CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-396

MEDICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: June 1, 2003

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-396
Prempro and Premphase
Conjugated estrogens and medroxyprogesterone acetate tablets
Wyeth Ayerst
Prevention of PMO

SUBJECT: NDA review issues and recommended action

Background

This is a type 6 NDA submitted to 510 in parallel with a submission to 580 proposing two new, lower, dosage strengths of Prempro and Premphase, 0.3 mg CE/1.5 mg MPA and 0.45 mg CE/1.5 mg MPA. On July 25, 2002, this application was AE'd because of manufacturing site deficiencies, now resolved, and citing clinical deficiencies. The sponsor addressed the following deficiencies in a December 3, 2002 complete response to the action letter:

1. an updated risk-benefit analysis for the prevention of PMO of these proposed new doses in light of the results of the WHI study results reported July 17, 2002.
2. A detailed analysis of cardiovascular adverse events recorded in the HOPE trial (which established the efficacy of these dosage strengths with regard to BMD).
3. Safety update/profile.

As per Drs. Colman and Schneider, the sponsor states that because there are no fracture data from HOPE and because there were too few CV adverse events and breast cancer cases in the trial, there are no data by which to address in a formal sense (as in WHI) the risk vs. benefit of these two doses of CE/MPA for the prevention of PMO. The division is satisfied with this response. It is worth noting that the current labeling (revised after WHI) for these and other estrogen or estrogen/progestin products recommends low doses for a duration sufficient to accomplish treatment goals. Additionally, labeling counsels that when used solely for the prevention of PMO (as opposed to for symptomatic relief of symptoms of hypoestrogenism) other therapeutic options (non HRT) should be considered. These lower doses are therefore rational additions to this product line and we are comfortable with labeling as negotiated.

The updated safety information is non-contributory with regard to the regulatory decision.

As Dr. Colman notes, additional labeling changes will be negotiated in the relative near term, involving DMEDP, DRUDP, and DNDP addressing the results of WHIMS showing an increased incidence of dementia in women treated with Prempro vs. placebo.

Recommendation: Approve

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/s/

David Orloff
6/1/03 07:49:33 PM
MEDICAL OFFICER

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MEMORANDUM

May 27, 2003

NDA: 21-396

DRUG: Prempro (0.45 mg/1.5 mg)(0.3 mg/1.5 mg)

COMPANY: Wyeth Ayerst

DATE OF SUBMISSION: 12/03/02

INDICATION: Prevention of Postmenopausal Osteoporosis

RE: Response to an approvable letter

This memo is in response to Wyeth Ayerst's submission responding to the Division's Approvable Letter issued on July 25, 2002.

Dr. Schneider, the primary reviewer of this application, has reviewed the material contained in this submission and considers it an adequate response to the deficiencies listed in the Approvable Letter.

Briefly, the following clinical deficiencies were defined in the Approvable Letter:

1. Risk Benefit Analysis taking into consideration the WHI findings reported in July, 2002.
2. Analyses of cardiovascular event data from the HOPE trial.
3. Safety update/profile.

Regarding points # 1 and # 2, the initial report of the WHI indicated that, compared with women treated with placebo, women treated with Prempro (0.625 mg/2.5 mg) over an average of 5.2 years had excess numbers of cardiovascular events and breast cancer. The company stated that due to differences in the designs of the WHI and HOPE trials (i.e., no fracture data from HOPE) and the extremely low number of cardiovascular events (i.e., 6 cases total) and cases of breast cancer in HOPE, it is not possible to calculate a risk-benefit equation for HOPE that is in any way meaningful. This reviewer agrees with the company's position.

Regarding point # 3 above, the updated safety information does not materially change the safety profile culled from the original submission.

The results of the WHI Memory Study (WHIMS) are to be published today in *JAMA*. According to a pre-publication manuscript, women 65 years of age and older who were treated with Prempro (0.625/2.5) had 45 cases of dementia per 10,000 person-years compared with 22 cases per 10,000 person-years in women treated with placebo (p=0.01).

Comment

I recommend that the 0.45 mg/1.5 mg and 0.3 mg/1.5 mg doses of Prempro be approved for the prevention of postmenopausal osteoporosis.

Eric Colman, MD

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/s/

Eric Colman
5/27/03 02:45:30 PM
MEDICAL OFFICER

David Orloff
6/1/03 07:01:42 PM
MEDICAL OFFICER
concur with Dr. Colman

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

May 27, 2003

NDA: 21-417

DRUG: Premarin 0.3 mg and 0.45 mg

COMPANY: Wyeth Ayerst

DATE OF SUBMISSIONS: 04/17/02 and 01/15/03

INDICATION: Prevention of Postmenopausal Osteoporosis

RE: Safety Updates

In these two submissions, Wyeth Ayerst provides safety update information for the above referenced pending supplemental NDA.

In the April 2002 submission, two IND safety reports are included for subjects who received premarin + MPA. One event was coded as ischemic colitis and the other as transient ischemic attack.

There was no new safety information to report in the January 2003 submission.

Comment

No new safety information has been submitted that materially changes the risk-to-benefit profile for the 0.3 mg or 0.45 mg doses of premarin. I recommend approval of this supplement.

