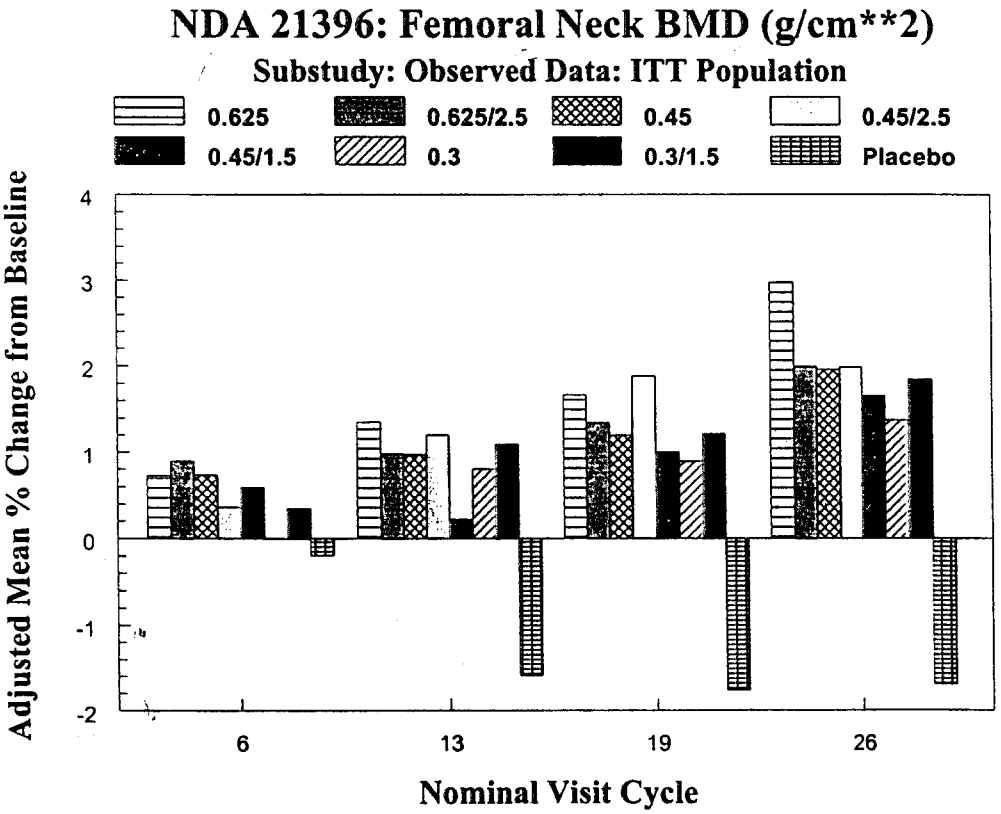
Adjusted mean here is least-squares mean adjusted by years since menopause and body weight at baseline

BMD of Femoral Neck. All the active treatment groups showed an increased mean BMD of femoral neck from baseline at Cycle 26 using the LOCF data, while the placebo group showed a decrease, -1.87% (Text Table 8). Although the % increases from baseline among the CE/MPA groups were in a dose-dependent fashion, they were close to each other (1.45%, 1.50%, 1.59%, and 1.63% for 0.3/1.5, 0.45/1.5, 0.45/2.5, and 0.625/2.5 mg, respectively). The CE groups did not have such findings (0.46%, 1.89%, and 1.68% for 0.3, 0.45, and 0.625 mg, respectively). Both LSD and Dunnett-Hsu tests showed that all the CE/MPA and CE

groups were highly significantly better than the placebo group in preventing bone loss based on the measurements of femoral neck BMD at Cycle 26 (Text Table 9). At least, 3.33% and 2.33% increases over the placebo group were observed in the lowest CE/MPA and CE dose groups, respectively, after two years of treatment. Note that the substudy was also designed to show 80% power to declare a 1.5% difference between the placebo and treated groups in annual percentage change from baseline (approximately 3.0% biannual) in femoral neck BMD based on 64 completers per group.

Except for Cycle 6, the 7 active treatment groups also showed significantly increased mean % changes from baseline in femoral neck BMD when compared with the placebo at Cycles 13, 19, and 26 based on the observed data (Text Figure 2). The mean % changes from baseline in femoral neck BMD were generally increased over time in each of the 7 active treatment groups and decreased in the placebo group.

