CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-417

MEDICAL REVIEW

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #: N21-417	**Application Type:** NDA
Sponsor: Wyeth	**Proprietary Name:** Premarin
Pharmaceutical Category: Conjugated Estrogen	**Route of Administration:** tablets, oral
Indication: Prevention of postmenopausal osteoporosis	**Dosage:** 0.30mg, 0.45mg
Reviewer: Theresa Kehoe, MD	**Date Review Completed:** 10/9/2002

Chemistry Reviewer: N/A
Pharmacology Reviewer: N/A
Biopharmaceutics Reviewer: N/A
Statistical Reviewer: Cynthia Liu

REVIEW SUMMARY: This review concentrates on the efficacy outcomes of the two-year metabolic sub-study of the sponsor's HOPE Trial. Based on results of the two-year sub-study, the sponsor proposes labeling claims for the efficacy of doses of conjugated estrogens (CE) 0.45mg and 0.3mg in reducing bone loss in postmenopausal women while maintaining efficacy in the relief of menopausal symptoms and acceptable bleeding and metabolic profiles. The trial employed a randomized, placebo-and active-controlled, parallel group, multicenter design. Subjects in the metabolic and osteoporosis substudy (N=822 postmenopausal women, 40-65 years of age) were randomly assigned to one of seven active-treatment groups or placebo (PBO), using equal allocation. Doses of CE alone were (in mg) 0.625, 0.45, and 0.3. Doses of CE/MPA (medroxyprogesterone acetate) were 0.625/2.5, 0.45/2.5, 0.45/1.5, and 0.3/1.5. The primary efficacy outcome was change from baseline in lumbar spine BMD. Secondary outcomes included BMD changes at other skeletal sites; biomarkers of bone turnover; lipid, carbohydrate, and coagulation profiles; and multiple gynecological assessments.

Results: At the lumbar spine, the placebo group lost BMD (2.46% in two years). In contrast, all active-treatment groups had mean BMD increases, ranging from 1.24% to 3.39% ($p<0.001$ for all comparisons with PBO and for all within-group changes from baseline). Similar results were obtained for BMD changes at the femoral neck, trochanter, and total body. All doses of CE and CE/MPA caused substantial and highly statistically significant reductions in biomarkers osteocalcin and NTX. Compared to baseline, all active-treatment groups had increases in HDL-C (8.5-18.8%), and decreases in LDL-C (0.5-8.2%), whereas, in PBO, LDL-C and HDL-C increased by 7.1% a 3.8%, respectively. Triglycerides increased by 17-47% in active-treatment groups, and by 5.5% in PBO. There was no indication of adverse effects of treatment on carbohydrate metabolism or on measured parameters of clotting and fibrinolysis.

The data support the use of lower doses of CE in the prevention of postmenopausal bone loss, while maintaining an acceptable metabolic profile. A separate safety review has been previously conducted by DRUDP (HFD-580) for the 0.45mg dose NDA# 04-782, supplement 115.

OUTSTANDING ISSUES: none

RECOMMENDED REGULATORY ACTION:

N drive location:

New clinical studies _____ **Clinical Hold** _____ **Study May Proceed**

NDA, Efficacy/Label supplement: _____ **Approvable** _____ **Not Approvable**

Approve

SIGNATURES: **Medical Reviewer:** **Date:** _____

Medical Team Leader: **Date:** _____

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Executive Summary

I. Recommendations

I.A: Recommendation on Approvability: Approve

I.B: Recommendation on Phase 4 Studies and Risk Management Steps: None

II. Summary of Clinical Findings

II.A: Brief Overview of Clinical Program

This application is submitted for review, seeking labeling indications for conjugated equine estrogens, trade name Premarin, at doses of 0.45mg, and 0.3mg tablets for the prevention of postmenopausal osteoporosis. A single trial, the Women's Health and Osteoporosis, Progestin and Estrogen (HOPE) trial #0713D2-309-US was submitted for review. This is a randomized placebo and active-controlled, prospective, parallel group, multicenter trial to evaluate the safety and efficacy of lower dose conjugated equine estrogen (CE) with and without medroxyprogesterone acetate (MPA). Doses of CE alone were (in mg) 0.625, 0.45, and 0.3. Doses of CE/MPA (medroxyprogesterone acetate) were 0.625/2.5, 0.45/2.5, 0.45/1.5, and 0.3/1.5. The main study consisted of two parts: a one-year basic study and a two-year osteoporosis and metabolic sub-study that is reviewed here. A total of 2805 subjects were enrolled in the trial with subjects randomly assigned to one of eight treatment groups (seven active-treatment groups and one placebo group). A total of 822 subjects were enrolled in the year 2 osteoporosis and metabolic substudy. The primary objective of this sub-study was to determine the effects of the continuous CE and CE/MPA regimens on lumbar spine BMD over a two-year period. Secondary objectives included assessment of BMD at three other skeletal sites; changes in biochemical markers of bone turnover; and changes in lipid, carbohydrate, and coagulation profiles. Safety evaluations included standard clinical and laboratory adverse event determinations and tabulations, as well as relevant gynecological safety parameters. The latter included breast and pelvic examinations, mammography, Pap smear, and endometrial biopsy.

II.B: Efficacy

The osteoporosis and metabolic sub-study clearly demonstrated that all doses of continuous CE alone including the lowest, were effective in preventing loss of lumbar spine BMD in postmenopausal women. This was true irrespective of the statistical approach used in the analysis (annualized BMD changes based on regression analysis, modified ITT analysis, by-cycle analysis, or ITT with LOCF). At the lumbar spine (the primary efficacy endpoint), women treated with 600mg calcium alone (the placebo group) had a mean annualized BMD decrease of 1.37%. In contrast, women treated with 600mg calcium plus active treatment regimens had mean annualized lumbar spine BMD increases of 0.54% in those treated with 0.3 mg dose, 1.27% in those treated with the 0.45mg dose and 1.49% in subjects treated with the currently approved dose of 0.625mg (based on the ITT analysis).

Confirming the efficacy of all doses of CE alone, there were significant decreases from baseline in both osteocalcin and NTX at all cycles and in all active-treatment groups. Multiple metabolic parameters were evaluated. Lipid metabolism was evaluated in depth. Compared to baseline, all

active-treatment groups had increases in HDL-C (8.5-18.8%), and decreases in LDL-C (0.5-8.2%), whereas, in PBO, LDL-C and HDL-C increased by 7.1% a 3.8%, respectively. Triglyceride increased by 17-47% in active-treatment groups, and by 5.5% in PBO. There was no worsening of carbohydrate metabolism in any active treatment group. There was no evidence of clinically significant changes in coagulation factors.

II.C: Safety

A total of 725 (97%) of the 749 patients in the evaluable population reported adverse events. Differences in incidence of any adverse event among groups were not statistically significant. A complete review of gynecologic safety has been completed by DRUDP, HFD-580. Briefly, significant differences in incidence of urogenital events that were clinically notable included a significantly higher incidence of breast pain in the combination-treatment groups than in the CE-alone groups and the highest incidence of endometrial hyperplasia and vaginal hemorrhage in the 0.625 mg CE-alone group. The incidence of endometrial hyperplasia was significantly higher in group A (0.625 mg) than in all the other treatment groups. The difference between the 0.625 mg CE group (27.7%), the 0.45 mg group (14.9%) and the 0.3mg group (3.2%) in the incidence was of clinical interest.

Adverse events led to withdrawal from the study for a total of 111 of 749 (15%) patients. Serious adverse events included four (4) patients with breast carcinoma during 2 years of participation in the study, two (2) subjects with vascular thromboses, four (4) with cholelithiasis and three (3) with other malignancies. Fractures were reported for 22 patients during the study. All the fractures were reported as the result of accidents.

II.D: Dosing

The data presented supports the use of CE alone at doses of 0.625mg, 0.45mg and 0.3 mg for the prevention of postmenopausal osteoporosis. The lowest effective dose of estrogen should be used.

II.E: Special Populations

None studied. HRT is indicated for use in women who have undergone a natural or surgical menopause.

Clinical Review

I. Introduction and Background

I.A: Drug - Conjugated equine estrogens [CE (AY-011152)], trade name Premarin.

Pharmacological category: estrogen, sex steroid

Sponsor: Wyeth-Ayerst Research, PO Box 42528, Philadelphia, PA 19101

Proposed indication: Prevention of postmenopausal osteoporosis.

Dose: CE oral tablets of 0.45mg, and 0.3mg.

Age Groups: Postmenopausal women between ages 40 and 65 years.

I.B: Background

Hormone replacement therapy (HRT) with estrogen is the most efficacious treatment for climacteric symptoms associated with menopause. HRT may offer other benefits, such as prevention of loss of bone mineral. As well, other potential benefits, including cardioprotection and maintenance of normal cognitive function, have been suggested. Recent evidence from the Women's Health Initiative suggests that the use of HRT (as in the combined therapy of estrogen and progestin) may in fact be detrimental. The major risk of unopposed estrogen therapy is promotion of endometrial cancer and probable increased risk of gallbladder disease, breast cancer, and thromboembolic events. Data from the WHI clearly links HRT (with combined CE/MPA) to increased breast cancer risk and use of HRT is contraindicated in women with known or suspected cancer of the breast. Women with an intact uterus taking unopposed estrogen at the currently approved dose are at increased risk of endometrial hyperplasia and cancer. In such women, the use of combination therapy with a progestin (sequentially or continuously) is effective in reducing the incidence of endometrial hyperplasia.

Most of the clinical safety and efficacy data related to conjugated estrogens (CE), trade name Premarin, are derived from subjects treated with the currently approved 0.625 mg dose of the drug. However, there are data that suggest that use of lower doses of CE may be effective in treating menopausal symptoms and reducing bone loss. In addition, lower doses of other estrogen preparations have demonstrated efficacy in both parameters. Wyeth hypothesizes that use of doses lower than 0.625 mg, alone or in combination with medroxyprogesterone acetate (MPA), will be effective in reducing bone loss and the incidence of endometrial hyperplasia, while still relieving menopausal symptoms and maintaining acceptable vaginal bleeding and metabolic profiles.

In the present application, the sponsor has submitted data from a trial of lower doses of continuous CE and combined CE/MPA in postmenopausal women. The overall study consisted of a one-year safety and efficacy trial and a two-year metabolic and osteoporosis sub-study. The first trial enrolled 2,805 subjects. This study examined the safety and efficacy of various CE and CE/MPA regimens in reducing postmenopausal vasomotor symptoms and preventing endometrial hyperplasia (the primary endpoint). Of the 2,805 postmenopausal women who were

originally enrolled, 822 remained on treatment for a second year. During the second year, the sponsor investigated the safety and efficacy of the various continuos CE and CE/MPA regimens in preventing postmenopausal osteoporosis and maintaining an acceptable metabolic profile. The safety evaluation included an endometrial biopsy at the end of the study. This review will evaluate the osteoporosis (and other metabolic) efficacy claims for continuous CE doses of 0.45mg and 0.3mg. A detailed analysis of the CE/MPA regimens (trade name Prempro and Premphase) was conducted in the submission of NDA#21-396 and is referenced in this review. A detailed analysis of the uterine safety and overall safety profiles data included in the submission of NDA#21-396. It was reviewed by DRUDP (HFD-580) and is again referenced in this review.

I.C: State of armamentarium for indication

Numerous estrogen and estrogen-progestin combination products have been approved and are available for use by postmenopausal women. Formulations available include both oral tablets and transdermal patches. While all products have been approved for menopausal symptoms, not all products have received approval for prevention of osteoporosis. Premarin (CE 0.625 mg) is among the preparations that have been approved for the indication of prevention of postmenopausal osteoporosis. Other drugs used to prevent and treat postmenopausal osteoporosis include the bisphosphonates (alendronate and risedronate), raloxifene (a SERM), and nasal salmon calcitonin. All currently approved drugs are anti-resorptive agents.

I.D: Important milestones in product development

Premarin was approved on May 8, 1942 for the treatment of vasomotor symptoms. Initially, 1.25 mg dosage strength was approved for the relief of vasomotor symptoms. Currently, five dosage strengths of Premarin are approved: 0.3 mg, 0.625 mg, 0.9 mg, 1.25 mg and 2.5 mg. Premarin is administered orally for the:

Treatment of moderate-to-severe vasomotor symptoms (VMS) associated with the menopause.
Treatment of vulvar and vaginal atrophy (VVA).
Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only).
Prevention of postmenopausal osteoporosis (0.625 mg only).

II. Clinically Relevant Findings From Chemistry, Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews:

These are included in previous reviews. A separate statistics review has been completed for the two-year study. There are no outstanding findings from other disciplines, with the exception of the statistics review.

III. Human Pharmacokinetics and Pharmacodynamics

Reviews of human Pk-Pd of various CE and CE/MPA dose combinations have been concluded previously.