Eric Colman, MD

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/s/

Eric Colman
5/27/03 12:20:24 PM
MEDICAL OFFICER

David Orloff
6/1/03 06:59:08 PM
MEDICAL OFFICER
Concur with Dr. Colman

MEMORANDUM FOR THE FILE

April 30, 2003

NDA# 21-396

Re: Wyeth's complete response to approvable letter of July 25, 2002.

Wyeth submitted a complete response to the approvable letter on December 4, 2002. The elements of the letter concerned the following:

1. An updated risk-benefit analysis for the lower doses of Prempro for the prevention of postmenopausal osteoporosis, taking into account the findings of the Womens' Health Initiative.
2. Analysis of cardiovascular event data from the HOPE trial.
3. Chemistry issues.
4. Safety profile.

It is my opinion that the sponsor's submission represents a complete response to the AE letter, as far as the clinical items (1, 2, and 4) are concerned. The results of the risk-benefit analyses for prevention of postmenopausal osteoporosis are adequately conveyed in the most recently approved label. An updated safety report has been submitted, and there are no outstanding issues.

BRUCE S. SCHNEIDER, MD
MEDICAL OFFICER, DMEDP, HFD-510

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/s/

Bruce Schneider
4/30/03 04:46:02 PM
MEDICAL OFFICER

APPEARS THIS WAY
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TEAM LEADER MEMO

NDA: 21-396

DRUG: Conjugated estrogen + medroxyprogesterone (Prempro and Premphase)

DOSES: 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA (tablets)

COMPANY: Wyeth Ayerst

INDICATION: Prevention of PMO

PRIMARY REVIEWER: Bruce Schneider, MD

DATE OF MEMO: July 11, 2002

Background

The subject of this supplemental NDA – a substudy of the HOPE trial – was conducted to satisfy a December, 1994 Phase 4 commitment to examine the minimum effective dose of conjugated estrogen (CE) and medroxyprogesterone acetate (MPA) for the prevention of postmenopausal osteoporosis (PMO). Wyeth is seeking approval of the 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA doses for the osteoporosis indication.

Prempro is approved as a single tablet containing either 0.625 mg CE with 2.5 mg MPA or 0.625 mg CE with 5.0 m MPA. Premphase is approved as a two tablet product: one tablet contains 0.625 mg CE and the other contains 0.625 mg CE with 5.0 mg MPA. These doses are approved for the treatment of vasomotor symptoms, vaginal atrophy, and the prevention of PMO.

[There are five dose strengths of CE currently approved: 0.3 mg, 0.625 mg, 0.9 mg, 1.25 mg, and 2.5 mg. The 0.625 mg dose of CE is currently the recommended dose for the prevention of PMO. Other approved indications for CE include vasomotor symptoms (0.625 mg), vaginal atrophy (0.3 to 1.25 mg or more), hypogonadism (0.3 to 0.625 mg), breast cancer (10 mg TID), and advance androgen-sensitive prostate cancer (1.25 to 2.5 mg).]

HOPE Trial

The Health and Osteoporosis, Progestin and Estrogen (HOPE) study was a double-blind, randomized, placebo/active-controlled trial of healthy postmenopausal with an intact uterus. A total of 2,673 primarily Caucasian women with a mean age of 52 years and an average BMI of 24 kg/m^2 were randomized in equal fashion to one of eight regimens:

A: 0.625 CE + placebo
B: placebo + 0.625 CE/2.5 MPA
C: 0.45 CE + placebo
D: placebo + 0.45 CE/2.5 MPA
E: placebo + 0.45 CE/1.5 MPA
F: 0.3 CE + placebo
G: placebo + 0.3 CE/1.5 MPA
H: placebo + placebo

The primary objective of this study during Year 1 was to examine the efficacy of lower doses of CE and MPA in reducing the incidence of endometrial hyperplasia and in reducing the incidence of vasomotor symptoms and vulvar and vaginal atrophy. The one-year data are the focus of attention for DRUDP.

The primary objective of the study during Year 2 was to examine, in 822 women, the efficacy of lower doses of CE and MPA (0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA) in the prevention of PMO and the maintenance of an acceptable metabolic profile (i.e., lipids, coagulation, and carbohydrate). This substudy is the focus of DMEDP's attention.

Bone Mineral Density and Markers of Bone Turnover

After reviewing the appropriate data, Dr. Schneider recommends that the 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA doses be approved for the prevention of PMO.

Of the 822 women enrolled into the second year of the HOPE study, 749 received at least one dose of study drug and were considered evaluable for Year 2 analyses. The withdrawal rates ranged from 21% in the 0.3 CE/1.5 MPA group to 54% in the 0.625 CE group – with adverse event as the most common reason for discontinuation. A similar percentage of patients in each treatment group were taking similar types of concomitant medications at baseline.

The mean percent changes in bone mineral density (BMD) at the lumbar spine from baseline to Year 2 were approximately –2.0% for the placebo group and 2.4% and 1.8% for the 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA doses, respectively ($p<0.001$) (Table). Similar positive and statistically significant effects on trochanteric, femoral neck, and total body BMD were also observed for the 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA doses relative to placebo. Of interest, the addition of MPA to the CE preparations led to greater increases in BMD, particularly at the lumbar spine.