Text Figure 2



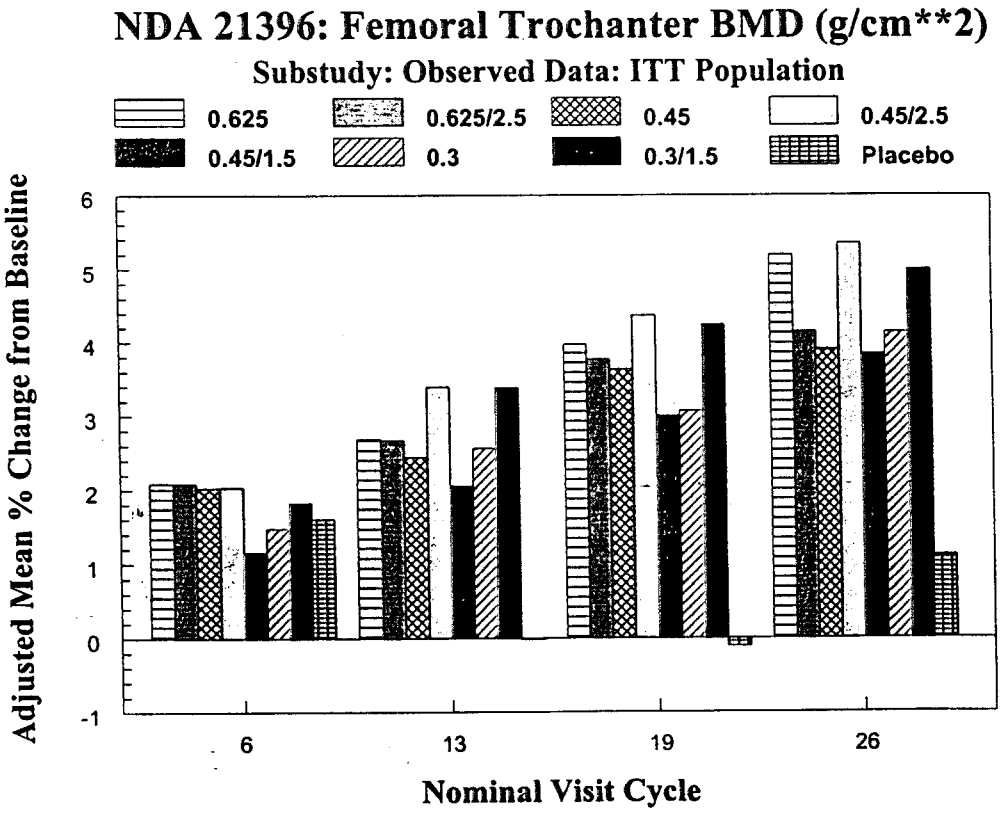
Adjusted mean here is least-squares mean adjusted by years since menopause and body weight at baseline

BMD of Femoral Trochanter. All the 8 treatment groups showed an increased mean BMD of femoral trochanter from baseline at Cycle 26 using the LOCF data, with the placebo group

showing the least increase, +0.88% (Text Table 8). In contrast to femoral neck, dose-dependent responses were observed in the CE groups (3.23%, 3.47%, and 3.74% for 0.3, 0.45, and 0.625 mg, respectively), but not in the CE/MPA groups (4.18%, 3.23%, 4.55%, and 3.76% for 0.3/1.5, 0.45/1.5, 0.45/2.5, and 0.625/2.5 mg, respectively). Both LSD and Dunnett-Hsu tests showed that all the CE/MPA and CE groups were significantly better than the placebo group in preventing bone loss based on the measurements of femoral trochanter BMD at Cycle 26 (Text Table 9). The smallest treatment differences among the comparisons of the CE/MPA or CE groups versus placebo were 2.35% for both 0.45/1.5 mg and 0.3 mg.

As in the case of femoral neck, except for Cycle 6, the 7 active treatment groups also showed significantly increased mean % changes from baseline in femoral trochanter BMD when compared with the placebo at Cycles 13, 19, and 26 based on the observed data (Text Figure 3). In addition, the mean % changes from baseline in femoral trochanter BMD were also generally increased over time in each of the 7 active treatment groups. Throughout the course of the substudy, the CE/MPA 0.3/1.5-mg group continuously showed a greater % increase from baseline in femoral trochanter BMD than the CE/MPA 0.45/1.5-mg group.