IV. Description of Clinical Data and Sources

All efficacy and safety data of subjects who participated in the two-year sub-study were submitted in this NDA#21-417 and NDA#21-396 and reviewed.

V. Clinical Review Methods

The submitted data were reviewed independently by this medical officer. The prior review of NDA#21-396 by Dr. Schneider and his numerous discussions and requests regarding the bone density results and statistical analysis, as well as discussions with staff in DRUDP (HFD-580) were also taken into account. This efficacy review will concentrate on Premarin 0.3 mg and 0.45 mg and the proposed labeling claims for the prevention of osteoporosis, as well as claims for metabolic outcomes.

VI. Review of Efficacy

VI.A: Conclusions

The osteoporosis and metabolic sub-study clearly demonstrated that all doses of continuous CE alone including the lowest, were effective in preventing loss of lumbar spine BMD in postmenopausal women. This was true irrespective of the statistical approach used in the analysis (annualized BMD changes based on regression analysis, modified ITT analysis, by-cycle analysis, or ITT with LOCF). At the lumbar spine (the primary efficacy endpoint), women treated with 600mg calcium alone (the placebo group) had a mean annualized BMD decrease of 1.37%. In contrast, women treated with 600mg calcium plus active treatment regimens had mean annualized lumbar spine BMD increases of 0.54% in those treated with 0.3 mg dose, 1.27% in those treated with the 0.45mg dose and 1.49% in subjects treated with the currently approved dose of 0.625mg (based on the ITT analysis).

Confirming the efficacy of all doses of CE alone doses, there were significant decreases from baseline in both osteocalcin and NTX at all cycles and in all active-treatment groups. Multiple metabolic parameters were evaluated. Lipid metabolism was evaluated in depth. Compared to baseline, all active-treatment groups had increases in HDL-C (8.5-18.8%), and decreases in LDL-C (0.5-8.2%), whereas, in PBO, LDL-C and HDL-C increased by 7.1% a 3.8%, respectively. Triglyceride increased by 17-47% in active-treatment groups, and by of 5.5% in PBO. There was no worsening of carbohydrate metabolism in any active treatment group. There was no evidence of clinically significant changes in coagulation factors.

VI.B: General Approach to Review of the Efficacy of the Drug

A single study, #0713D2-309-US - The Women's HOPE trial is submitted in support of the proposed labeling claims. As above, review of this trial is conducted with specific attention to the Premarin 0.3 mg and 0.45 mg doses. Parallel reviews of the HOPE trial data have been done under NDA #21-396 (DMEDP for efficacy and DRUDP (HFD 580) for safety) and NDA #04-782 for Premarin 0.45mg (DRUDP).

VI.C: Detailed Review of Trials

The following is a detailed review of trial #0713D2-309-US, with specific attention to the continuous estrogen only groups.

VI.C.1: Objectives:

The primary objective of the osteoporosis and metabolic sub-study was to determine the effects of various continuous CE and CE/MPA regimens on lumbar spine BMD over a two-year period. Secondary objectives included assessment of BMD at three other skeletal sites; changes in

biochemical markers of bone turnover; and changes in lipid, carbohydrate, and coagulation profiles.

VI.C.2: Study design:
This is a randomized placebo and active-controlled, prospective, parallel-group, multicenter trial to evaluate the safety and efficacy of lower dose conjugated equine estrogen (CE) with and without medroxyprogesterone acetate (MPA). The main study consisted of two parts: a one-year basic study and a two-year osteoporosis and metabolic sub-study. Subjects were randomly assigned to one of eight treatment groups (seven active-treatment groups and one placebo group), using equal allocation. Doses of CE alone were 0.625mg, 0.45mg and 0.3mg. Doses of CE/MPA included (in milligrams): 0.625/2.5, 0.45/2.5, 0.45/1.5, and 0.3/1.5. All patients in active-treatment and placebo groups were supplemented with 600mg elemental calcium/day. The one-year basic study enrolled 2,805 subjects, and a sub-set of 822 individuals entered the two-year sub-study.

VI.C.3: Population
This study enrolled healthy postmenopausal women with vasomotor symptoms. For subjects in the basic (initial study), every effort was made to recruit those with at least seven moderate to severe hot flushes per day.

Inclusion criteria:

- Subjects were generally healthy postmenopausal women, between 45 and 60 years of age, inclusive.
- Subjects had an intact uterus.
- The last natural menstrual period was completed at least 12 consecutive months prior to screening and not > 4 years before screening in the two-year sub-study group.
- Serum FSH $\geq$ 30 IU/L and 17β-estradiol $\leq$ 184 pmol/L during screening.
- Subjects were within 20% of "desirable weight range."
- The osteoporosis sub-study subjects must have two pre-study DEXA scans of the lumbar spine, femoral neck and trochanter, and total body, with the lumbar spine scans differing by < 5%.
- Signed informed consent. In the opinion of the investigator, subjects must have "sufficient intelligence and motivation" to continue the study through completion.

Exclusion criteria:

These are extensive and as listed by the sponsor:
1. Thrombophlebitis, thrombosis, or thromboembolic disorders related to estrogen use.
2. Myocardial infarction and ischemic heart disease.
3. Chronic renal or hepatic disease.
4. Cerebrovascular accident, stroke, or transient ischemic attack (TIA).
5. Known or suspected estrogen-dependent neoplasia.
6. Use of any estrogen-, progestin-, or androgen-containing medication within a minimum of 12 weeks before prestudy screening in substudy patients.
7. Endometrial hyperplasia.

8. Gallbladder disease (patients who had a cholecystectomy were permitted to be enrolled).
9. Neuro-ocular disorders, eg, retinal vasculitis.
10. Known hypersensitivity to estrogens and/or progestins.
11. History of malignancy, with the exception of basal cell carcinoma of the skin.
12. Use of medications known to affect vasomotor symptoms, eg, bellergal and clonidine (Catapres), within 2 weeks of prestudy screening.

The active presence of the following also prevented enrollment:
1. Elevated sitting blood pressure (> 160 mm Hg systolic or > 90 mm Hg diastolic during therapy). Patients were not to be using more than 2 antihypertensive agents.
2. Clinically important abnormal liver function test results (ie, > 1.5 times the upper limit of normal).
3. Endocrine disease except for controlled thyroid disease (see additional exclusions for the osteoporosis and metabolic substudy).
4. Any malignancy with the exception of basal cell carcinoma of the skin.
5. Thrombophlebitis, thrombosis, or thromboembolic disorders.
6. Malabsorption disorders.
7. Smoking more than 15 cigarettes a day.
8. Known substance abuse (alcohol or drug).
9. Use of an intrauterine device within the last 3 months.
10. Evidence of malignant changes on the prestudy mammogram.
11. Fasting total cholesterol (total-C) > 7.77 mmol/L (300 mg/dL) or triglyceride (TG) values > 3.39 mmol/L (300 mg/dL). For patients enrolled in the substudy, inclusion/exclusion criteria are based on the results of the first total-C and TG specimen. The results of the second pretreatment lipid specimen would not affect inclusion/exclusion criteria.
12. Fasting glucose > 6.94 mmol/L (125 mg/dL).
13. Cervical Papanicolaou smear of class III or greater, any reported dysplasia, or a Bethesda system report of squamous intraepithelial lesions or greater.

Additional exclusions for the osteoporosis and metabolic substudy included the following:
1. Clinically active rheumatoid arthritis.
2. Clinically evident large-joint osteoarthritis.
3. Treatment with calcitonin within the past 6 months or any prior use of bisphosphonates.
4. Any use of therapeutic fluoride for more than 1 year and/or any use of therapeutic fluoride within the previous year.
5. Parathyroid disease, hyperthyroidism, uncontrolled hypothyroidism, or treated hypothyroidism with abnormal TSH or renal impairment as defined by serum creatinine > 141.44 µmol/L (1.6 mg/dL).
6. Diseases that might affect bone metabolism, eg, hypercalcemia or hypocalcemia, osteogenesis imperfecta, chronic gastrointestinal disease, Paget's disease, and renal or hepatic impairment.
7. Clinically important degenerative changes in the lumbar spine that might interfere with DXA, eg, spinal fusion.
8. Significant scoliosis based on DXA.

9. Two (2) or more abnormal lumbar vertebrae in the region of the first to the fourth lumbar vertebrae (L1 to L4), inclusive, based on DXA. (If 1 of the lumbar vertebrae [L2, L3, or L4] is abnormal, L1 is measured in its place throughout the study.)
10. Lumbar spine baseline BMD measurement greater than 3 standard deviations below the mean for normal young women based on the Lunar Corporation's reference population database.

Comment: The inclusion and exclusion criteria appear appropriate for this prevention study

VI.C.4: Treatments and Procedures
Treatment medication consisted of 3 tablets, all taken simultaneously in the morning. One standard supplemental calcium (600mg) tablet, one CE tablet and one CE/MPA tablet. Subjects were randomized to one of eight treatment arms as follows:

SCHEDULED DOSAGES

	Dose (mg)	
Regimen	Conjugated Estrogens	Conjugated Estrogens Medroxyprogesterone Acetate
A	0.625	Placebo
B	Placebo	0.625/2.5
C	0.45	Placebo
D	Placebo	0.45/2.5
E	Placebo	0.45/1.5
F	0.3	Placebo
G	Placebo	0.3/1.5
H	Placebo	Placebo

a: All treatments were taken on cycle days 1 to 28.

Use of calcium was prohibited except for the 600 mg of elemental calcium provided. The established use of multiple vitamin and mineral supplements (excluding those containing > 200 mg elemental calcium per day) was allowed to continue. Vitamin D therapy could be continued for those patients who had a pretrial established use of ≤ 400 IU/day, but doses higher than 400 IU/day were prohibited during the study.

Patients were permitted to use up to 2 antihypertensive agents. Long-term use (longer than 10 days) of steroids, use of any estrogen or progestin other than study medication, and use of any androgen were prohibited. Also, use of medications known to affect vasomotor symptoms, eg, bellergal and clonidine, was prohibited.

For the osteoporosis and metabolic substudy, long-term or continued use of medication that might affect bone calcium metabolism was prohibited. Also prohibited were the use of any lipid-lowering agents or anticoagulants, the use of aspirin-containing products during the 2 weeks before blood sampling, use of diuretics, calcitonin, therapeutic fluoride, antithyroid preparations, and bisphosphonates, and daily use of nonsteroidal anti-inflammatory drugs. The regular use of laxatives and pharmacologic doses of fiber as a laxative on a regular basis was also prohibited.

All study procedures are outlined in the following table. Subjects were given diary cards to be filled out daily. Missed doses were to be recorded on the diary card. All bone density studies were performed using the [redacted], manufactured by [redacted]
The Regional Bone Center at Helen Hayes Hospital served as the Bone Quality Control Center (BQCC) for the analysis of BMD.

STUDY FLOW CHART

	Segment:	Prestudy			On-Therapy									
	Month:		-1		0	3	6	9	12	15	18	21	24	
	Visit:	1	2[a]	3	4	5	6	7	8	9	10	11	12	13
Study Procedures	Cycle:				0	3	6	9	13	16[b]	19[b]	22[b]	26[b]	
History		X												
Physical examination			X				X		X		X		X	
Vital signs			X			X	X	X	X	X	X	X	X	
Papanicolaou smear			X				X		X		X		X	
Laboratory safety screen and			X				X		X		X		X	
quality-of-life questionnaire														
FSH, 17β-estradiol			X											
Mammography			X[c]						X				X	
Endometrial biopsy			X				X[d]		X[d]		X[d]		X[d]	
Daily diary		X		X	X								X	
TSH & Lp(a) phenotype[b]			X											
Lipids and coagulation[b]			X[e]	X[e]			X		X		X		X	
Carbohydrates[b]			X				X		X		X		X	
Bone markers[b,f]			X				X		X		X		X	
Bone measurements[b]			X[g]	X[g]			X		X		X		X[h]	X[h]
Treatment daily					X								X	
Dispense medication					X	X	X	X	X	X	X	X		

a: Following a minimum 8-week washout period (12 weeks for osteoporosis and metabolic substudy group) for prior estrogen, progestin, or androgen therapy (if required).
b: For osteoporosis and metabolic substudy - a subgroup of 768 patients at designated investigational sites.
c: Previous mammogram within 6 months was acceptable.
d: Performed on cycle days 15 to 28.
e: To be performed approximately 7-14 days apart but not to exceed 3 weeks. Second coagulation specimen was analyzed only if the first specimen was unsuitable for analysis.
f: Serum osteocalcin and urinary calcium, creatinine, and N-telopeptide.
g: To be performed approximately 7 to 14 days apart but not to exceed 3 weeks. The two lumbar spine scans must have differed by less than 5%; otherwise, a third lumbar spine scan was performed before randomization.
h: To be performed approximately 14 days apart but not to exceed 3 weeks.
Abbreviations: FSH = follicle-stimulating hormone; TSH = thyroid-stimulating hormone (thyrotropin); LP = lipoprotein.