The mean changes in markers of bone turnover, osteocalcin (formation) and NTX (resorption), support the changes noted in BMD.

Adjusted Mean Change in LS BMD from Baseline to Year 2 (evaluable population)			
Treatment Group	N	% change from baseline	P-value
0.625	66	2.8	<0.001
0.625/2.5	76	3.8	<0.001
0.45	77	2.3	<0.001
0.45/2.5	79	3.1	<0.001
0.45/1.5	75	2.5	<0.001
0.3	76	1.5	<0.001
0.3/1.5	82	1.8	<0.001
Placebo	78	-2.6	

Lipids

As expected, relative to treatment with placebo, the mean changes in total, LDL, and HDL cholesterol were favorable in the 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA dose groups. Also as expected, mean TG levels increased by a greater degree with active vs. placebo treatment. In general, the addition of MPA to CE attenuated the favorable lipid effects.

Metabolic Variables

In the women who participated in the 2-year substudy, an evaluation was made of the effect of treatment on levels of plasma glucose, insulin, and a variety of standard coagulation factors. In short, no clinically meaningful changes were noted in any of the dose groups. Wyeth has not proposed that any of these data be included in the labeling.

Safety

Adverse Event Reporting

Deaths

There were no deaths in the 2-year substudy.

Serious Adverse Events

A total of 48 patients reported 50 serious adverse events (SAE). There were no obvious imbalances among groups in reporting rates for SAEs. Four women were diagnosed with breast cancer during the 2-year period: one each in the 0.625 mg, 0.45 mg, 0.45/1.5, and placebo groups. Two vascular thrombosis cases were reported: one in the 0.625/2.5 group and one in the 0.45 group. No vascular thrombotic events were reported during Year 2

Withdrawals Due to Adverse Events

The 0.625 CE group had a significantly higher percentage of patients who discontinued due to an adverse event (37%) compared with the other treatment groups including placebo (8-15%). A large portion of the patients in the 0.625 CE group discontinued because of endometrial hyperplasia and vaginal bleeding.

Treatment-Emergent Adverse Events

In an analysis of the percentage of patients reporting $\geq$ 5% treatment emergent adverse events, a number of comparisons were associated with a nominal p-value of $\leq$ 0.05. Some difference were expected, such as breast pain and endometrial hyperplasia, which were reported by a significantly greater percentage of women on unopposed estrogen vs. placebo. Other events such as bronchitis and ear disorder are nonspecific terms, they lack biological plausibility, and they are not serious, life-threatening events. Interpretation of these nominally significant results is particularly difficulty given the extremely large number of comparison that were made in the tabulation of adverse event reporting rates.
In my opinion these findings do not warrant further analysis.

Clinical Chemistry

Some clinical chemistry parameters were affected by active treatment. As expected, therapy with estrogen (with or without progestin) was associated with small reductions in levels of mean plasma calcium (reduced bone resorption) and alkaline phosphatase (reduced bone formation). I do not believe that any of the statistically significant changes in clinical chemistry parameters in the active vs. placebo groups were of clinical significance.

Endometrium

In her consult of 6 June 2002, Dr. Van Der Vlugt, medical officer from HFD-580, concluded that "both the 0.45 mg CE/1.5 MPA and the 0.3 mg CE/1.5 MPA dosages are successful in protecting the endometrium over the 2-years of treatment in the osteoporosis and metabolic substudy group....."

Fractures

The HOPE trial was not designed to evaluate the efficacy of estrogen plus progestin on risk for osteoporotic fracture. However, as safety data, 22 women sustained a fracture during the study. Although there were 5 women in the placebo group compared with 2 in the 0.625 CE group who had fractures, some of the fractures occurred following trauma and at skeletal sites not considered in an evaluation of osteoporotic fractures. There is certainly no evidence that treatment with estrogen or estrogen plus progestin had a detrimental affect on fracture risk in this population of early postmenopausal women.

Cardiovascular Disease

Given that the Writing Group for the WHI study recently published a paper in which they conclude that the "overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal women," a detailed evaluation of the cardiovascular events from the HOPE trial is in order[1].

Pediatric Rule: The sponsor should be issued a waiver for the requirement to study pediatric patients under the Pediatric Rule — postmenopausal osteoporosis is obviously not a condition that affects children or adolescents.

Phase 4 Commitment: I believe the data presented in this supplemental NDA satisfy the phase 4 commitment to study the lowest effective dose of CE and MPA for the prevention of PMO.

DSI: An audit by DSI was not requested for this supplemental NDA.

Conclusions and Recommendation

The BMD data submitted in this supplemental NDA support the efficacy of 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA in the "prevention of PMO." If not for the recent publication of data from the WHI study, which reported an unacceptable risk – benefit profile of 0.625 mg CE/2.5 mg MPA in healthy postmenopausal women, I would recommend approval. However, during recent discussions among Office and Center-level personnel, it was decided that any pending supplements for an estrogen and an estrogen + progestin product would be designated approvable pending outcome of an Advisory Committee meeting to be held in September, 2002.