Text Figure 3

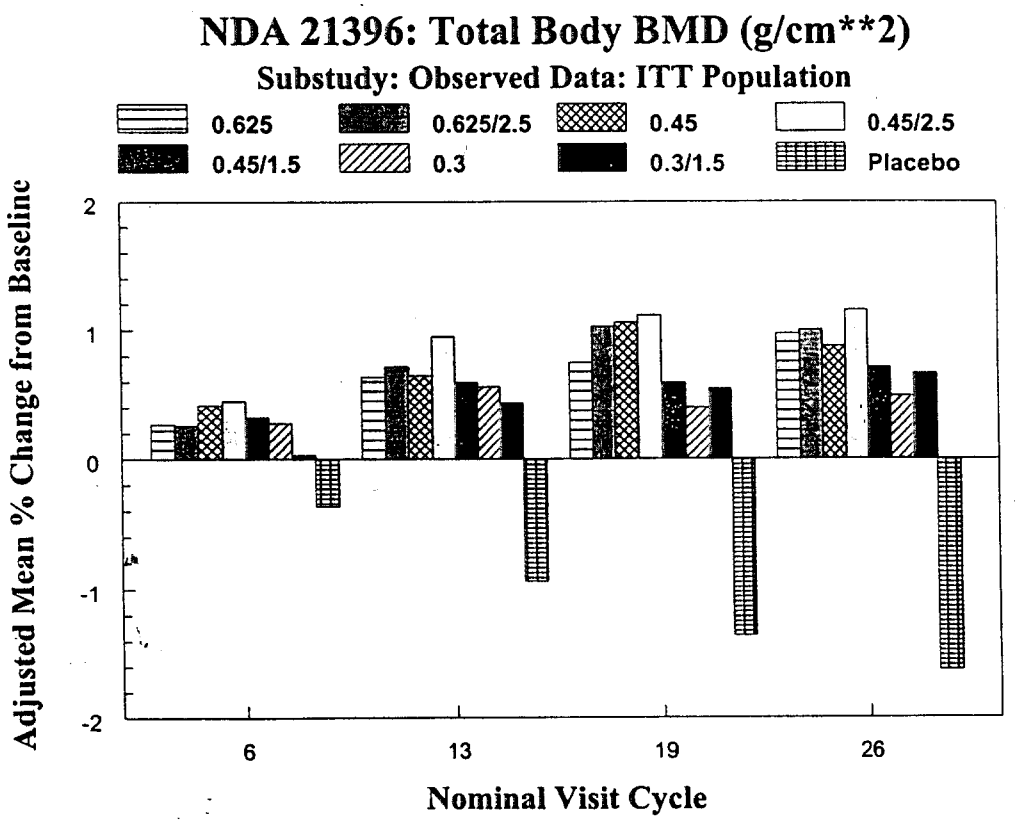


Adjusted mean here is least-squares mean adjusted by years since menopause and body weight at baseline

BMD of Total Body (L2-L4). All the active treatment groups showed an increased mean BMD of total body from baseline at Cycle 26 using the LOCF data, while the placebo group showed a decrease, -1.49% (Text Table 8). No dose-dependent % increases were observed in the CE/MPA groups (0.55%, 0.61%, 0.99%, and 0.94% for 0.3/1.5, 0.45/1.5, 0.45/2.5, and 0.625/2.5 mg, respectively) or in the CE groups (0.41%, 0.78%, and 0.67% for 0.3, 0.45, and 0.625 mg, respectively). Nevertheless, both LSD and Dunnett-Hsu tests showed that all the CE/MPA and CE groups were highly significantly better than the placebo group in preventing bone loss based on the measurements of total body BMD at Cycle 26 (Text Table 9). At least, 2.04% and 1.90% increases over the placebo group were observed in the lowest CE/MPA and CE dose groups, respectively, after two years of treatment.

As in the case of lumbar spine, the 7 active treatment groups also showed significantly increased mean % changes from baseline in total body BMD when compared with the placebo at Cycles 6, 13, 19, and 26 based on the observed data (Text Figure 4).

Text Figure 4



Text Table 8 – Substudy: Descriptive Statistics for BMD Using LOCF Data at Cycle 26 for ITT Population