Comments: Screening and study procedures and bone mineral density quality control procedures appear appropriate. Current guidelines for calcium and Vitamin D supplementation in postmenopausal women recommend a total of 1000 – 1200mg calcium/day and 400 IU Vitamin D/day. Despite the required 600mg daily calcium, enrolled subjects with deficient diets may not have maintained sufficient calcium and Vitamin D intake to meet these recommendations. This could impact negatively on bone mineral density.

VI.C.4.1: Protocol Amendments

One protocol amendment was submitted on 12 Jan 1999. This specified that preliminary summary data by treatment group (not individual patient data) would be provided confidentially to investigators from the National Institutes of Health (NIH) and associated persons responsible for conducting the Women's Health Initiative. Information provided was data from a substudy of

subjects assigned to treatment between 23 Aug 1995 and 31 Jul 1998. This information consisted of prestudy and cycle 6 data for high-density lipoprotein cholesterol (HDL-C), HDL_2-C, low-density lipoprotein cholesterol (LDL-C), lipoprotein (LP) (a), fibrinogen activity, factor VIII activity, antithrombin III activity, and plasminogen activator inhibitor-1 (PAI-1) antigen.

VI.C.4.2: Efficacy Measurements

For study year 2, the primary efficacy variable was the prevention of bone loss based on measurements of BMD by DXA. The primary parameter was the BMD of the anteroposterior lumbar spine (L2 to L4). BMD measurements of the femoral neck and trochanter and total body were also analyzed. The primary time point of interest was cycle 26. During the study, the BMD of the anteroposterior lumbar spine (L2 to L4), femoral neck and trochanter, and total body were to be measured once during cycles 6, 13, and 19, and twice during cycle 26 (7 to 14 days apart but not more than 3 weeks apart). If a patient participated in the study for 13 or more cycles and discontinued treatment, 2 final BMD measurements were to be performed 7 to 14 days apart but not more than 3 weeks apart.

Secondary efficacy variables for the sub-study included indices of bone turnover (serum osteocalcin, urine calcium, and urine NTX/Cr), relief of vasomotor symptoms, reduction in vaginal atrophy, and incidence of endometrial hyperplasia. Other metabolic indices evaluated as part of the two-year sub-study included changes in lipid parameters, carbohydrate metabolism, and coagulation profile. Of these, labeling claims are made for lipid parameters alone.

The relief of vasomotor symptoms was evaluated by measuring the number and severity of menopausal hot flushes. The vasomotor endpoints were the average daily number of hot flushes and the average daily severity of hot flushes as recorded by patients on daily diary cards. Hot flushes were recorded and scored as:

1. Mild: fleeting warm sensation, no sweating; does not disrupt activity.
2. Moderate: warm sensation with sweating; does not disrupt activity.
3. Severe: hot sensation with sweating; disrupts activity.

Vaginal atrophy was assessed by using the VMI, which was reported as the proportion of vaginal superficial cells, relative to the numbers of parabasal and intermediate cells, in a lateral vaginal wall smear.

The incidence of endometrial hyperplasia based on endometrial biopsies was also assessed. For purposes of uniformity, all endometrial biopsies were read by 2 pathologists. For the consensus analysis, a patient was considered to have hyperplasia if both of the primary pathologists agreed on this diagnosis. If they disagreed, a third pathologist was consulted, and the final decision regarding the presence of hyperplasia was based on the diagnosis of the majority (for the primary analysis).

Comments: These methods and procedures appear appropriate.

VI.C.4.3: Safety Measurements

Safety evaluations included standard clinical and laboratory adverse event determinations and tabulations, as well as relevant gynecological safety parameters. The latter included breast and

pelvic examinations, mammography, Pap smear, and endometrial biopsy. The laboratory safety screen included hematologic and blood chemistry tests and a urinalysis.

Comments: These methods and procedures appear appropriate.

VI.C.4.4: Statistical Analysis

The BMD measurements were evaluated by first doing a linear regression on the values over time for each patient. An estimate of the annual change as a percentage of baseline was then calculated based on the slope of the regression line. This was done by multiplying the slope (representing change per day) by 365 and then dividing by the baseline value. The baseline BMD value was defined as the average of the prestudy readings (if more than 2, the baseline was the average of the 2 within 5% of 1 another and closest to the mean of all baseline scans). The percent annual changes were analyzed by analysis of covariance (ANCOVA) with time since menopause and weight being included as covariates. The analysis of the slopes was the principal analysis of the BMD data. However, an analysis was also done based on percentage change from baseline at the final evaluation for each patient eligible for analysis. For patients who had 2 DXA determinations at the termination visit(s), the average of these 2 was considered the final evaluation. The ANCOVA model described above was used again. In the analysis of osteoporosis, if the comparison of the combination versus placebo was significant at the 0.05 level, then CE alone was subsequently compared with placebo.

The primary analyses were based on evaluable patients. An evaluable patient in the substudy was one who had at least 1 prestudy BMD measurement and at least 2 measurements during the study with no more than 1 of these being the termination visit(s). Also, a patient must have taken at least 80% of study medication during the interval between the previous BMD evaluation and the current BMD evaluation. As soon as one interval failed to meet these criteria, then the BMD value collected at the end of that interval and all subsequent intervals was excluded. Patients could also be excluded due to chronic use of nonstudy medication that could affect bone calcium metabolism. Supplementary analyses including all patients who had at least 1 post-baseline visit (ie, ITT analyses) were also done. In the BMD analysis, slope estimates for patients who dropped out were based on the observations that were available.

Biochemical indices of bone metabolism were analyzed by 1-way ANCOVA with baseline values serving as the covariate. Within-group changes from baseline were analyzed by paired t-tests. The coagulation and carbohydrate data were evaluated by using an analysis of variance (ANOVA) based on changes from baseline. The lipid data were evaluated by using ANOVA based on percentage changes from baseline, except for the LP (a) phenotype, which was summarized at screening only.

The LSD procedure was used for pairwise comparisons, as defined for the analysis of vasomotor symptoms. All tests were 2-sided at the 0.05 level. No adjustment to the alpha level due to multiple comparisons was necessary because of the sequential manner of testing that was performed for a limited number of pairwise comparisons. At each of the 3 dose levels of CE, the CE and CE/MPA dose combinations were compared with placebo. These comparisons were performed in descending order beginning with the highest dose of CE (0.625 mg) or CE/MPA (0.625 mg/2.5 mg) and proceeding to the next lower dose only if statistical significance at the

0.05 level was found. The population of interest was the ITT population, defined as all patients randomly assigned to the osteoporosis and metabolic substudy who recorded taking study medication and who had values at baseline and during therapy.

Sample size for the substudy was based on osteoporosis considerations. The BMD of the lumbar spine was the primary endpoint. Based on data from previous studies, it was estimated that the change from baseline in the BMD of the lumbar spine would be a decrease of 3% for the placebo group and the standard deviation would be 4%. To have 80% power to declare a 75% reduction in the percentage decrease from baseline to be statistically significant at the 0.05 level, approximately 50 patients per group would be required.

The substudy was also designed to have adequate power to show a significant difference between groups in the change in BMD of the femoral neck. It was estimated that the percentage change in the placebo group would be decrease of 2% and the standard deviation would be 3%. Having 80% power to declare a reduction of 75% to be statistically significant at the 0.05 level required 64 patients per group. To adjust for the fact that up to one-third of the patients might not have the minimum of 3 data points required for inclusion in the primary analysis, approximately 768 (96 per group) were enrolled to allow for a minimum of 64 subjects in each treatment group to be evaluable for bone loss.

Comments: Please see the Biometrics review. Please see Dr. Schneider's review of NDA#21-396. As described in Dr. Schneider's review, Wyeth submitted analyses based on the efficacy evaluable population, which are not acceptable as the sole support for the labeling claims in the prevention of osteoporosis. The ITT data were submitted and evaluated by Biometrics.

VI.C.5 Efficacy outcomes

VI.C.5.1: Patient Disposition

A total of 822 patients were randomly assigned to 8 study groups in the substudy; 749 of these were evaluable patients who received at least 1 dose of study drug (281 received CE, 374 received CE/MPA, and 94 received placebo).

749 Patients Received Medication or Placebo (519 completed, 230 withdrew)															
n =97 Group A CE 0.625		n = 86 Group B CE 0.625 / MPA 2.5		n = 95 Group C CE 0.45		n = 96 Group D CE 0.45 / MPA 2.5		n = 94 Group E CE 0.45 / MPA 1.5		n = 89 Group F CE 0.3		n = 98 Group G CE 0.3 / MPA 1.5		n = 94 Group H Placebo	
n = 45 Completed		n = 65 Completed		n = 65 Completed		n = 65 Completed		n = 65 Completed		n = 65 Completed		n = 65 Completed		n = 65 Completed	
n = 52 (53.6) Withdrew		n = 21 (24.4) Withdrew		n = 32 (33.7) Withdrew		n = 25 (26.0) Withdrew		n = 23 (24.5) Withdrew		n = 24 (27.0) Withdrew		n = 21 (21.4) Withdrew		n = 32 (34.0) Withdrew	
AE	30	AE	11	AE	11	AE	9	AE	10	AE	7	AE	4	AE	4
FR	9	FR	2	FR	1	FR	3	FR	2	FR	5	FR	6	FR	6
oME	5	oME	0	oME	2	oME	2	oME	3	oME	2	oME	3	oME	3
nME	1	nME	4	nME	7	nME	1	nME	2	nME	3	nME	1	nME	1
PR	4	PR	4	PR	4	PR	4	PR	6	PR	5	PR	2	PR	3
PV	2	PV	0	PV	1	PV	4	PV	0	PV	1	PV	3	PV	2
UE	1	UE	0	UE	6	UE	2	UE	0	UE	1	UE	2	UE	13

Abbreviations: AE - Adverse Event; FR - failed to return; oME - other medical event; nME -other nonmedical event; PR - patient request, PV - protocol violation; UE - unsatisfactory efficacy - endometrial hyperplasia, increased vasomotor symptoms or BMD loss of >7.5%.

VI.C.5.1.1: Demographics

Baseline demographics were comparable across all treatment groups. The mean age at entry was 51.5 years, ranging from 40 to 65. All the subjects were female who started menopause naturally at ages between 38 and 62, with a mean age 49.2 years old. The average number of years since menopause was about 2.3 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.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR WOMEN IN THE SUBSTUDY

	Group A	Group B	Group C	Group D	Group E	Group F	Group G	Group H		
	0.625	0.625/2.5	0.45	0.45/2.5	0.45/1.5	0.3	0.3/1.5	Placebo	Total	
Characteristic	(n = 97)	(n = 86)	(n = 95)	(n = 96)	(n = 94)	(n = 89)	(n = 98)	(n = 94)	(n = 749)	p-Value
Age, years										
Mean	51.9	51.5	52	51.5	51.1	52.3	51.3	51.3	51.6	0.383[a]
Standard deviation	3.3	4.1	3.7	3.8	3.5	3.9	3.5	4.1	3.7	
Ethnic origin, n (%)										
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)	0.791[b]
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)	
Height, cm										
Mean	164.5	164.2	164.3	164.1	165.3	162.7	163.6	163.5	164.0	0.148[a]
Standard deviation	5.2	6.2	6.5	6.4	6.1	5.9	6.1	5.6	6.0	
Weight, kg										
Mean	67.1	65.7	65.7	65.4	67.7	64.7	65.3	64.9	65.8	0.223[a]
Standard deviation	8.9	8.9	8.5	8.9	9.4	8.0	8.5	8.9	8.8	
Body mass index, kg/m^2										
Mean	24.8	24.3	24.3	24.3	24.7	24.4	24.4	24.3	24.4	0.825[a]
Standard deviation	2.8	2.8	2.6	2.7	2.9	2.7	2.8	3.0	2.8	
Age at menopause, years										
Mean	49.6	49.2	49.4	49.0	48.8	49.9	49.0	48.9	49.2	0.353[a]
Standard deviation	3.1	4.2	3.4	3.7	3.3	3.6	3.4	3.8	3.6	
Years since menopause										
Mean	2.2	2.2	2.5	2.5	2.3	2.3	2.3	2.4	2.3	0.349[a]
Standard deviation	0.9	0.9	1.0	0.9	0.9	1.0	1.0	0.9	0.9	
Parity										
Mean	2.8	2.6	2.8	2.8	2.8	2.8	3.0	2.6	2.8	0.874[a]
Standard deviation	1.8	1.6	1.7	1.8	2.1	1.8	1.7	1.6	1.8	

a: Analysis of variance with treatment as factor.
b: Pearson chi-square test.
Treatment groups identified by dose (mg) of CE or CE/MPA.
Data from CDR 1-6.