I recommend that this application be deemed **approvable**. A reassessment of its regulatory status should be made after:

1. An Advisory Committee is held to discuss the full implications of the recently published data from the WHI study.
2. Wyeth provides the Division with detailed analyses of the cardiovascular data from the HOPE trial. To the extent possible, the analyses should mimic those reported in the July 17, 2002, WHI publication.
3. Wyeth provides the Division with an updated risk – benefit analysis of CE/MPA when used in the prevention of PMO.

Eric Colman, MD
Medical Team Leader
HFD-510

[1] Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA*. 288: 321-333. 2002.

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/s/

Eric Colman
7/25/02 03:39:38 PM
MEDICAL OFFICER

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CONSULTATION

Type 6 NDA 21-396

Date NDA Submitted: 9/24/01
Date Consult Received: 5/22/02
Consult Completed: 6/6/02

Sponsor:	**Wyeth-Ayerst** **P.O. Box 8299** **Philadelphia, PA 19101-8299**
Drug Name:	
Generic:	**Conjugated Estrogens (CE)** **Medroxyprogesterone Acetate (MPA)**
Trade:	**Prempro™**
Pharmacologic category:	**Estrogen**
Dosage Form:	**Oral tablet**
Strength:	**0.45 mg CE/1.5 mg MPA** **0.3 mg CE/1.5 mg MPA**
Proposed Indications:	**Treatment of postmenopausal osteoporosis**
Related Submission:	**IND 21,696** **NDA 20,527**
Consultation Instructions:	**Perform a clinical review of the endometrial safety data and the bleeding profile submitted in Type 6 NDA 21-396**

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Consultation Clinical Review

1. FINDINGS

The data presented in Type 6 NDA 21-396 demonstrates that both the 0.45 mg CE/1.5 mg MPA and the 0.3 mg CE/1.5 mg MPA dosages strengths are successful in protecting the endometrium over the 2-years of treatment in the osteoporosis and metabolic substudy group in Study 0713D2-309-US.

A review of the bleeding profile data submitted demonstrates that the 0.3 mg CE/1.5 mg MPA dosage strength exhibited a greater percentage of consecutive cycles of amenorrhea than the approved Prempro™ 2.5 at cycle 26. The 0.45 mg CE/1.5 mg MPA dosage strength exhibited similar consecutive cycles of amenorrhea as the approved Prempro™ 2.5 at cycle 26.

2. SUMMARY OF CLINICAL FINDINGS

2.1. Brief Overview of the Clinical Program

Prempro™ is an approved oral drug product that consist of hormones in combination, conjugated estrogens (CE) found in Premarin® Tablets and medroxyprogesterone acetate (MPA), a derivative of progesterone. Two dosage strengths of Prempro™ are currently approved. Prempro™ 2.5 (0.625 mg CE/2.5 mg MPA) and Prempro™ 5 (0.625 mg CE/5 mg MPA) are administered orally in a continuous daily regimen for the:

1. Treatment of moderate-to-severe vasomotor symptoms (VMS) associated with the menopause.
2. Treatment of vulvar and vaginal atrophy (VVA) associated with the menopause.
3. Prevention of postmenopausal osteoporosis.

Premphase® is also an approved product containing CE and MPA administered orally in a sequential regimen (0.625 mg CE alone administered orally on days 1-14 and 0.625 mg CE/5 mg MPA administered orally on days 15-28 of a 28-day cycle) for the treatment of VMS, VVA, and the prevention of postmenopausal osteoporosis.

On December 30, 1994, with the initial approval of Prempro™ and Premphase® under NDA 20-303, the Agency requested a Phase 4 commitment to investigate the lowest dose combination of CE/MPA for the prevention of postmenopausal osteoporosis.

Two dosage strengths of combined conjugated estrogens/medroxyprogesterone acetate (0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA) were submitted to the Agency on June 15, 2000 in NDA 20-527/S-017 for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause. On April 3, 2001, during the review cycle of NDA 20-527/S-017, the Sponsor withdrew, without prejudice, the 0.3 mg CE/1.5 mg MPA dosage strength from consideration.

On April 13, 2001, Prempro™ 0.45 mg CE/1.5 mg MPA received an approvable action from the Agency. The Sponsor was advised that before the application could be approved it would be necessary to address the following:

- A number of deficiencies noted during inspection of the Guayama, Puerto Rico manufacturing facility; and
- Submit copies of final printed labeling revised as the enclosed labeling for NDA 20-527/S-017.

Combined 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA, the dosage strengths that are the subject of this Type 6 NDA submitted on September 25, 2001, were investigated in a single, controlled

clinical trial to satisfy the post-approval Phase 4 commitment under NDA 20-303. Study 0713D2-309-US was a double-blind, placebo/active drug-controlled clinical trial that randomized 2,805 postmenopausal women between 40 to 65 years of age to one of 8 treatment groups for a 2 year duration of treatment. The Phase 3, 2-year Study 0713D2-309-US, Health and Osteoporosis, Progestin and Estrogen (HOPE), was specifically designed to investigate the lowest dose combination of CE/MPA for the prevention of postmenopausal osteoporosis.