			Baseline	Cycle 26	% Change from Baseline
Skeletal Site	Regimen	N	Mean ± SD	Mean ± SD	Adjusted Mean ± SE
L2-L4	A (0.625)	83	1.1710 ± 0.1524	1.1968 ± 0.1491	2.3693 ± 0.3519
	B (0.625/2.5)	81	1.1440 ± 0.1643	1.1827 ± 0.1706	3.4768 ± 0.3542
	C (0.45)	91	1.1350 ± 0.1549	1.1587 ± 0.1534	2.1149 ± 0.3358
	D (0.45/2.5)	87	1.1516 ± 0.1707	1.1859 ± 0.1752	2.9770 ± 0.3446
	E (0.45/1.5)	89	1.1584 ± 0.1406	1.1831 ± 0.1424	2.2014 ± 0.3396
	F (0.3)	87	1.1398 ± 0.1504	1.1546 ± 0.1551	1.3295 ± 0.3427
	G (0.3/1.5)	90	1.1386 ± 0.1460	1.1571 ± 0.1467	1.6916 ± 0.3355
	H (Placebo)	85	1.1438 ± 0.1437	1.1144 ± 0.1434	-2.5138 ± 0.3473
F. Neck	A (0.625)	84	0.9067 ± 0.1365	0.9199 ± 0.1276	1.6838 ± 0.4350
	B (0.625/2.5)	81	0.8872 ± 0.1375	0.9000 ± 0.1365	1.6251 ± 0.4407
	C (0.45)	91	0.8858 ± 0.1319	0.9019 ± 0.1283	1.8871 ± 0.4177
	D (0.45/2.5)	87	0.8919 ± 0.1470	0.9057 ± 0.1477	1.5868 ± 0.4287
	E (0.45/1.5)	89	0.8861 ± 0.1164	0.8982 ± 0.1129	1.4962 ± 0.4226
	F (0.3)	87	0.8632 ± 0.1125	0.8668 ± 0.1099	0.4600 ± 0.4265
	G (0.3/1.5)	91	0.8593 ± 0.1141	0.8717 ± 0.1135	1.4540 ± 0.4144
	H (Placebo)	85	0.8835 ± 0.1357	0.8668 ± 0.1346	-1.8733 ± 0.4322
F. Trochanter	A (0.625)	84	0.7769 ± 0.1251	0.8029 ± 0.1218	3.7371 ± 0.5713
	B (0.625/2.5)	81	0.7743 ± 0.1360	0.7999 ± 0.1344	3.7550 ± 0.5788
	C (0.45)	91	0.7572 ± 0.1191	0.7814 ± 0.1163	3.4661 ± 0.5486
	D (0.45/2.5)	87	0.7609 ± 0.1439	0.7931 ± 0.1462	4.5494 ± 0.5631
	E (0.45/1.5)	89	0.7554 ± 0.1201	0.7774 ± 0.1211	3.2292 ± 0.5551
	F (0.3)	87	0.7487 ± 0.1048	0.7712 ± 0.1008	3.2320 ± 0.5601
	G (0.3/1.5)	91	0.7565 ± 0.1191	0.7860 ± 0.1154	4.1781 ± 0.5443
	H (Placebo)	85	0.7521 ± 0.1238	0.7572 ± 0.1237	0.8801 ± 0.5677
Total Body	A (0.625)	84	1.1487 ± 0.0801	1.1572 ± 0.0793	0.6729 ± 0.1646
	B (0.625/2.5)	81	1.1388 ± 0.0847	1.1501 ± 0.0827	0.9406 ± 0.1668
	C (0.45)	91	1.1360 ± 0.0776	1.1460 ± 0.0755	0.7766 ± 0.1581
	D (0.45/2.5)	87	1.1329 ± 0.0828	1.1452 ± 0.0798	0.9906 ± 0.1622
	E (0.45/1.5)	89	1.1379 ± 0.0710	1.1455 ± 0.0690	0.6072 ± 0.1599
	F (0.3)	87	1.1373 ± 0.0740	1.1428 ± 0.0735	0.4103 ± 0.1614
	G (0.3/1.5)	91	1.1322 ± 0.0792	1.1389 ± 0.0783	0.5467 ± 0.1568
	H (Placebo)	85	1.1299 ± 0.0808	1.1144 ± 0.0849	-1.4897 ± 0.1636

N = Sample size; SD = Standard deviation; SE = Standard error

Adjusted mean here is the least-squares mean adjusted by years since menopause and body weight at baseline.

Text Table 9 – Substudy: Results for % Change from Baseline in BMD Using LOCF Data at Cycle 26 (ITT)

Skeletal Site	Group Comparison	Treatment Difference	LSD		Dunnett-Hsu	
			p-value	(LCL, UCL)	Adjusted p-value	(LCL, UCL)
L2-L4	0.625 vs. PLA	4.8831	<.0001	(3.93, 5.83)	<.0001	(3.61, 6.15)
	0.625/2.5 vs. PLA	5.9906	<.0001	(5.03, 6.95)	<.0001	(4.72, 7.27)
	0.45 vs. PLA	4.6287	<.0001	(3.70, 5.56)	<.0001	(3.39, 5.87)
	0.45/2.5 vs. PLA	5.4908	<.0001	(4.55, 6.43)	<.0001	(4.24, 6.74)
	0.45/1.5 vs. PLA	4.7151	<.0001	(3.78, 5.65)	<.0001	(3.47, 5.96)
	0.3 vs. PLA	3.8433	<.0001	(2.91, 4.78)	<.0001	(2.59, 5.09)
	0.3/1.5 vs. PLA	4.2054	<.0001	(3.27, 5.14)	<.0001	(2.96, 5.45)
F. Neck	0.625 vs. PLA	3.5571	<.0001	(2.38, 4.74)	<.0001	(1.98, 5.13)
	0.625/2.5 vs. PLA	3.4984	<.0001	(2.31, 4.69)	<.0001	(1.91, 5.09)
	0.45 vs. PLA	3.7604	<.0001	(2.60, 4.92)	<.0001	(2.22, 5.30)
	0.45/2.5 vs. PLA	3.4602	<.0001	(2.29, 4.63)	<.0001	(1.90, 5.02)
	0.45/1.5 vs. PLA	3.3695	<.0001	(2.21, 4.53)	<.0001	(1.82, 4.92)
	0.3 vs. PLA	2.3333	<.0001	(1.17, 3.50)	0.0006	(0.78, 3.89)
	0.3/1.5 vs. PLA	3.3273	<.0001	(2.17, 4.48)	<.0001	(1.79, 4.87)
F. Trochanter	0.625 vs. PLA	2.8569	0.0003	(1.31, 4.41)	0.0021	(0.79, 4.92)
	0.625/2.5 vs. PLA	2.8749	0.0003	(1.31, 4.44)	0.0021	(0.79, 4.96)
	0.45 vs. PLA	2.5860	0.0009	(1.07, 4.10)	0.0055	(0.56, 4.61)
	0.45/2.5 vs. PLA	3.6693	<.0001	(2.14, 5.20)	<.0001	(1.62, 5.71)
	0.45/1.5 vs. PLA	2.3490	0.0026	(0.82, 3.88)	0.0156	(0.31, 4.38)
	0.3 vs. PLA	2.3518	0.0026	(0.82, 3.88)	0.0159	(0.31, 4.39)
	0.3/1.5 vs. PLA	3.2980	<.0001	(1.78, 4.81)	0.0002	(1.28, 5.32)
Total Body	0.625 vs. PLA	2.1626	<.0001	(1.72, 2.61)	<.0001	(1.57, 2.76)
	0.625/2.5 vs. PLA	2.4302	<.0001	(1.98, 2.88)	<.0001	(1.83, 3.03)
	0.45 vs. PLA	2.2663	<.0001	(1.83, 2.70)	<.0001	(1.68, 2.85)
	0.45/2.5 vs. PLA	2.4803	<.0001	(2.04, 2.92)	<.0001	(1.89, 3.07)
	0.45/1.5 vs. PLA	2.0968	<.0001	(1.66, 2.54)	<.0001	(1.51, 2.68)
	0.3 vs. PLA	1.8999	<.0001	(1.46, 2.34)	<.0001	(1.31, 2.49)
	0.3/1.5 vs. PLA	2.0363	<.0001	(1.60, 2.47)	<.0001	(1.45, 2.62)