Comments: There were no statistically significant differences in baseline demographic parameters between all active treatment and placebo subsets.

VI.C.5.1.2: Withdrawals

Please refer to the disposition table on the previous page. Patients could be withdrawn because of adverse events, failure to comply with the protocol, or at their own request. If a patient dropped out prematurely, but after more than three cycles since the last laboratory and physical examination, the investigator was to try to perform a physical examination, laboratory safety screen, Pap smear, and endometrial biopsy. A mammogram was performed if the patient had participated for more than six cycles. Data from 51 patients were not included in any efficacy or safety analysis. All data from one of the sub-study sites (site 30952) were excluded for non-compliance with Good Clinical Practice (leading to early termination of the trial at this site).

A total of 230 (31%) of 749 patients withdrew from the study for any reason. A total of 86 (11%) of 749 patients withdrew for adverse events. Examination of the individual adverse events leading to discontinuation disclosed that most of these were referable to the GU system. Overall, significant ($p < 0.001$) differences among groups were seen only in the number who withdrew for any reason, because of adverse events, and because of an unsatisfactory efficacy response. The discontinuation category "unsatisfactory response - efficacy" refers to patients who withdrew because of endometrial hyperplasia, increased vasomotor symptoms, or annualized loss > 7.5% in lumbar spine BMD.

Group A (CE alone, 0.625 mg) had the highest percentage (54%) of patients who discontinued for any reason. This group also had the highest percentage of patients who withdrew because of adverse events (31%, 30/97). The data show that the majority were urogenital such as endometrial hyperplasia, vaginal bleeding, and other uterine AEs. These were almost completely absent in the 0.625/2.5 mg CE/MPA group. In addition, there was an increase in endometrial hyperplasia in the 0.45 mg CE group that was abolished in the combined 0.45/2.5 mg group. There was no apparent increase in breast cancer in any group (1 case each in the CE 0.625 mg alone and placebo). As expected, the highest number of patients who withdrew from the study for lack of efficacy was in the placebo group (14%).

VI.C.5.1.3: Protocol violations

Protocol violations are divided into violations that led to withdrawal (either as primary or secondary reason for withdrawal) and those that did not.

Eighteen (2.4%) patients had protocol violations either as primary or secondary reasons for withdrawal. These were roughly evenly distributed across treatment groups.

Patients who remained in the study despite protocol violations:

Decrease in BMD: Three patients, all in the placebo group, had an annualized BMD decrease > 7.5% from baseline at cycles 13 or 19. All were diagnosed at cycle 13. One withdrew by cycle 17, one by cycle 15, and the other remained in the study until completion.

Postmenopausal status: 6 patients had pre-study screening visits < 12 months after their LMP. The shortest duration was about 10 months. There were also 29 patients who were >4 years postmenopausal (range 2-5.37 years).

Laboratory values: Twenty-four (3.2%)) of the 749 patients had out-of-range estradiol or FSH levels at initial screening, but these were within range following re-testing (184 pmol/L [50 pg/mL] for estradiol and =30 IU/L for FSH). Two patients had fasting glucose levels > 6.94 mmol/L (125 mg/dL). Two other patients had diabetes mellitus at study entry. Ten patients with initial cholesterol levels >7.77 mmol/L (>300 mg/dL), and 14 with TG levels >3.39 mmol/L (300 mg/dL) had normal values on repeat testing, with the exception of three individuals with elevated cholesterol levels (listed in application). Five (5) patients had liver function test values more than 1.5 times the upper limit of normal. One (1) of these patients had normal values on repeat testing. Forty-two patients had initial TSH levels that were out of range; repeat testing showed

normal TSH levels (0.5 to 5.0 mIU/L) in 24 of these. The remaining 18 patients were randomly assigned to a treatment group. These are listed in the NDA.

Vital signs and weight: Four patients had elevated blood pressure at screening and 21 had a BMI > 28 kg/m^2. These patients were equally distributed among the eight treatment groups, and all treatment groups had at least one such individual.

Concomitant medication not permitted by protocol: Prohibited medications that were received by some patients in the study included steroids (chronic), androgens, estrogens or progestins other than study medication, medications known to affect vasomotor symptoms, lipid-lowering agents, and diuretics. All patients who received such concomitant therapy during the treatment period are listed in the NDA (Table 8.1.2.3A). A review of this table showed that five patients received androgens and 16 received steroids (> 10 days). These were roughly evenly distributed among treatment groups. Seven patients received progestin, six of these in the CE 0.625 mg group. Seventeen patients received cholesterol or triglyceride-lowering medication, nearly all in Groups C and G (CE 0.45mg, and CE 0.3 mg/MPA 1.5 mg, respectively). A list of the patients who received diuretics, by treatment group, appears in this table as well. There were 37 such patients, roughly evenly divided across the groups.

Comments: The protocol violations are somewhat evenly distributed among treatment groups and should not have a significant influence on the primary efficacy outcomes of the study.

VI.C.5.2: BMD results

Wyeth's analyses of the BMD data showed that each of the seven active treatments (the three CE-alone doses and the four CE/MPA doses) were significantly more effective than placebo in prevention of bone loss at the lumbar spine (the primary skeletal site), as well as at the three other sites (femoral neck, trochanter, and total body).

At the lumbar spine, all seven active treatment groups had a net annualized gain in bone mineral density, with adjusted mean increases ranging from 0.54% in group F (0.3 mg CE alone) to 1.81% in Group B (0.625/2.5 mg). In contrast, the placebo group experienced a mean decrease in lumbar spine BMD (-1.37%). All comparisons with placebo were statistically significant ($p<0.001$ for all comparisons except Group F where $p<0.003$). See table on next page for full results.

		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 the Biometric 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.

Graphical results of BMD changes are shown below:

FIGURE 9.4.1.1B CE ALONE FOR L2 TO L4 (GROUPS A, C, F, AND PLACEBO): MEAN % CHANGE FROM BASELINE IN BMD IN EFFICACY-EVALUABLE POPULATION

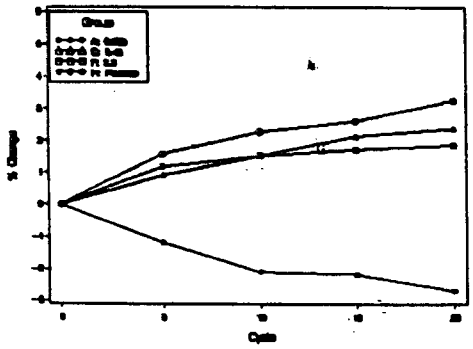


FIGURE 9.4.1.1D CE ALONE FOR FEMORAL NECK: MEAN % CHANGE FROM BASELINE IN BMD IN EFFICACY-EVALUABLE POPULATION

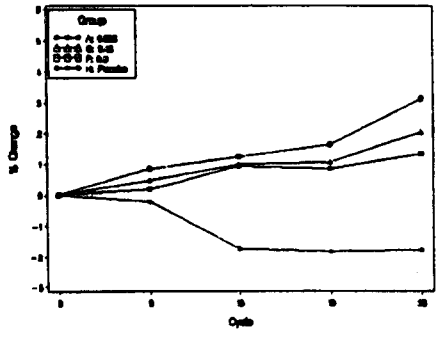


FIGURE 9.4.1.1F. CE ALONE FOR FEMORAL TROCHANTER:
MEAN % CHANGE FROM BASELINE IN BMD IN EFFICACY-EVALUABLE POPULATION

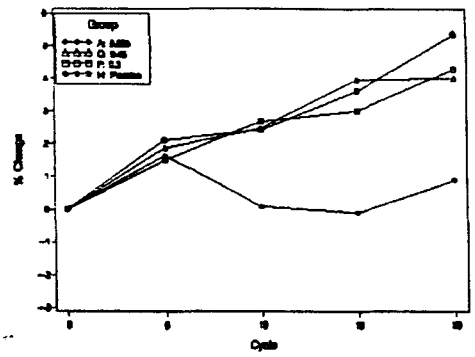
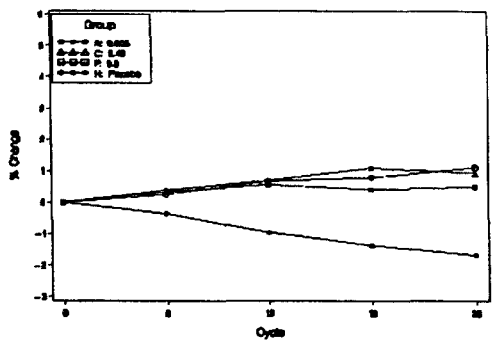


FIGURE 9.4.1.1H. CE ALONE FOR TOTAL BODY:
MEAN % CHANGE FROM BASELINE IN BMD IN EFFICACY-EVALUABLE POPULATION



Comment: All analyses of the BMD data showed each of the 3 CE-alone doses to be significantly more effective than placebo in the prevention of bone loss. This was true for all four BMD measures and for both types of analysis (slopes and by cycle). The study was not powered to show significant differences between the active-treatment groups. The data supports the labeling indications proposed by Wyeth.

Subgroup Analyses

Age differences across treatment groups for all 4 BMD endpoints were stratified into 3 cohorts: 40 to < 50, 50 to < 55, and 55 to 65 years. Both the L2 to L4 and total body BMD were significantly greater for all active-treatment groups, in all age categories, compared with placebo. Changes in femoral neck BMD did not reach statistical significance in the youngest cohort (40-50 years) with the CE 0.3mg dose. Changes in femoral trochanter BMD did not reach statistical significance in the youngest cohort with either the 0.45 or the 0.3mg CE dose. Results of the analysis are adapted from Table 9.4.1.2.2A.

BONE MINERAL DENSITY ANNUALIZED PERCENT CHANGE FROM BASELINE WITHIN AND BETWEEN GROUPS EFFICACY-EVALUABLE POPULATION, BY AGE

Region Evaluated	Treatment Group[a]	Age Group[b]	No. of Pairs	Baseline Mean	Baseline SD	% Change from Baseline Adjusted Mean[c]	% Change from Baseline SE	p-Values Within Group	p-Values vs Placebo
L2 to L4	Group A 0.625	40 to < 50	12	1.17	0.12	0.98	0.66	0.18	<0.001
		50 to < 55	41	1.15	0.15	1.76	0.28	<0.001	<0.001
		55 to 65	13	1.16	0.15	1.78	0.54	<0.001	<0.001
	Group C 0.45	40 to < 50	14	1.12	0.15	0.50	0.60	0.25	<0.001
		50 to < 55	48	1.13	0.16	1.40	0.26	<0.001	<0.001
		55 to 65	15	1.17	0.17	1.66	0.50	0.003	<0.001
	Group F 0.3	40 to < 50	19	1.11	0.13	-0.25	0.52	0.48	0.004
		50 to < 55	33	1.15	0.18	0.53	0.32	0.027	<0.001
		55 to 65	24	1.15	0.12	1.86	0.40	<0.001	<0.001
	Group H Placebo	40 to < 50	23	1.19	0.16	-2.30	0.48	<0.001	
		50 to < 55	40	1.15	0.15	-1.22	0.29	<0.001	
		55 to 65	15	1.09	0.11	-0.97	0.50	0.011	
Femoral neck	Group A 0.625	40 to < 50	12	0.94	0.12	0.51	0.86	0.93	0.057
		50 to < 55	41	0.89	0.15	0.89	0.34	0.003	<0.001
		55 to 65	13	0.88	0.13	2.66	0.66	<0.001	<0.001