Study 0713D2-309-US was comprised of two parts:

- A 1-year basic study with a total of 2,673 treated postmenopausal women (includes 749 substudy subjects); primary objective of study year 1 was to evaluate the efficacy of lower doses of CE and MPA in reducing the incidence of endometrial hyperplasia associated with the use of unopposed estrogen (12 month treatment duration), secondary objective was to evaluate the lower doses of CE and MPA in reducing the incidence of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy (12 week treatment duration).
- A 2-year osteoporosis and metabolic substudy with a total of 749 treated postmenopausal women; primary objective of the 2-year substudy was to evaluate the efficacy of lower doses of CE and MPA in the prevention of postmenopausal osteoporosis and the maintenance of an acceptable metabolic profile.

The HOPE study investigated 8 treatment groups as summarized below:

Group (N)	CE (mg)	CE/MPA (mg)
A (348)	0.625	Placebo
B (331)	Placebo	0.625/2.5
C (338)	0.45	Placebo
D (340)	Placebo	0.45/2.5
E (331)	Placebo	0.45/1.5
F (326)	0.3	Placebo
G (327)	Placebo	0.3/1.5
H (332)	Placebo	Placebo

The 2.5 mg MPA dose was used because it is currently the lowest approved dose to reduce the incidence of endometrial hyperplasia in women with a uterus receiving 0.625 mg CE alone. The 1.5 mg MPA dose was selected for use because the Sponsor postulated that this lower dose would be sufficient to oppose lower dose of CE in the prevention of endometrial hyperplasia. Furthermore, the Sponsor postulated that the 1.5 mg MPA dose may also "provide additional benefit to CE in the prevention of postmenopausal osteoporosis and provide less attenuation of the positive lipid effects of lower doses of CE." A placebo group was included for comparison in the analyses of VMS, VVA, and bone mineral density (BMD) assessments.

On November 5, 2001, the Sponsor resubmitted the 0.3 mg CE/1.5 mg MPA dosage strength (withdrawn without prejudice from NDA 20-517/S-017 on April 3, 2001) as NDA 20-527/S-024 for the treatment of moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause.

2.2. Efficacy

An interim analyses was performed at the completion of year 1 of Study 0713D2-309-US. Data on a total of 2,673 treated postmenopausal women (the basic study group), of which 749 were substudy subjects (the osteoporosis and metabolic substudy group), was presented in NDA 20-527/S-017.

Effects on Vasomotor Symptoms

Supplement-017 contained final data, for the 0.45 mg CE/1.5 mg MPA dosage strength, from a 12-week treatment duration for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause.

The 0.45 mg CE/1.5 mg MPA dosage strength was effective in reducing the frequency and severity of moderate-to-severe vasomotor symptoms at weeks 4, 8, and 12 as compared to placebo ($p<0.001$ at all time points).

Effects on Vulvar and Vaginal Atrophy

Supplement-017 also contained final data, for the 0.45 mg CE/1.5 mg MPA dosage strength, from a 12-month treatment duration for the treatment of vulvar and vaginal atrophy associated with the menopause.

The vaginal maturation index results showed that the percentages of vaginal superficial cells increased significantly from screening values at cycles 6 and 13, and that the differences were statistically significant from placebo for the 0.45 mgCE/1.5 mg MPA dosage strength ($p<0.001$).

Reviewer's Comments

Please see the Medical Officer's Review of NDA 20-527/S-017, dated April 6, 2001, for a full description of year 1 of the HOPE study.

2.3. Safety

Effects on the Endometrium

In year 1 of Study 0713D2-309-US, endometrial biopsies were obtained at cycles 6 and 13. The population of interest was an efficacy-evaluable population. Evaluable subjects are those who had a prestudy endometrial biopsy, had taken at least one dose of study medication, and had an endometrial biopsy performed during cycles 5 to 7 and cycles 12 to 14 or who developed endometrial hyperplasia (or endometrial cancer) at any time during the first year of the study. The analysis done at year 1 was considered a final analysis for the 2,153 evaluable subjects in the basic study (including the ≅ 749 substudy subjects).

No endometrial carcinoma was reported during the first year of the HOPE study. However, two subjects had endometrial biopsy readings of endometrial carcinoma in the 1-year interim data submitted. The endometrial biopsy pathology reports for Subject 30912-0049 (age 58) in the 0.45 mg CE/1.5 mg MPA treatment group, and Subject 30924-0011 (age 63) in the 0.3 mg CE treatment group were reviewed by the clinical review team (the reviewer medical officer, a second medical officer [also a board-certified pathologist], and the team leader). For Subject 30912-0049, the clinical review team agreed that the final diagnosis for this subject should be well-differentiated endometrial adenocarcinoma. For Subject 30924-0011, the clinical review team followed the most conservative approach and accepted the "worst-case" diagnosis of endometrial adenocarcinoma. As a result of the reclassification of two cases of reported endometrial hyperplasia as endometrial adenocarcinoma, a total of 30 subjects developed endometrial hyperplasia by cycle 13 (1.4%, 30 cases in 2,153 evaluable subjects across the 8 treatment groups), and 2 subjects developed endometrial adenocarcinoma in the first year of the HOPE study.