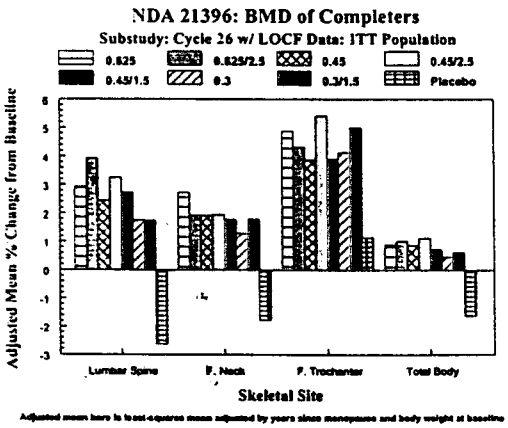
PLA = Placebo; LCL = 95% lower confidence limit; UCL = 95% upper confidence limit
Treatment difference in positive direction favors the active treatment (Prempro).

Note that with such small p-values of group comparisons, as shown in Text Table 9, for each of the 4 skeletal sites, no p-values adjustments over the sites would render them non-significant.

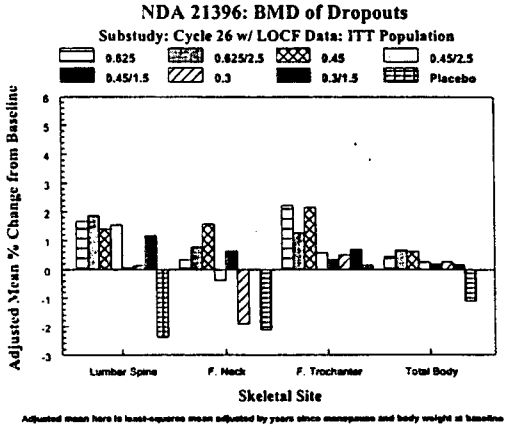
In general, the mean % changes from baseline in lumbar spine BMD at Cycle 26 with LOCF were slightly larger than those at the final visit(s) for the ITT population (see Text Table 2), but were smaller than those derived from the slope estimates (also see Text Table 2). The former finding was caused by 40 subjects (6, 6, 8, 6, 3, 3, 4, and 4 for Regimens A through H, respectively) having their final scan(s) done after Cycle 26, at which time the study medications had been stopped. The latter finding might be due to overestimation of the slopes for some early withdrawn subjects (see Subject Disposition). Similar comparisons were also seen in total body BMD, but not in femoral neck or femoral trochanter BMD.

Since the overall withdrawal rate was about 31% (= 230/749), this reviewer also did the analyses of Cycle 26 with LOCF data for the completers and dropouts separately. Basically, the response patterns of the completers (Text Figure 5) were similar to the ones based on all the ITT subjects. The CE/MPA and CE groups of the completers all showed significantly more effective than the placebo in preventing bone loss in each of the 4 skeletal sites. In the case of the dropouts with at least one dose of exposure, the 7 active treatment groups also exhibited numerically better efficacy (not necessarily statistically significant) than the placebo in preventing bone loss in each of the 4 skeletal sites (Text Figure 6).

Text Figure 5



Text Figure 6



2.4 Findings in Special/Subgroup Populations

Treatment effects on % change from baseline in BMD at Cycle 26 with LOCF were consistent across the subgroups of age, body mess index, body weight at baseline, and years since menopause, as defined below, for each of the 4 skeletal sites (all interaction $p \geq 0.10$).

No subgroup analysis for race and gender were performed since the majority of the subjects were White (almost 92%) and all the study subjects were females.