Region Evaluated	Treatment Group[a]	Age Group[b]	No. of Pairs	Baseline Mean	Baseline SD	% Change from Baseline Adjusted Mean[c]	% Change from Baseline SE	p-Values Within Group	p-Values vs Placebo
Femoral neck	Group C 0.45	40 to < 50	14	0.88	0.12	0.79	0.79	0.13	0.020
		50 to < 55	48	0.88	0.13	1.08	0.32	<0.001	<0.001
		55 to 65	15	0.94	0.13	1.79	0.61	0.029	0.007
	Group F 0.3	40 to < 50	19	0.85	0.11	-0.68	0.67	0.29	0.35
		50 to < 55	33	0.88	0.11	0.18	0.38	0.27	0.002
		55 to 65	24	0.85	0.13	1.39	0.49	0.040	0.014
	Group H Placebo	40 to < 50	23	0.89	0.14	-1.53	0.63	0.019	
		50 to < 55	40	0.90	0.14	-1.36	0.35	<0.001	
		55 to 65	15	0.83	0.13	-0.44	0.61	0.10	
Femoral trochanter	Group A 0.625	40 to < 50	12	0.80	0.12	3.19	0.92	0.006	0.069
		50 to < 55	41	0.76	0.13	2.21	0.44	<0.001	<0.001
		55 to 65	13	0.77	0.14	2.07	0.77	0.029	0.11
	Group C 0.45	40 to < 50	14	0.76	0.11	-0.05	0.85	0.53	0.29
		50 to < 55	48	0.75	0.12	2.32	0.41	<0.001	<0.001
		55 to 65	15	0.81	0.12	2.91	0.71	0.001	0.010
	Group F 0.3	40 to < 50	19	0.74	0.12	0.89	0.73	0.44	0.85
		50 to < 55	33	0.75	0.09	1.61	0.50	<0.001	0.017
		55 to 65	24	0.74	0.12	2.70	0.58	<0.001	0.009
	Group H Placebo	40 to < 50	23	0.77	0.14	1.08	0.68	0.15	
		50 to < 55	40	0.76	0.13	0.04	0.45	0.83	
		55 to 65	15	0.71	0.12	0.43	0.72	0.75	
Total body	Group A 0.625	40 to < 50	12	1.16	0.06	0.15	0.26	0.55	<0.001
		50 to < 55	41	1.13	0.08	0.40	0.14	<0.001	<0.001
		55 to 65	13	1.13	0.10	0.61	0.28	0.006	<0.001
	Group C 0.45	40 to < 50	14	1.15	0.07	0.21	0.24	0.24	<0.001
		50 to < 55	48	1.13	0.08	0.46	0.13	<0.001	<0.001
		55 to 65	15	1.15	0.07	0.82	0.26	0.001	<0.001
	Group F 0.3	40 to < 50	19	1.13	0.07	0.33	0.20	0.19	<0.001
		50 to < 55	33	1.15	0.08	0.11	0.15	0.096	<0.001
		55 to 65	24	1.12	0.08	0.41	0.21	0.022	<0.001
	Group H Placebo	40 to < 50	23	1.15	0.09	-1.10	0.19	<0.001	
		50 to < 55	40	1.14	0.07	-0.62	0.14	<0.001	
		55 to 65	15	1.08	0.07	-1.13	0.26	<0.001	

a: Identified by dose (mg) of CE or CE/MPA.
b: In years.
c: Adjusted annualized mean change from baseline from analysis of variance, with treatment and site as factors.
Data from statistical report BMD.1c.

Years since menopause (YSM) was categorized into 3 groups: 0 to < 2 years, 2 to < 3 years, and =3 years. Within each YSM subgroup, each treatment group showed statistically significant differences from placebo for L2 to L4 and total body BMD. Significant differences from the placebo group with regard to femoral neck was found for all YSM subgroups within each treatment group with the exception of Group F (0.3 mg CE) in the youngest cohort (40-50 years). Statistical significance for results at the femoral trochanter were more sporadic, with no significant differences noted in various cohorts of all three CE doses. Results of the analysis are adapted from Table 9.4.1.2.3A.

BONE MINERAL DENSITY ANNUALIZED PERCENT CHANGE FROM BASELINE WITHIN AND BETWEEN GROUPS EFFICACY-EVALUABLE POPULATION, BY YEARS SINCE MENOPAUSE

								p-Values	
		Years Since	No. of	Baseline		% Change from Baseline		Within	Versus
Region Evaluated	Treatment Group[a]	Menopause	Pairs	Mean	SD	Adjusted Mean[b]	SE	Group	Placebo
L2 to L4	Group A 0.625	0 to < 2 years	31	1.17	0.17	1.46	0.36	<0.001	<0.001
		2 to < 3 years	21	1.17	0.11	2.07	0.47	<0.001	<0.001
		≥ 3 years	14	1.11	0.14	1.77	0.46	<0.001	<0.001
	Group C 0.45	0 to < 2 years	26	1.17	0.17	0.77	0.39	0.12	<0.001
		2 to < 3 years	29	1.11	0.15	1.20	0.41	0.002	<0.001
		≥ 3 years	22	1.13	0.15	2.19	0.37	<0.001	<0.001
	Group F 0.3	0 to < 2 years	34	1.11	0.16	0.38	0.35	0.39	0.002
		2 to < 3 years	18	1.14	0.13	0.68	0.52	0.20	<0.001
		≥ 3 years	24	1.19	0.15	1.46	0.33	<0.001	<0.001
	Group H Placebo	0 to < 2 years	35	1.15	0.11	-1.07	0.35	<0.001	
		2 to < 3 years	19	1.13	0.16	-2.31	0.50	<0.001	
		≥ 3 years	24	1.16	0.17	-1.24	0.34	<0.001	
Femoral neck	Group A 0.625	0 to < 2 years	31	0.93	0.15	1.05	0.45	0.047	<0.001
		2 to < 3 years	21	0.87	0.13	1.17	0.57	0.021	<0.001
		≥ 3 years	14	0.84	0.13	1.63	0.58	0.016	<0.001
	Group C 0.45	0 to < 2 years	26	0.91	0.13	0.50	0.49	0.62	0.008
		2 to < 3 years	29	0.87	0.15	2.02	0.50	<0.001	<0.001
		≥ 3 years	22	0.90	0.11	1.19	0.47	0.010	<0.001
	Group F 0.3	0 to < 2 years	35	0.85	0.10	-0.25	0.43	0.44	0.11
		2 to < 3 years	17	0.87	0.12	0.86	0.64	0.12	0.006
		≥ 3 years	24	0.86	0.13	0.73	0.43	0.073	0.001
	Group H Placebo	0 to < 2 years	35	0.89	0.14	-1.17	0.43	0.003	
		2 to < 3 years	19	0.88	0.16	-1.60	0.60	0.012	
		≥ 3 years	24	0.88	0.13	-1.24	0.44	0.013	
Femoral trochanter	Group A 0.625	0 to < 2 years	31	0.79	0.14	2.80	0.51	<0.001	0.009
		2 to < 3 years	21	0.76	0.12	2.49	0.70	<0.001	0.017
		≥ 3 years	14	0.73	0.13	0.94	0.74	0.24	0.17
	Group C 0.45	0 to < 2 years	26	0.77	0.13	1.79	0.56	0.016	0.28
		2 to < 3 years	29	0.75	0.12	1.57	0.61	0.001	0.12
		≥ 3 years	22	0.77	0.11	3.07	0.60	<0.001	<0.001
	Group F 0.3	0 to < 2 years	35	0.75	0.10	1.56	0.50	0.009	0.40
		2 to < 3 years	17	0.73	0.12	1.00	0.78	0.093	0.39
		≥ 3 years	24	0.75	0.11	2.39	0.55	<0.001	<0.001
	Group H Placebo	0 to < 2 years	35	0.74	0.13	1.00	0.50	0.080	
		2 to < 3 years	19	0.76	0.14	0.08	0.73	0.80	
		≥ 3 years	24	0.77	0.12	-0.30	0.55	0.79	
Total body	Group A 0.625	0 to < 2 years	31	1.16	0.09	0.28	0.18	0.073	<0.001
		2 to < 3 years	21	1.14	0.05	0.59	0.18	<0.001	<0.001
		≥ 3 years	14	1.09	0.10	0.58	0.23	0.009	<0.001
	Group C 0.45	0 to < 2 years	26	1.16	0.08	0.35	0.19	0.095	<0.001
		2 to < 3 years	29	1.14	0.08	0.46	0.16	0.001	<0.001
		≥ 3 years	22	1.12	0.07	0.82	0.18	<0.001	<0.001
	Group F 0.3	0 to < 2 years	34	1.13	0.08	0.14	0.17	0.33	<0.001
		2 to < 3 years	18	1.13	0.07	0.37	0.20	0.038	<0.001
		≥ 3 years	24	1.15	0.08	0.44	0.17	0.008	<0.001
	Group H Placebo	0 to < 2 years	35	1.13	0.07	-0.78	0.17	<0.001	
		2 to < 3 years	19	1.13	0.09	-1.15	0.19	<0.001	
		≥ 3 years	24	1.13	0.10	-0.71	0.17	<0.001	

a: Identified by dose (mg) of CE or CE/MPA
b: Adjusted annualized mean change from baseline from analysis of variance with treatment and site as factors.
Data from statistical report BMD.1a.

Body Weight: The 8 treatment groups were divided into 3 subgroups by body weight at baseline: 40 to < 60 kg, 60 to < 70 kg and ≥ 70 kg. Subgroup comparisons between the active-treatment groups and the placebo group were done for all 4 BMD endpoints. L2 to L4 was significantly higher than in the placebo group for all body weight categories and all active-treatment groups. Total body BMD was significantly higher than in the placebo group for all body weight categories and CE groups. BMD data by body weight for all treatment groups are adapted from Table 9.4.1.2.4A.

BONE MINERAL DENSITY ANNUALIZED PERCENT CHANGE FROM BASELINE WITHIN AND BETWEEN GROUPS EFFICACY EVALUABLE POPULATION, BY BODY WEIGHT

				Baseline		% Change from Baseline		p-Values	
Region Evaluated	Treatment Group[a]	Body Weight (kg)	No. of Pairs	Mean	SD	Adjusted Mean[b]	SE	Within Group	Versus Placebo
L2 to L4	Group A 0.625	40 to < 60	14	1.13	0.11	1.17	0.53	0.009	<0.001
		60 to < 70	24	1.15	0.18	1.34	0.38	<0.001	<0.001
		≥ 70	28	1.18	0.14	2.13	0.42	<0.001	<0.001
	Group C 0.45	40 to < 60	19	1.12	0.17	2.38	0.45	<0.001	<0.001
		60 to < 70	35	1.13	0.15	1.16	0.33	0.001	<0.001
		≥ 70	23	1.15	0.17	0.81	0.45	0.052	<0.001
	Group F 0.3	40 to < 60	24	1.10	0.11	0.39	0.43	0.16	<0.001
		60 to < 70	35	1.17	0.18	0.65	0.32	0.11	<0.001
		≥ 70	17	1.13	0.14	1.49	0.52	0.004	<0.001
	Group H Placebo	40 to < 60	29	1.11	0.14	-1.60	0.37	<0.001	
		60 to < 70	27	1.14	0.14	-1.48	0.36	<0.001	
		≥ 70	22	1.21	0.15	-1.45	0.46	<0.001	
Femoral neck	Group A 0.625	40 to < 60	14	0.81	0.11	1.35	0.72	0.089	<0.001
		60 to < 70	24	0.90	0.16	0.61	0.49	0.19	0.002
		≥ 70	28	0.94	0.13	1.56	0.46	<0.001	0.001
	Group C 0.45	40 to < 60	19	0.85	0.15	1.89	0.62	0.003	<0.001
		60 to < 70	35	0.90	0.10	0.80	0.42	0.040	<0.001
		≥ 70	23	0.92	0.16	1.35	0.49	0.007	0.005
	Group F 0.3	40 to < 60	23	0.85	0.11	0.25	0.59	0.25	0.007
		60 to < 70	36	0.87	0.12	-0.17	0.41	0.66	0.037
		≥ 70	17	0.86	0.12	1.02	0.56	0.083	0.038
	Group H Placebo	40 to < 60	29	0.84	0.15	-1.75	0.50	0.002	
		60 to < 70	27	0.89	0.13	-1.41	0.46	0.002	
		≥ 70	22	0.94	0.13	-0.54	0.50	0.12	
Femoral trochanter	Group A 0.625	40 to < 60	14	0.70	0.12	3.27	0.88	0.002	<0.001
		60 to < 70	24	0.77	0.13	2.14	0.60	<0.001	0.069
		≥ 70	28	0.81	0.12	2.16	0.52	<0.001	0.075
	Group C 0.45	40 to < 60	19	0.73	0.13	3.10	0.75	<0.001	<0.001
		60 to < 70	35	0.75	0.09	1.82	0.52	<0.001	0.12
		≥ 70	23	0.81	0.14	1.60	0.56	0.001	0.32
	Group F 0.3	40 to < 60	23	0.71	0.12	1.73	0.72	0.005	0.021
		60 to < 70	36	0.75	0.11	1.81	0.50	0.001	0.11
		≥ 70	17	0.77	0.09	1.63	0.64	0.041	0.35
	Group H Placebo	40 to < 60	29	0.68	0.11	-0.35	0.61	0.71	
		60 to < 70	27	0.77	0.12	0.66	0.57	0.41	
		≥ 70	22	0.83	0.11	0.83	0.57	0.16	
Total body	Group A 0.625	40 to < 60	14	1.12	0.07	0.20	0.27	0.20	<0.001
		60 to < 70	24	1.14	0.10	0.16	0.18	0.11	<0.001
		≥ 70	28	1.15	0.07	0.73	0.16	<0.001	<0.001
	Group C 0.45	40 to < 60	19	1.12	0.07	0.75	0.23	<0.001	<0.001
		60 to < 70	35	1.14	0.07	0.38	0.16	<0.001	<0.001
		≥ 70	23	1.16	0.09	0.37	0.17	0.031	0.005
	Group F 0.3	40 to < 60	24	1.11	0.07	0.18	0.22	0.067	<0.001
		60 to < 70	35	1.15	0.08	0.10	0.15	0.23	<0.001
		≥ 70	17	1.14	0.07	0.56	0.19	0.006	0.001
	Group H Placebo	40 to < 60	29	1.10	0.08	-0.91	0.19	<0.001	

60 to < 70	27	1.13	0.07	-1.31	0.17	<0.001
≥ 70	22	1.18	0.08	-0.27	0.17	0.040

a: Identified by dose (mg) of CE or CE/MPA.
b: Adjusted annualized mean change from baseline from analysis of variance with treatment and site as factors.
Data from statistical report BMD.1b.