The incidence of endometrial hyperplasia or cancer at cycle 13 (year 1) of Study 0713D2-309-US for the 8 treatment groups are shown in Table 1.

Table 1: Incidence of Endometrial Hyperplasia or Cancer at Cycle 13, Year 1 of Study 0713D2-309-US, Basic Study Group, EE Population

Treatment by dose (mg) of CE or CE/MPA	N	Total Number Hyperplasia/ Carcinoma[a]	Hyperplasia Rate (%)	One-sided 95% CI (%)[b]
Group A 0.625 mg CE	249	20	8.03	(0, 11.5)
Group B 0.625 mg CE/2.5 mg MPA	278	0	0.00	(0, 1.1)
Group C 0.45 mg CE	279	9	3.23	(0, 5.6)
Group D 0.45 mg CE/2.5 mg MPA	273	0	0.00	(0, 1.1)
Group E 0.45 mg CE/1.5 mg MPA	272	1[c]	0.37	(0, 1.8)
Group F 0.3 mg CE	269	1[d]	0.37	(0, 1.8)
Group G 0.3 mg CE/1.5 mg MPA	272	1	0.37	(0, 1.8)
Group H Placebo	261	0	0.00	(0, 1.2)

Source: Prepared by the Division of Reproductive and Urologic Drug Products from combined numbers of hyperplasia or cancer.

[a] Total number of hyperplasias or cancer calculated as number of patients.

[b] Confidence interval calculated by the statistical reviewer.

[c] Hyperplasia reclassified as cancer by the clinical review team for NDA 20-527/S-017.

[d] Hyperplasia reclassified as cancer by the clinical review team for NDA 20-527/S-017.

Reviewer's comments

The overall incidence of abnormal endometrial pathology in year 1 of Study 0713D2-309-US is low. Thirty subjects (30), across the 8 treatment groups, developed endometrial hyperplasia (1.4%, 30 cases in 2,153 evaluable subjects), and 2 subjects developed endometrial carcinoma. Other large controlled studies of estrogen alone or estrogen/progestin combination hormone replacement therapy (HRT) drug products have reported endometrial hyperplasia rates ranging from 0% to 40%, and zero to one case of endometrial cancer. The results in Study 0713D2-309-US at year 1 are consistent with these findings.

The data presented in Table 1 shows a dose-dependent response in endometrial hyperplasia or cancer within the CE alone groups with the 0.625 mg CE alone treatment group producing the highest endometrial hyperplasia rate and the 0.30 mg CE alone treatment group producing the lowest endometrial hyperplasia rate:

- **hyperplasia rate of 8.03% in Group A (0.625 mg CE)**
- **hyperplasia rate of 3.23% in Group C (0.45 mg CE)**
- **hyperplasia/rate of 0.37% in Group F (0.3 mg CE).**

No case of hyperplasia was reported in the placebo group.

The data in Table 1 also demonstrates that the combined endometrial hyperplasia or cancer rate is lower in the CE/MPA treatment groups than in the corresponding CE alone groups with the exception of the 0.3 mg CE alone and the 0.3 mg CE/1.5 mg MPA groups (0.37% in both) as shown below:

CE alone groups		CE/MPA groups
• 8.03% in 0.625 mg CE alone	versus	0.00% in 0.625 mg CE/2.5 mg MPA
• 3.23% in 0.45 mg CE alone	versus	0.00% in 0.45 mg CE/2.5 mg MPA
• 3.23% in 0.45 mg CE alone	versus	0.37% in 0.45 mg CE/1.5 mg MPA
• 0.37% in 0.3 mg CE alone	versus	0.37% in 0.3 mg CE/1.5 mg MPA

Per the proposed revision of the 1995 HRT Guidance for Industry, for combination drug products intended to demonstrate endometrial safety, the results from the clinical trial should demonstrate a hyperplasia rate that is less than or equal to 1% with an upper bound of a one-sided 95 % confidence interval for that rate which does not exceed 4% at one year. As shown in Table 1, calculating the combined endometrial hyperplasia or cancer rate for both the 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA dosage strengths, an incidence rate of 0.37% for hyperplasia or cancer is found with a one-sided 95% confidence interval of 0, 1.8, well below the one-sided 95% confidence interval upper limit of 4%.

Twelve (12) of the 30 cases of endometrial hyperplasia (not hyperplasia or cancer) diagnosed at cycle 13 in year 1of the HOPE study occurred in substudy subjects. Seven of these 12 cases of hyperplasia occurred in substudy subjects receiving 0.625 mg CE alone (hyperplasia rate of 10%, 7 of 67 subjects), and 5 cases of hyperplasia occurred in the 0.45 mg CE alone treatment group (hyperplasia rate of 7%, 5 of 76 subjects).