Age: <50 years, 50-54 years, and ≥55 years (defined by the sponsor)
Years since menopause: <2 years, 2-3 years, and ≥3 years (defined by the sponsor)
Body weight at baseline: <60 kg, 60-70 kg, and ≥70 kg (defined by the sponsor)
Body mess index: <20 kg/m^2, 20-30 kg/m^2, and ≥30 kg/m^2 (defined by this reviewer)

According to the statistical analysis plan, the sponsor pooled 8 centers with enrollment less than 32 subjects each into one dummy center for the purpose of statistical analysis. Regardless of 19 centers or 12 centers (due to pooling) used in the analysis, treatment effects were similar across the centers for each of the 4 skeletal sites, i.e., no significant treatment-by-center interaction ($p \geq 0.10$) was observed. However, the overall response magnitudes varied from center to center.

2.5 Statistical and Technical Issues

As discussed previously, since the analysis of dropouts revealed the same qualitative findings (despite the difference in magnitude of treatment effects) as the analysis of completers, and the number of completers per group was close to the sample size required (64) that the trial was powered on, this reviewer felt that the ~1/3 withdrawal rate should not cause any major bias in the determination of treatment efficacy. No serious statistical or technical issues were noted for this trial.

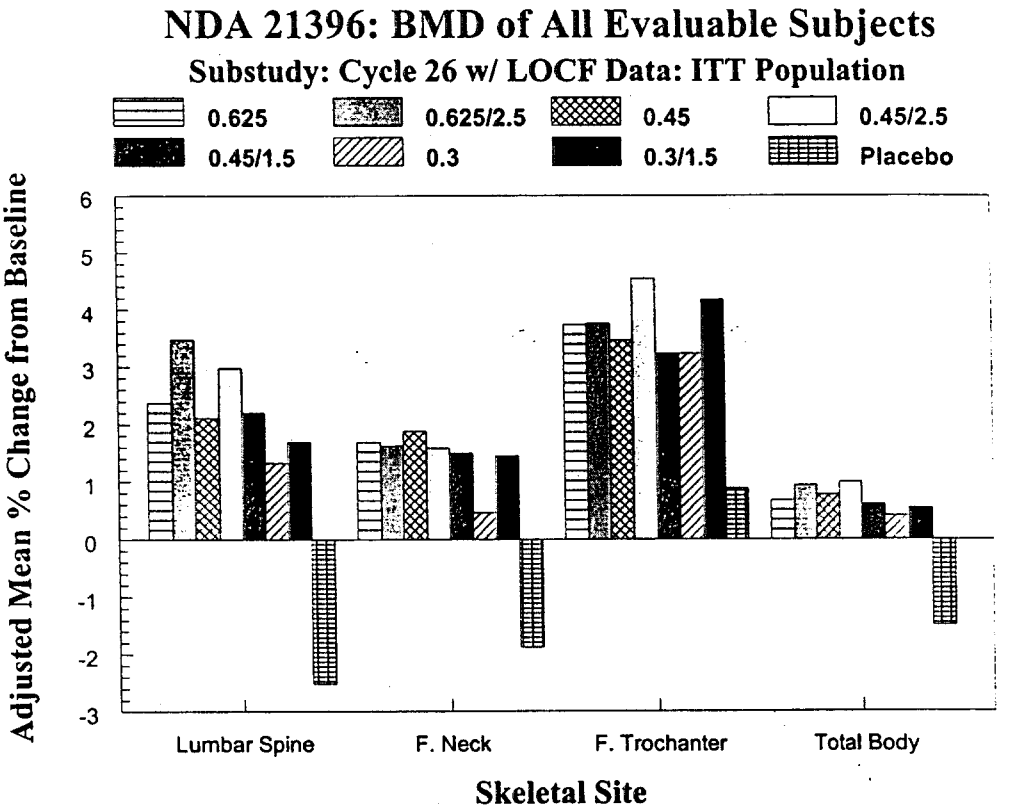
2.6 Statistical Evaluation of Collective Evidence

Across the 4 skeletal sites, the % increases in BMD in the active treatment groups were all statistically significantly greater than that of the placebo group. In fact, the placebo group exhibited a mean % decrease in lumbar spine BMD, femoral neck BMD, and total body BMD at Cycle 26 using the LOCF data (Text Figure 7).

The % increases from baseline in BMD of lumbar spine (primary skeletal site) were dose-dependent in the CE/MPA groups (1.69%, 2.20%, 2.98%, and 3.48% for 0.3/1.5, 0.45/1.5, 0.45/2.5, and 0.625/2.5 mg, respectively) and CE groups (1.33%, 2.11%, and 2.37% for 0.3, 0.45, and 0.625 mg, respectively). The smallest treatment differences, observed in the lowest CE/MPA and CE doses when compared with the placebo (-2.51%), were 4.21% and 3.84%, respectively, favoring the active treatment groups. Although the comparisons between CE/MPA and CE doses were not the major interest of the study, it is evident that the CE/MPA doses consistently showed greater % increases from baseline in lumbar spine BMD when compared with the corresponding CE doses.