Comments: For the primary efficacy endpoint (lumbar spine BMD) and for total body BMD, all CE doses produced BMD increases that were significantly greater than placebo in all subgroups (age, years since menopause, and body weight). At the femoral neck and trochanter, there were several subgroup comparisons with placebo that failed to demonstrate statistical significance. However, there was no consistent pattern for age effects on drug efficacy at the hip. Therefore, the subgroup analysis supports the conclusion that all tested doses of CE are likely to provide beneficial effects at the lumbar spine, independent of age, years since menopause, and baseline body weight. The analysis also provides some assurance that most patient subgroups will benefit from all doses of CE at other skeletal sites.

VI.C.5.3 Bone Turnover Markers

Serum osteocalcin, urinary calcium, and N-telopeptide were used as bone turnover markers (BTM) at cycles 6, 13, 19, and 26. Both serum osteocalcin and N-telopeptide significantly decreased ($p < 0.001$) for all active-treatment groups at all cycles compared with the placebo group. In all cases, larger mean decreases from baseline were seen with the active groups than with the placebo group.

ABSOLUTE CHANGE IN BONE TURNOVER MARKERS FROM BASELINE WITHIN AND BETWEEN GROUPS - INTENT-TO-TREAT POPULATION

Treatment			——Baseline——		——Observed——		Change from Baseline		p-Values
Group[a]	Cycle	No. of Pairs	Mean	SD	Mean	SD	Adjusted Mean[b]	SE	vs Placebo
Osteocalcin (µg/L)									
Group A 0.625	6	81	9.94	2.69	7.06	1.96	-2.69	0.28	<0.001
	13	65	10.38	3.59	6.67	2.10	-3.37	0.37	<0.001
	19	51	10.62	3.88	6.42	2.06	-3.80	0.40	<0.001
	26	40	10.85	4.20	7.04	2.80	-3.41	0.46	<0.001
Group C 0.45	6	84	10.46	2.93	7.79	2.46	-2.49	0.27	<0.001
	13	67	10.86	2.87	7.30	2.22	-3.26	0.36	<0.001
	19	62	10.91	2.98	7.06	2.13	-3.54	0.36	<0.001
	26	56	11.28	2.99	7.11	1.91	-3.91	0.39	<0.001
Group F 0.3	6	77	11.33	4.38	9.34	3.23	-1.85	0.29	<0.001
	13	75	11.37	4.38	8.36	2.94	-2.73	0.34	<0.001
	19	64	11.76	4.55	8.39	3.18	-3.01	0.36	<0.001
	26	59	11.71	4.71	8.30	3.79	-3.08	0.39	<0.001
Group H Placebo	6	81	10.74	3.66	11.11	3.93	0.52	0.28	-
	13	75	11.03	3.65	10.95	4.02	0.14	0.34	-
	19	59	11.35	3.72	10.92	3.27	-0.21	0.37	-
	26	55	11.14	3.55	10.95	3.90	-0.01	0.40	-
Collagen C-link N-telopeptide (nmol bce[c]/nmol creatinine)									
Group A 0.625	6	81	54.40	23.15	30.93	12.12	-22.55	2.19	<0.001
	13	65	58.62	34.29	31.66	19.55	-25.43	2.58	<0.001
	19	51	56.67	36.30	32.43	27.35	-22.22	3.17	<0.001
	26	40	55.83	39.39	30.35	23.27	-23.11	3.31	<0.001
Group C 0.45	6	84	56.37	18.03	32.36	13.21	-23.16	2.15	<0.001
	13	67	58.55	17.73	29.69	12.46	-27.62	2.55	<0.001
	19	61	58.31	18.76	26.52	9.69	-30.23	2.87	<0.001
	26	56	58.57	18.91	29.21	9.69	-27.60	2.81	<0.001
Treatment			——Baseline——		——Observed——		Change from Baseline		p-Values

Group[a]	Cycle	No. of Pairs	Mean	SD	Mean	SD	Adjusted Mean[b]	SE	vs Placebo
Group F 0.3	6	79	60.16	23.96	41.10	18.50	-18.54	2.22	<0.001
	13	74	59.66	24.15	36.57	18.75	-21.87	2.43	<0.001
	19	64	63.03	25.06	39.73	21.01	-21.57	2.83	<0.001
	26	59	62.31	22.96	36.34	14.29	-23.98	2.75	<0.001
Group H Placebo	6	79	58.38	25.11	57.30	27.45	-0.49	2.23	-
	13	74	58.85	24.56	55.15	21.75	-2.91	2.42	-
	19	57	59.11	25.72	57.53	26.89	-0.81	2.95	-
	26	53	59.23	25.89	51.47	17.09	-6.13	2.88	-
Urinary calcium, random (µg/mgcreatinine)									
Group A 0.625	6	81	123.95	71.29	111.40	98.35	-9.98	9.86	0.14
	13	65	130.17	75.48	122.65	124.72	-0.75	11.98	0.42
	19	51	122.20	71.50	129.82	119.76	16.81	13.54	0.79
	26	40	119.88	74.56	118.03	99.21	5.08	14.72	0.56
Group C 0.45	6	84	128.00	70.82	87.50	53.76	-37.00	9.68	<0.001
	13	67	133.75	74.85	109.01	81.32	-18.59	11.82	0.055
	19	61	130.61	74.44	104.69	69.54	-20.45	12.28	0.016
	26	56	133.89	75.62	120.25	87.43	-8.11	12.50	0.17
Group F 0.3	6	79	135.78	74.93	114.80	91.36	-17.90	9.96	0.043
	13	74	135.22	76.97	123.66	91.01	-6.67	11.26	0.23
	19	64	137.98	79.57	119.72	77.08	-10.70	12.08	0.059
	26	59	138.75	78.31	132.17	94.93	0.51	12.22	0.36
Group H Placebo	6	79	136.18	93.52	142.61	92.87	10.15	10.02	-
	13	74	135.26	94.32	142.32	89.02	12.09	11.22	-
	19	57	136.00	90.96	152.96	93.48	21.61	12.62	-
	26	53	136.04	92.60	144.38	99.37	16.22	12.79	-

a: Treatment group identified by dose (mg) of CE or CE/MPA.
b: Adjusted mean change from baseline obtained from analysis of variance with treatment and site as factors.
c: Bone control equivalent.
Data from statistical report BTM1.

Comments: Bone turnover markers were significantly decreased by all estrogen doses used in the study. These data confirm the expected antiresorptive effect of estrogen. The bone turnover marker data substantiate the bone mineral density improvements seen with these regimens of HRT.

VI.C.5.4: Endometrial Biopsies

Results of the cycle 13 analysis and the cycle 26 analysis showed that endometrial hyperplasia occurred in all of the CE-alone groups. There was no endometrial hyperplasia in any of the CE/MPA groups in either year of the substudy. Within the CE-alone groups, a dose-response was demonstrated in that the rate of hyperplasia was highest in the group with the highest dose of CE and lowest in the group with the lowest dose of CE. There were 15 cases in group A (0.625 mg CE; 27%), 10 in group C (0.45 mg CE; 15%) and 2 in group F (0.3 mg; 3%). These findings demonstrate the efficacy of the lower dose regimens of CE/MPA (0.45 mg/2.5 mg, 0.45 mg/1.5 mg and 0.3 mg/1.5 mg) in reducing the incidence of endometrial hyperplasia.

HYPERPLASIA RATES FOR EFFICACY-EVALUABLE POPULATION CYCLE 26

Treatment Group[a]	Total Cases of Hyperplasia[b]	Total Number of Patients	Hyperplasia Rate	95% Confidence Interval[c]	p-Value vs CE Alone[d]
Group A 0.625	**15**	**55**	**27.27%**	**(16.14%, 40.96%)**	
Group B 0.625/2.5	0	62	0.00%	(0.00%, 5.78%)	<0.001
Group C 0.45	**10**	**67**	**14.93%**	**(7.40%, 25.74%)**	
Group D 0.45/2.5	0	66	0.00%	(0.00%, 5.44%)	0.001
Group E 0.45/1.5	0	69	0.00%	(0.00%, 5.21%)	<0.001
Group F 0.3	**2**	**63**	**3.17%**	**(0.39%, 11.00%)**	
Group G 0.3/1.5	0	75	0.00%	(0.00%, 4.80%)	0.21
Group H Placebo	**0**	**61**	**0.00%**	**(0.00%, 5.87%)**	

a: Identified by dose (mg) of CE or CE/MPA.
b: Total number of cases of hyperplasia calculated as the number of patients with hyperplasia recorded by at least 2 pathologists.
c: Confidence intervals calculated using exact methods.
d: Pairwise comparisons: group B compared with group A, groups D and E compared with group C, group G compared with group F.
Data from statistical report EB.1.

VI.C.5.5: Relief of Vasomotor Symptoms (Hot Flushes)

The vasomotor endpoints were the average daily number and severity of hot flushes. There were significant decreases from baseline in the number and severity of hot flushes for the intent-to-treat population. These decreases were maintained through cycle 26. More importantly, there were also a significantly lower number of hot flushes in all active-treatment groups compared with the placebo group. All active-treatment groups had a significant ($p < 0.001$) decrease in the severity of hot flushes. A statistically significant effect was seen in the treatment groups that received the lower of both the CE-alone and CE/MPA combination treatments.

VI.C.5.6: Vaginal Maturation Index Results

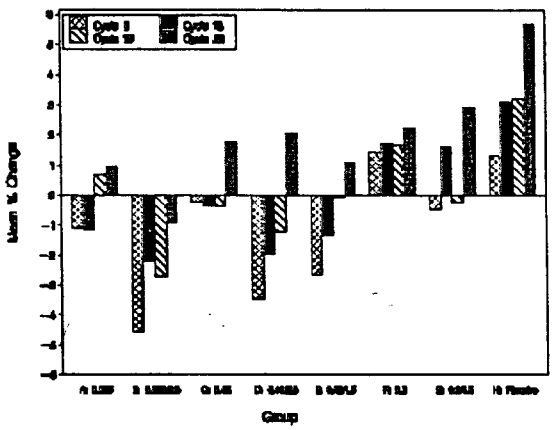
There was a statistically significant increase in the superficial cell count in the vaginal epithelium for all active-treatment groups compared with the placebo group at cycles 6, 13, 19, and 26. There was clearly an estrogenic effect in the presence of these hormones.

Comments: These findings would support [redacted] of lower incidence of endometrial hyperplasia with lower doses of CE. Lower does of estrogen also appear to appropriately treat the menopausal vasomotor symptoms.

VI.C.5.7: Lipid Metabolism

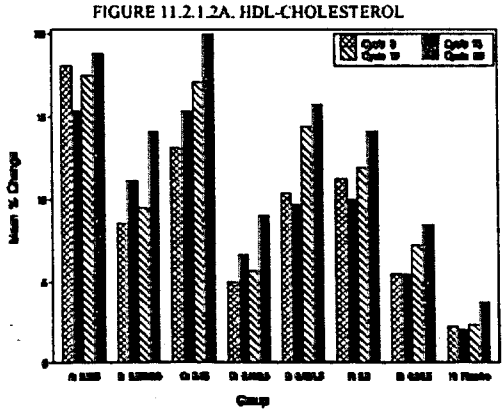
The mean percent changes from pretreatment total cholesterol (total-C) concentrations during cycles 6, 13, 19, and 26 of treatment are shown below. During the first year of treatment with 0.625 mg and 0.45 mg CE, with and without MPA, there was a modest mean percent decrease, 0.22% to 4.58%, in total-C concentrations from baseline values. During the second year of treatment, the mean percent change from baseline was equivocal, ranging from –2.73% to +2.08%. During 2 years of treatment with 0.3 mg of CE alone or with 1.5 mg MPA, the mean percent change from baseline ranged from -0.44% to +2.90%; with placebo there was a mean percent increase of 1.34% to 5.68%.