Osteoporosis and metabolic substudy subjects (518 evaluable population) had 2 additional endometrial biopsies performed during year 2 of Study 0713D2-309-US (cycles 19 and 26). A total of fifteen additional cases of endometrial hyperplasia in substudy subjects were documented after cycle 13 and either at or before cycle 26. Eight of the 15 cases of endometrial hyperplasia occurred in substudy subjects receiving 0.625 mg CE alone (hyperplasia rate of 14.5%, 8 of 55 subjects); 5 cases of hyperplasia occurred in the 0.45 mg CE alone group (7.46%, 5 of 67 subjects), and 2 cases of endometrial hyperplasia occurred in the 0.3 mg CE alone treatment group (2.66%, 2 of 63 subjects).

No cases of endometrial hyperplasia or cancer were diagnosed in the placebo treatment group or any of the combination CE/MPA treatment groups in year 2 of Study 0713D2-309-US. See Table 2 for a comparison of years 1 and 2 in the osteoporosis and metabolic substudy group.

Table 2: Osteoporosis and Metabolic Substudy Group, Incidence of Endometrial Hyperplasia at Cycle 13 (Year 1) and at Cycle 26 (Years 2), Study 0713D2-309-US

	Year 1 Substudy Group			Year 2 Substudy Group		
Treatment by dose (mg) of CE or CE/MPA	N	Total Number Hyperplasia Or Cancer[a]	Hyperplasia Rate (%)	N	Total Number Hyperplasia Or Cancer[a]	Hyperplasia Rate (%)
Group A 0.625 mg CE	67	7	10.4	55	8	14.5
Group B 0.625 mg CE/2.5 mg MPA	76	0	0.00	62	0	0.00
Group C 0.45 mg CE	76	5	6.58	67	5	7.46
Group D 0.45 mg CE/2.5 mg MPA	78	0	0.00	66	0	0.00
Group E 0.45 mg CE/1.5 mg MPA	75	0	0.00	69	0	0.00
Group F 0.3 mg CE	74	0	0.00	63	0	0.00
Group G 0.3 mg CE/1.5 mg MPA	83	0	0.00	75	2	2.66
Group H Placebo	79	0	0.00	61	0	0.00

Source: Adapted from Final Report CSR-41303, Tables 9.4.2.2.3A/9.4.2.2.3B, page 136.
[a] Total number of hyperplasias calculated as number of patients with hyperplasia recorded by at least 2 pathologists.

Reviewer's Comments

The occurrence of 30 cases of endometrial hyperplasia, in a study population of 2,153 evaluable subjects after one year of study medication, is not unexpected, and is lower than the reported cases of endometrial hyperplasia in other large, controlled HRT clinical trials. The occurrence of one case of endometrial adenocarcinoma in a polyp in the 0.45 mg CE/1.5 mg MPA treatment group, and one case of endometrial adenocarcinoma in the 0.3 mg CE alone treatment group, in Study 0713D2-309-US do not present serious safety concerns. Furthermore, year 2 data from the 2-year osteoporosis and metabolic substudy for Study 0713D2-309-US presented no additional evidence of endometrial hyperplasia or cancer in any of the combination CE/MPA treatment groups.

Data presented in the submission demonstrates that both the 0.45 mg CE/1.5 mg MPA and the 0.3 mg CE/1.5 mg MPA dosages strengths are successful in protecting the endometrium over the 2-years of treatment in the osteoporosis and metabolic substudy group in Study 0713D2-309-US.

Effects on Uterine Bleeding or Spotting

Bleeding profiles were summarized according to entries recorded by the subject in daily diary cards over the full two years in Study 0713D2-309-US. "Bleeding" was defined as vaginal bleeding requiring sanitary protection. "Spotting" was defined as vaginal bleeding that did not require sanitary protection. "Amenorrhea" was defined as the absence of any vaginal bleeding or spotting during the study period. In the submission, "no bleeding" was defined as the absence of vaginal bleeding regardless of the presence or absence of spotting.

Amenorrhea is the desired endpoint for the effects on uterine bleeding or spotting. The rate of cumulative amenorrhea over time is represented in labeling as the percentage of women in all treatment groups with no bleeding or spotting at a given month through month 12 for the intent-to-treat population using the LOCF approach.

In study year 1, the percentages of subjects in all treatment groups who became amenorrheic and remained so throughout the 13 cycles increased with each consecutive cycle. Overall, subjects in the CE-alone and CE/MPA treatment groups exhibited significantly fewer consecutive cycles of amenorrhea than subjects on placebo. However, only the 0.625 mg CE alone group (Group A) was significantly different from placebo at each analyzed time point.

Across the 8 treatment groups in study year 1, the percentage of subjects with consecutive cycles of amenorrhea for cycles 1 to 13 ranged from 16.6% (0.625/2.5, Group B) to 44.9% (placebo, Group H). See representation below. For cycles 7-13, the percentage of subjects with consecutive cycles of amenorrhea ranged from 31.6% (0.625 alone, Group A) to 53.3% (Placebo, Group H). At cycle 13, the percentage of cumulative amenorrhea cycles ranged from 44.0% (0.625 alone, Group A) to 69.3% (Placebo, Group H).