No consistent findings were observed in femoral neck, femoral trochanter, and total body BMD with regard to dose response patterns in the CE/MPA or CE groups, and comparisons between the CE/MPA and CE groups, as seen in lumbar spine BMD. Also, the significant efficacy observed in femoral trochanter was generally not as strong as in the other skeletal sites, according to the 95% lower confidence limit (Text Table 9).

Text Figure 7



Adjusted mean here is least-squares mean adjusted by years since menopause and body weight at baseline

2.7 Conclusions and Recommendations

There was only 1 controlled clinical trial submitted by the sponsor for the indication. All the CE/MPA and CE doses were statistically superior to the placebo (with small p-values) in preventing postmenopausal bone loss based on the BMD measurements of lumbar spine (L2-L4), femoral neck, femoral trochanter, and total body, regardless of which type of analyses was performed. However, the strength of overall efficacy based on this reviewer's findings was generally slightly smaller than that of the sponsor's because the primary conclusions of the sponsor were based on the estimates derived from the regression (slope) analysis for the

efficacy evaluable population, while Cycle 26 with LOCF for the intention-to-treat population was the focus of this review.

In conclusion, data from the substudy demonstrate that all the CE/MPA and CE doses were efficacious in increasing bone mineral density, and consequently support the efficacy of lower doses of CE/MPA (0.45/1.5 and 0.3/1.5 mg for NDA 21-396) and CE (0.45 and 0.3 mg for NDA 21-417) claimed by the sponsor.

2.8 Notes on Labeling

In the proposed labeling for NDA 21-396 and NDA 21-417, the findings stated under the HOPE study for osteoporosis are based on the data set submitted on 2/1/02, which does not reflect any later corrections mentioned under Data Analyzed and Sources in this review report. In addition, it is not clear to this reviewer why the sponsor indicates that patients should be started at Prempro ——— mg daily for prevention of osteoporosis, even though Prempro 0.3/1.5 mg is listed as the lowest available regimen (see Dosage and Administration for NDA 21-396) and has been shown to be an efficacious dose.

Cynthia Liu, MA Date
Statistical Reviewer

Concur:

Todd Sahlroot, Ph.D. Date
Team Leader

Ed Nevius, Ph.D. Date
Director of Division of Biometrics II

CC: HFD-510/SWu, EColman, BSchneider
HFD-715/ENevius, TSahlroot, CLiu
HFD-700/CAnello