FIGURE 11.2.1.1A. TOTAL CHOLESTEROL



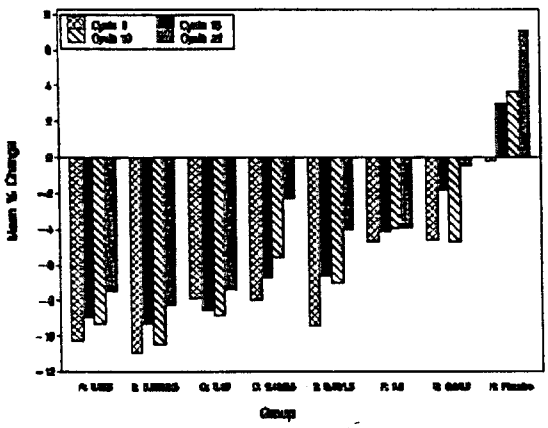
HDL-cholesterol (HDL-C): During the 2 years of therapy, all active-treatment groups group had statistically significant mean percent increases in HDL-C, ranging from 5% to 20%, which were greater than the 2% to 4% mean percent increases that occurred with placebo. The mean increases generally were significantly greater in the CE-only groups. HDL_2-C concentrations also showed a statistically significant mean percent increases from baseline HDL_2-C values in all groups treated with CE, with or without MPA, at all dosages, compared with no significant change in women who received placebo. HDL_3-C values also were statistically significant in all CE alone treatment groups at most measurement times.

FIGURE 11.2.1.2A. HDL-CHOLESTEROL



LDL-C: The mean percent decreases in LDL-C with active treatment were significantly different from the mean changes with placebo at most cycles. These decreases were statistically significant with each active treatment except with CE 0.3 mg alone at cycle 26. A statistically significant mean percent increase in LDL-C was seen in patients who received placebo during cycles 13, 19, and 26.

FIGURE 11.2.1.5A. LDL-CHOLESTEROL



VLDL-C concentrations showed a statistically significant mean percent increases in VLDL-C were seen in all CE alone treatment groups at cycle 26. There were statistically significant mean percent increases in VLDL-TG in all CE alone treatment groups at cycles 6, 13, 19, and 26, with the exception of the 0.3 mg CE group at cycle 26. Triglyceride (TG) concentrations showed a statistically significant mean percent increases from baseline in all active-treatment groups, and there were no significant differences between comparable CE-alone groups and those receiving comparable does of CE combined with MPA except between the 0.45 mg CE-alone group and each of the 0.45 mg CE/MPA combination groups at cycle 6. Overall, the CE-alone group had larger mean increases than the CE/MPA groups. The increases with lower active doses generally were not significantly different from the increases with placebo. The mean percent increase from baseline in the placebo group was significant only at cycle 6.

Apolipoprotein A1 concentrations showed statistically significant mean percent increases from baseline values in all groups of women treated with CE, either alone or combined with MPA, and these changes were significantly different from those in the placebo group, in which there was no significant change from baseline. Generally, there were small mean percent decreases from baseline apolipoprotein B values after treatment with active medication. Decreases were statistically significant for patients treated with 0.625 mg CE and with 0.45 mg CE. Decreases from baseline Lp(a) concentrations in women treated with CE with or without MPA were, in general, statistically significant. Treatment with placebo had no significant effect on this variable and no median percent changes were seen at any cycle.

Comment: Overall, these findings support Wyeth's claims regarding increases in HDL-C and decreases in LDL-C for all CE alone doses. The findings suggest that subjects treated with CE alone have a more favorable increase in HDL-C and HDL_2-C concentrations than

those treated with combination CE/MPA. The decrease in LDL-C concentrations was similar in subjects treated with CE alone and CE/MPA.

VI.C.5.8: Carbohydrate Metabolism
No labeling claims are made for changes in carbohydrate metabolism. The results of these analyses are briefly reviewed here.

Glucose and insulin AUCs were highly variable within and between treatment groups. The adjusted mean increase from baseline in the glucose AUC during cycle 6 of treatment with 0.625 mg of CE, with and without 2.5 mg of MPA, was statistically significant. In subjects treated with placebo, the glucose AUC decreased ($p = 0.024$ during cycle 6). Because of the decreases in glucose AUC in the placebo group, many increases in the active-treatment groups were significantly different from the changes in the placebo group. There were no statistically significant adjusted mean changes in insulin AUC except for increases during cycles 19 and 26 with 0.625 mg CE. In the placebo group, no significant changes were seen in mean insulin AUCs.

Forty-three (43) patients who were identified as having impaired glucose metabolism according to the criteria in They were also included in the analyses.

Comment: The unpredictable distribution of changes in glucose and insulin concentrations during testing is not indicative of treatment-related alterations in glucose metabolism. There is no reason to suspect that estrogen replacement, with or without a progestin, will result in deterioration of glucose tolerance in normal individuals or diabetics.

VI.C.5.9: Coagulation Factors
No labeling claims are made for changes in coagulation factors. The results of these analyses are briefly reviewed here. Wyeth analyzed a number of coagulation-related parameters as part of the metabolic sub-study. These included prothrombin time, prothrombin time ratio, partial thromboplastin time, partial thromboplastin time ratio, Factor VIII, fibrinogen activity, tissue plasminogen activity antigen, plasminogen activity, plasminogen activator inhibitor 1 activity, plasminogen activator inhibitor 1 antigen, antithrombin III activity, and protein C and protein S activities.

Prothrombin Time - There were no statistically significant changes in prothrombin time between patients taking CE with MPA and those taking CE without MPA. There were occasional small and clinically unimportant within-group decreases from baseline and differences between the active–treatment groups and the placebo group. Prothrombin Time Ratio (Patient/Control) - There were occasional slight changes from baseline prothrombin time ratios and differences from placebo that were statistically significant. However, there were no significant differences in the adjusted mean changes from baseline ratios between CE alone and comparable CE/MPA treatment groups.

Partial Thromboplastin Time - There were occasional changes from pretreatment that reached statistical significance. There was no difference in these changes across treatment groups, including placebo. There were also small and sporadic differences in changes between

subjects given CE alone and those given the comparable dose of CE/MPA or between active-treatment groups and the placebo group.

Factor VIII: During the initial cycles 6 and 13, There were no statistically significant mean changes from pretreatment values in factor VIII activity with placebo or any treatment except for a slight increase in patients treated with 0.3 mg/1.5 mg CE/MPA. Following cycles 19 and 26, there was a slight mean decrease in factor VIII in all treatment groups, with no difference between the placebo group and any active-treatment groups.

Fibrinogen Activity: There were small but statistically significant mean decreases from pretreatment fibrinogen activity in women in all CE alone treatment groups during cycle 6 and at cycle 13 for all groups except the 0.45 mg CE-alone group. In the active-treatment groups, the only significant mean increase from pretreatment fibrinogen activity occurred during cycle 19 in the 0.45 mg/2.5 mg CE/MPA group. There were no significant differences in fibrinogen activity between CE alone and comparable CE/MPA treatment groups at any measurement time.

Tissue Plasminogen Activity Antigen: Tissue plasminogen activity antigen values were significantly decreased from baseline in all CE only treatment groups except and during cycles 13, 19, and 26 with the 0.3 mg dose. There were no differences between treatment with CE alone and with the comparable CE/MPA treatments, but most changes with active treatment were significantly different from those with placebo. Plasminogen Activity: Statistically significant mean increases in plasminogen activity were seen in all active-treatment groups and were significantly greater than the changes with placebo. There were no significant differences in plasminogen activity between CE alone and the comparable CE/MPA treatments at any measurement time. Plasminogen Activator Inhibitor 1 (PAI-1) Activity: There were statistically significant mean decreases from baseline PAI-1 activity in all CE only treatment groups. Most of the mean decreases with active treatment were significantly different from the mean increases seen with placebo. There were no significant differences in PAI-1 activity between CE alone and the comparable CE/MPA treatment groups except during cycle 6 in the 0.45 mg/2.5 mg group. Plasminogen Activator Inhibitor 1 (PAI-1) Antigen: Statistically significant mean decreases from baseline PAI-1 antigen values were seen during cycles 6, 13, 19, and 26 of treatment with 0.625 mg CE alone and during cycles 6, 19, and 26 with 0.45 mg CE alone. There were no significant differences in changes in PAI-1 antigen between CE alone and comparable CE/MPA treatment groups except during cycles 6 and 26 in the 0.45 mg/2.5 mg group.

Antithrombin III Activity: Small but statistically significant mean decreases in antithrombin III activity were seen in all treatment groups except during cycle 13 in the 0.3 mg/1.5 mg CE/MPA group and during cycles 6, 13, and 19 in the placebo group. There were significant differences during cycle 6 between the placebo group and the 0.45 mg and 0.3 mg CE-alone groups. There were no significant differences in antithrombin III activity between the CE-alone groups and the comparable CE/MPA treatment groups for any cycle. Protein C: Sporadic small but statistically significant mean increases and decreases from pretreatment concentrations of protein C were not indicative of a consistent difference due to treatment. Three (3) patients (group G, patients 30920-0013 and 30964-0078, and group F, patient 30964-0029) were found to have lower than normal protein C levels in pretreatment and on-therapy samples. Protein S Activity: Statistically significant decreases in protein S activity occurred in women in all treatment groups except the

0.3 mg/1.5 mg CE/MPA and placebo groups. These decreases were significantly different from those seen in the placebo group for all treatment groups except the 0.3 mg CE group at cycle 26 and the 0.3 mg/1.5 mg CE/MPA group for all time points. There were no differences in protein S activity between the CE-alone groups and comparable CE/MPA treatment groups except during cycle 6 with 0.45 mg/2.5 mg and during cycles 6 and 13 with 0.3 mg/1.5 mg CE/MPA, when the decrease from baseline was less than that with CE alone.

Comments: Overall, the patterns of mean changes in coagulation factors do not suggest any clinically significant alterations in homeostasis that could be attributed to treatment with any of the CE regimens.

VI.D: Efficacy Conclusions

There are solid increases in BMD at all sites tested with all doses of CE in this trial. The results were seen in the efficacy evaluable population and confirmed in the ITT population. Analysis of data on bone biomarkers confirms the expected antiresorptive effect of estrogen in all dose groups. There was significantly less endometrial hyperplasia with lower doses of continuous estrogen therapy.

VII: Review of Safety

A clinical review of the endometrial safety data and the bleeding profile was performed by submitted in Type 6 NDA 21-396 Note that data on adverse events are cumulative for the substudy population over the 2-year study period.

VII.A: Safety Summary

A total of 725 (97%) of the 749 patients in the evaluable population reported adverse events. Differences in incidence of any adverse event among groups were not statistically significant. However, statistically significant differences in incidence of urogenital events that were clinically notable included a significantly higher incidence of breast pain in the combination-treatment groups than in the CE-alone groups and the highest incidence of endometrial hyperplasia and vaginal hemorrhage in the 0.625 mg CE-alone group. The incidence of vaginal hemorrhage was significantly higher in group A (0.625 mg) than in all the other treatment groups. The difference between the 0.625 mg CE group (20%) and the 0.45 mg CE group (4%) in the incidence of this event was of clinical interest.

VII.B: Description of Patient Exposure

The table below lists the assessment of exposure to active medication for each active treatment group.

ASSESSMENTS OF EXPOSURE TO ACTIVE MEDICATION

Parameter	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
Days in Study							
n	97	86	95	96	94	89	98
Mean	496.1	626.4	582.7	607	609.7	613.3	617.9
SD*	252.3	198.2	221.3	223.7	224	203.4	222.7
Range	28-756	1-742	41-757	42-758	7-756	82-756	28-756

VII.C: Specific Findings of Safety Review

VII.C.1: Deaths

No deaths occurred in the substudy population throughout the 2 years of the study.

Two (2) deaths were reported in the total study population (subjects 30921-0018 and 30937-0129). Subject 30921-0018, a 53 year old woman assigned to the 0.3 mg CE alone dosage strength (Group F) for 134 days, was diagnosed with adenocarcinoma of the lung following treatment for pneumonia and a persistent cough. She developed severe hypercalcemia, became comatose, and died of cardio-pulmonary failure. Subject 30937-0129, a 50 year old woman assigned to the 0.45 mg CE/2.5 mg MPA dosage strength (Group D) for 217 days, was diagnosed with lung cancer (type unspecified) and died.

VII.C.2: Serious Adverse Events

A total of 50 serious adverse events were reported for 48 patients; these patients are listed by treatment group with their serious events in Table 10.3.1.2A. Four (4) of these patients were not in the evaluable population; patients 30952-0023, 30952-0041, and 30952-0053 were from the disqualified site (see Attachment 1) and patient 30940-0041 was in the cohort for which no diary cards were returned.