2.9 Appendix

Figure 1

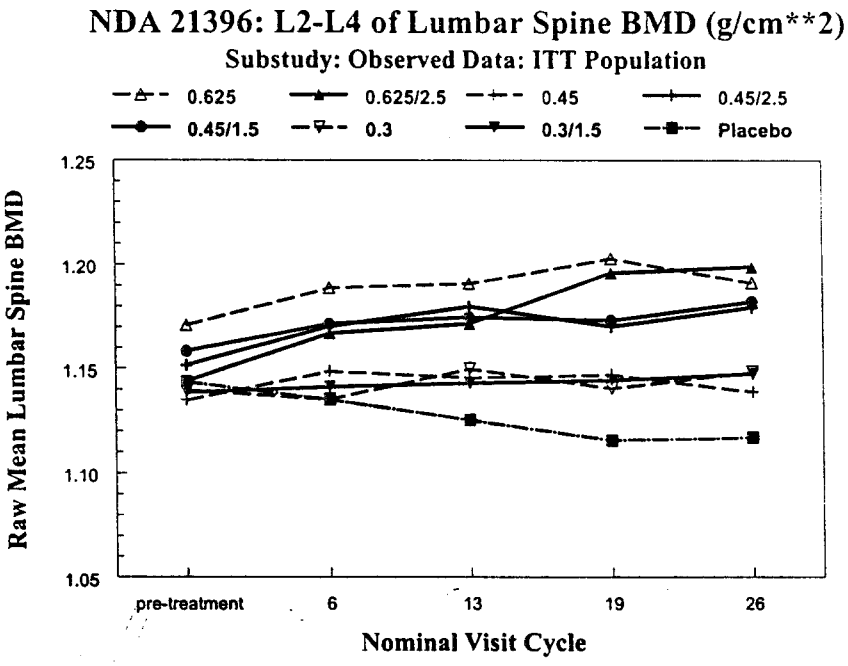


Figure 2

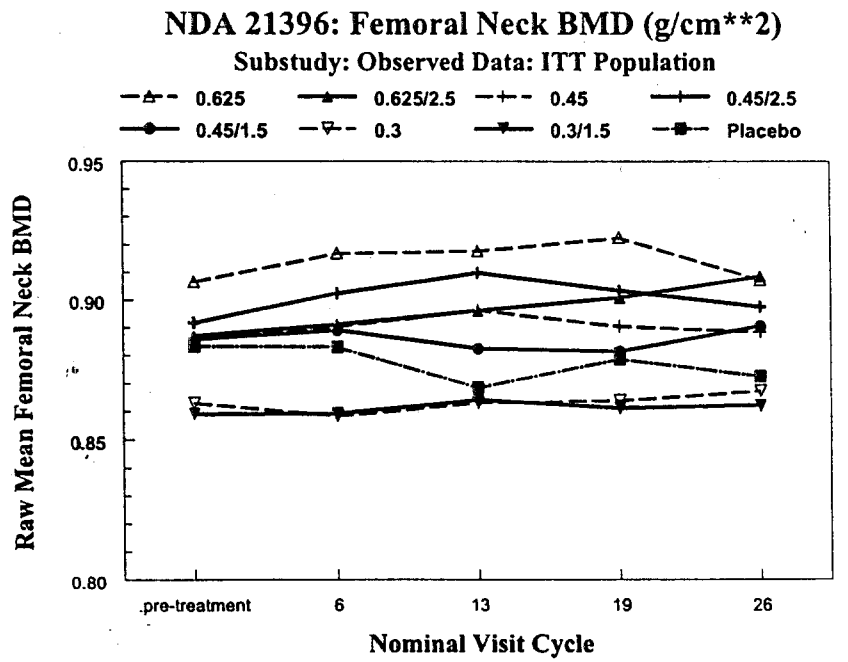


Figure 3

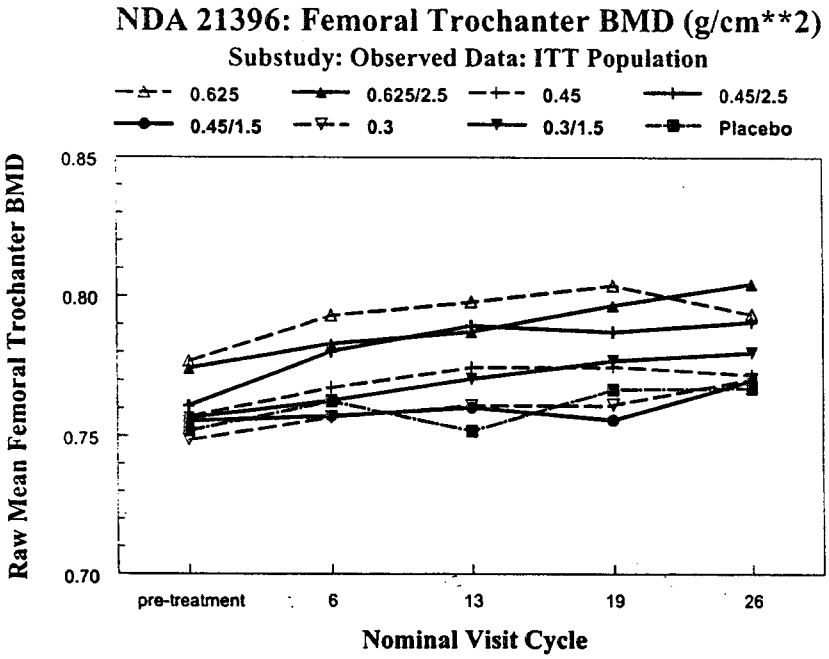
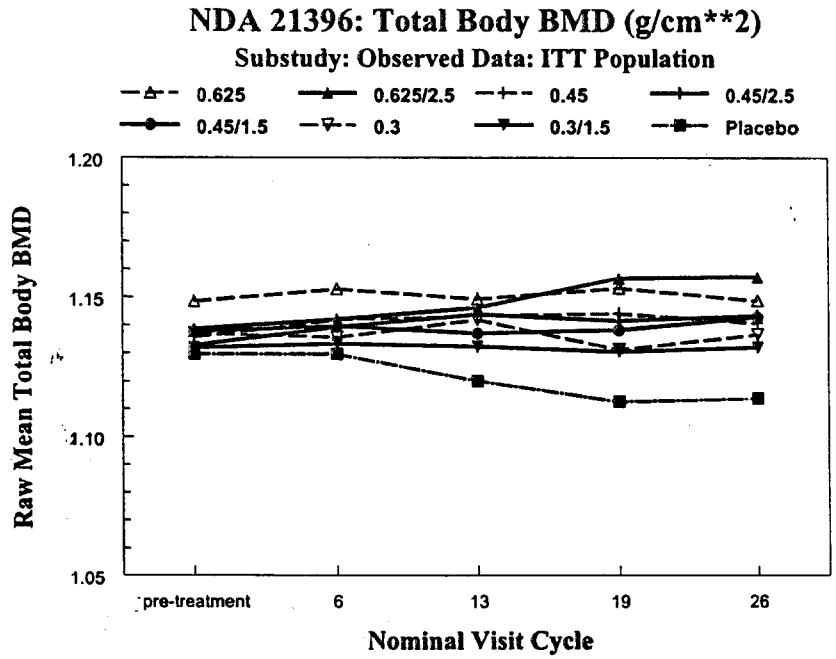


Figure 4



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Cynthia Liu
6/10/02 12:50:51 PM
BIOMETRICS

Todd Sahlroot
6/11/02 07:59:31 AM
BIOMETRICS

S. Edward Nevius
6/11/02 09:48:51 AM
BIOMETRICS
Concur with review.