VII.C.2.1: Breast Cancer

Four (4) substudy patients were reported to have breast carcinoma during 2 years of participation in the study: group A (0.625 mg CE, reported in year 1), 1 (1%); group C (0.45 mg CE), 1 (1%); group E (0.45 mg/1.5 mg CE/MPA), 1 (1%); and group H (placebo). Overall, a total of 13 cases of breast cancer were reported in the 2673 subjects enrolled in the study. Two in the placebo group and 11 in active treatment groups.

Comments: A total of 13 cases of breast cancer in 2763 subjects does not represent a higher incidence of breast cancer than reported for other large HRT clinical trials conducted over a two year period.

VII.C.2.2: Hysterectomies Associated With Endometrial Hyperplasia
One (1) substudy patient in treatment group A (0.625 mg CE) had a hysterectomy performed as a result of endometrial hyperplasia or malignancy diagnoses by pathologists. This hysterectomy was also reported in the year 1 results. There were no additional cases of surgery associated with endometrial hyperplasia during year 2.

VII.C.2.3: Vascular Thromboses
Two (2) patients had vascular thromboses: 1 (1%) in group B (Subject 30940-0041, being treated with 0.625 mg CE/2.5 mg MPA, was diagnosed with a TIA during cycle 5 and discontinued medication on April 25, 1998. On May 21, 1998, she was diagnosed with left parietal subacute cerebral vascular accident) and 1 (1%) in group C (Subject 30965-0050 was diagnosed with a pulmonary embolism during cycle 9 of treatment with 0.45 mg CE). Both of these events occurred in year 1. There were no additional cases of vascular thromboses for year 2. In total, there were 7 cases of vascular thromboses reported in this study. Other reported events include: Subject 30931-0045 was diagnosed with a "stroke" during cycle 6 of treatment with 0.625 mg CE, Subject 30914-0055 was diagnosed with a transient ischemic attack (TIA) during cycle 5 of 0.45 mg CE/1.5mg MPA treatment, Subject 30953-0031 on 0.45 mg CE/1.5 mg MPA was diagnosed in cycle 9 of treatment with deep vein thrombosis of the left leg, Subject 30963-0014 developed a blood clot in cycle 1 of treatment with 0.625 mg CE/2.5 mg MPA after being run over by a car, and Subject 30948-0045 was diagnosed with an acute inferior myocardial infarction during cycle 8 of placebo treatment.

Comment: These 4 reported cases of arterial thrombosis and 3 cases of venous thromboembolism in 2763 treated patients do not raise concern that this is a treatment related effect.

VII.C.2.4: Cholelithiasis
Four (4) patients had cholelithiasis: 2 (2%) in group D (0.45 mg/2.5 mg CE/MPA); 1 (1%) in group F (0.3 mg CE); and 1 (1%) in group G (0.3 mg/1.5 mg CE/MPA). Three (3) of these subjects were treated and completed the study. One (1) patient in group D discontinued her participation in the study during year 1 as a result of cholelithiasis and subsequently had a laparoscopic cholecystectomy.

VII.C.2.5: Carcinomas Other than Breast Cancer
Three (3) patients had carcinomas other than breast carcinomas. Bladder carcinoma (30909-0070) and thyroid carcinoma (30958-0014) were seen in 1 patient each in group D (0.45 mg/2.5 mg CE/MPA). One (1) additional patient (in the placebo group, H) reported bronchogenic carcinoma after the study.

VII.C.3: Adverse Events Leading to Withdrawal
Adverse events led to withdrawal from the study for a total of 111 of 749 (15%) patients. Adverse events caused the discontinuation of the following numbers of patients in each treatment group: 36 (37%) in group A (0.625 mg CE), 11 (13%) in group B (0.625 mg/2.5 mg CE/MPA), 14 (15%) in group C (0.45 mg CE), 12 (13%) in group D (0.45 mg/2.5 mg CE/MPA), 13 (14%) in group E (0.45 mg/1.5 mg CE/MPA), 9 (10%) in group F (0.3 mg CE), 8 (8%) in group G (0.3

mg/1.5 mg CE/MPA), and 8 (9%) in group H (placebo). Differences among treatment groups were statistically significant for incidence of any adverse event causing discontinuation, as well as for adverse events of endometrial hyperplasia ($p < 0.001$) and vaginal hemorrhage ($p < 0.001$). The highest incidences of these 2 events reported as reasons for discontinuation were in group A (0.625 mg CE).

VII.C.4: Fractures

Fractures were reported for 22 patients during the study. All the fractures were reported as the result of accidents. Five (5) of the fractures were considered serious adverse events. The table below provides a summary of the patients with fractures.

PATIENTS WITH CLINICALLY IMPORTANT FRACTURES

Treatment Group[a]	Cycle[b]	Age	Ethnic Origin	Fracture[c]
Group A (0.625)	1	48	White	Rib
	9	51	White	Left foot, 2nd toe
Group B (0.625/2.5)	9	58	White	Compression fracture left wrist
	23	56	White	Left elbow
	17	48	White	Left foot
Group C (0.45)	4	54	White	Left patella
	10	44	White	Left wrist, left thumb
	Poststudy	53	White	Left wrist
Group D (0.45/2.5)	12	52	White	Two toes, left foot
	4	53	White	Right humerus
Group E (0.45/1.5)	14	55	White	Left distal radius
	5	53	White	Nose
	10	50	White	Left 5th metatarsal
Group F (0.3)	5	53	White	Coccyx
	1	50	White	Right tibia and fibula
Group G (0.3/1.5)	23	52	White	Clavicle, ribs, pelvis
	18	44	White	Right 5th finger
Group H (Placebo)	5	57	White	Left Tibia
	7	50	White	Right foot, 5th phalange
	16	47	Hispanic	Right middle toe
	2	50	White	Right metatarsal
	14	60	White	Left ankle and tibia

VII.D: Adequacy of Safety Testing

The safety procedures and data appear to be adequate.

VII.E: Safety Summary and Limitations

Overall, the cumulative safety profile of the substudy patients in year 2 was similar to that reported for all patients in year 1. Differences between study groups were not statistically significant overall. No dose relationship was apparent in incidence of AEs overall in the active-treatment groups. However, clinically notable and statistically significant differences between groups were seen in incidence of the following most commonly reported urogenital AEs: breast pain, dysmenorrhea, endometrial hyperplasia, menorrhagia, metrorrhagia, uterine spasm, vaginal dryness, and vaginal hemorrhage.

Forty-eight (48) patients experienced 50 serious adverse events over the 2 years of the substudy. Generally the same kinds of serious adverse events were seen in the substudy patients over 2 years of participation as in all of the patients during year 1 and were not unexpected in this population of postmenopausal women. Three (3) cases of breast cancer were seen in the

substudy population during year 2, 1 in the placebo group. One (1) additional case of breast cancer was reported after completion of year 2 of the substudy. There were no additional cases of vascular thromboses or surgery associated with endometrial hyperplasia during year 2. Two (2) cases of cholelithiasis were considered serious adverse events; 1 of these was also reported in year 1. Three (3) cases of cancer other than breast cancer were reported for year 2: thyroid carcinoma (in group D, 0.45 mg/2.5 mg CE/MPA), bronchogenic carcinoma (in the placebo group, H), and bladder carcinoma (group D, 0.45 mg/2.5 mg CE/MPA), the latter 2 reported after the study.

Cardiovascular event data was not specifically reported. Given recent discontinuation of the combined CE/MPA arms of the WHI, this data will be important for the labeling of any estrogen product.

VIII. Dosing, Regimen, and Administration Issues

The well recognized benefits of HRT in postmenopausal women are prevention of osteoporosis and treatment of postmenopausal symptoms. HRT has been shown to improve lipid parameters that are associated with increased cardiovascular risk. The beneficial effect of HRT on clinical cardiovascular outcomes has come under great scrutiny. Recently, researchers with the WHI discontinued of the combination CE/MPA arms of the trial secondary to higher than expected adverse outcomes. These results call into question the benefit of estrogen plus progestin therapy for prevention of cardiovascular adverse events. The CE only arms of the WHI trial continue and data are not available, therefore it is not possible to comment on cardiovascular benefits in this population.

The risks of HRT include increased incidence of endometrial cancer. This risk can be largely eliminated by concurrent administration of a progestin. While this trial showed a decreased incidence of endometrial hyperplasia with the lower doses of continuous CE, the incidence did not disappear. For this reason, use of continuous CE products should remain limited to women without an intact uterus.

A given patient may require a higher dose of HRT for alleviation of the vasomotor symptoms of menopause. Her response to therapy should guide the choice of dose regimen.

IX. Use in Special Populations

HRT with continuous conjugated estrogens is indicated for postmenopausal women.

X. Conclusions and Recommendations

X.A: Conclusions

The metabolic and osteoporosis sub-study was adequately designed to test the safety and efficacy of two years of treatment with various doses of CE alone and combination CE/MPA. Baseline characteristics of individuals in all eight treatment groups were virtually indistinguishable. The drop-out rates were similar across treatment groups and essentially the same across all CE alone groups and placebo. The overall retention rate (about 70% after two years) was typical of osteoporosis trials and sufficient to fulfill the goals of the study. The percent of subjects with protocol violations was small and roughly evenly distributed across treatment groups.

The study was not powered to detect significant differences between active-treatment groups. There were no apparent differences in efficacy between a CE-alone group and the corresponding CE/MPA-combination groups, based on 95% confidence intervals.

The trial clearly demonstrated that all doses of conjugated equine estrogen, including the lowest 0.3 mg dose, were effective in preventing loss of BMD in postmenopausal women. This was true irrespective of the statistical approach used in the analysis. Based on the ITT analysis provided by Biometrics, women treated with 600mg calcium alone (the placebo group) had a mean annualized BMD decrease of 1.37% at the lumbar spine (the primary efficacy endpoint). In contrast, women treated with 600mg calcium plus active treatment regimens had mean annualized lumbar spine BMD increases ranging from 0.54% in the 0.3 mg group, 1.27% in the 0.45mg group and 1.49% in the 0.625mg group. When calculated as percent change from baseline to cycle 26, the results were similar, with BMD increases ranging from 1.24% in the lowest dose of CE to 2.32% in the group receiving 0.625mg. The placebo group lost 2.46% in this analysis. All comparisons with placebo were statistically significant ($p<0.001$).

Similar results were obtained for the BMD endpoints at the other three skeletal sites; the statistical comparisons between CE alone and placebo groups remained essentially the same (with p-values <0.001) across different analytical approaches. At the trochanter, the mean increases were generally numerically greater than those seen for L2 to L4, and the changes in femoral neck and total body BMD were generally smaller than those seen for L2 to L4.

Bone turnover markers substantiated the efficacy of all doses of continuous CE. There were statistically significant decreases from baseline in both osteocalcin and NTX at all cycles and in all active-treatment groups, compared to placebo, in which there was essentially no change form baseline ($p<0.001$).

Detailed analyses of multiple parameters related to lipid metabolism were performed. The results of these analyses confirmed earlier data regarding effects of HRT on lipid metabolism. There were small reductions in total-C in groups receiving the highest dose of CE alone. There were increases in total-C in the placebo group. All active-treatment groups had increases in HDL-C (ranging from 5-20%). All these were significantly greater than the 2-4% increases seen in placebo. For LDL-C, there were mean percent decreases from baseline that were significantly different from placebo at most cycles. The levels of LDL-C increased during the trial. For TG, there were significant increases from baseline in all active-treatment groups, in the range 20-50% (the largest increases were in association with the highest doses). The ratio LDL-C/HDL-C was <3.0 in all groups at baseline. During the trial, there were significant mean percent decreases in this ratio in all active-treatment groups, whereas there was no significant change in placebo. These changes were all highly significant, compared to placebo, at all cycles, and for all treatment groups.

X.B: Recommendations

I recommend approval of the 0.45mg and 0.3mg doses of conjugated equine estrogen for the prevention of postmenopausal osteoporosis, pending the outcome of the November 2002 advisory committee meeting and final agreed upon product labeling.

XI. Appendix

Financial Disclosure Data:

Wyeth has submitted the names of all clinical investigators whose sites enrolled patients in the osteoporosis and metabolic sub-study. One hundred forty-two investigators returned financial disclosure forms. Nine failed to return forms. Of these, seven were no longer at the site and there was no forwarding address. One was incapacitated and one has not responded to several requests. Further information is pending. It is unlikely that the integrity of the efficacy or safety data could have been compromised because of the blinded nature of the trial and because the seven investigators were at a site that contributed data from 16 subjects.

Two principal investigators and one sub-investigator received substantial financial benefits from Wyeth-Ayerst. Because of the double-blind randomized nature of the study, these potential conflicts of interest were unlikely to affect the outcome of the study.

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