At the start of treatment (cycles 1-13), all of the CE/MPA combination groups (except Group B) had significantly smaller percentages of subjects exhibiting consecutive cycles of amenorrhea versus the corresponding CE alone groups:

Group A vs. Group B		Group C vs. Group D or Group E			Group F vs. 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
22.1%	16.6%	38.5%	25.6%	29.9%	43.9%	33.0%	44.9%

By cycles 7-13, similar percentages of subjects exhibited consecutive cycles of amenorrhea between the CE and CE/MPA combination treatment groups, especially Groups B:

Group A vs. Group B		Group C vs. Group D or		Group E	Group F vs. 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
31.6%	32.6%	50.6%	41.5%	42.3%	53.1%	46.6%	53.3%

By cycle 13, however, the percentages of subjects with amenorrhea in the CE/MPA groups were greater or near equal to that in the corresponding CE alone groups:

Group A vs. Group B		Group C vs. Group D or		Group E	Group F vs. 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
44.0%	62,2%	62.4%	66.2%	62.8%	67.8%	67.6%	69.3%

Reviewer's Comments

These findings are not unexpected. As the dosage strength of CE alone decreased the percentages of subjects with cumulative amenorrhea increased. In the active treatment groups (Groups A - G), the percentage of subjects exhibiting cumulative amenorrhea increased with decreasing dosages of CE. The highest CE alone dosage strength (0.625 mg) exhibited fewer cycles of cumulative amenorrhea than the 0.45 mg and 0.3 mg dosage strengths. The lowest CE alone dosage strength (0.3 mg) and placebo were not different at any time point analyzed.

At the start of treatment, all of the CE/MPA combination dosage strengths had significantly smaller percentages of subjects exhibiting consecutive cycles of amenorrhea versus the corresponding CE alone dosage strengths (16.6% vs. 22.1%; 25.6% and 29.9% vs. 38.5%; and 33.0% vs. 43.9%, respectively). By cycle 13, the lower dose CE/MPA dosage strengths (Groups D, E and G) had similar percentages of subjects with cumulative amenorrhea versus the corresponding CE alone dosage strengths (62.2% and 62.8% vs. 62.4%; 67.6% vs. 67.8%, respectively), while Group B (0.625/2.5) was now higher than Group A (0.625). The 0.3 mg CE/1.5 mg MPA dosage strength and placebo were not different at cycle 13 (67.6% vs. 69.3%).

In this submission, by cycle 13 in the osteoporosis and metabolic substudy group ITT-1 population (749 subjects), the percentages of substudy subjects with amenorrhea in the CE/MPA groups were similar or greater than the corresponding CE alone groups:

Group A vs. Group B		Group C vs. Group D or		Group E	Group F vs. 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
53.6%	62.8%	58.9%	70.8%	60.6%	70.8%	69.4%	72.3%

By cycle 26 in the osteoporosis and metabolic substudy group ITT-1 population (595 subjects), the percentages of substudy subjects with amenorrhea in the CE/MPA groups continued to be greater than the corresponding CE alone group with the exception of the 0.45 mg CE/1.5 mg MPA group. However, the result in the 0.45/1.5 treatment group (Group E) was similar to the result in the 0.625/2.5 treatment group (Group B):

Group A vs. Group B		Group C vs. Group D or		Group E	Group F vs. 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
43.1%	60.0%	64.9%	74.7%	56.0%	71.2%	84.8%	80.0%

Reviewer's Comments

At cycle 13, the findings in the osteoporosis and metabolic substudy group alone were similar to the findings of the basic study group, which included the substudy subjects. In both the basic and substudy groups of subjects, the highest CE alone dosage strength (0.625 mg) exhibited fewer cycles of cumulative amenorrhea than the 0.45 mg CE alone and 0.3 mg CE alone dosage strengths. Likewise, by cycle 13 in the osteoporosis and metabolic substudy, the two lower dosage strengths of CE/MPA (Groups E and G) had similar percentages of subjects with cumulative amenorrhea versus the corresponding CE alone dosage strengths (60.6% vs. 58.9% and 69.4% vs. 70.8%, respectively).

However, by cycle 26, the findings in the osteoporosis and metabolic substudy group show that both the 0.625 mg CE/2.5 mg MPA (Group B) and the 0.3 mg CE/1.5 mg MPA dosage strengths (Group G) reported larger percentages of subjects with cumulative amenorrhea versus the corresponding CE alone dosage strengths (60.0% vs. 43.1% and 84.8% vs. 71.3%), while the 0.45 mg CE/1.5 mg MPA dosage strength (Group E) showed a slightly lower percentage of subjects with cumulative amenorrhea versus the corresponding CE alone dosage strength (56.0% vs. 64.9%).

Overall, for cycles 14 to 26 in year 2 of Study 0713D2-309-US, subjects in each active treatment group had fewer consecutive cycles of amenorrhea then subjects in the placebo treatment group with the exception of subjects in Group G (0.3 mg CE/1.5 mg MPA). By cycle 26, the 0.3 mg CE/1.5 mg MPA dosage strength had a slightly higher percentage of subjects with consecutive cycles of amenorrhea than placebo (84.8% and 80.0%, respectively).

Data presented in the submission demonstrates that the 0.3 mg CE/1.5 mg MPA dosage strength exhibited a greater percentage of consecutive cycles of amenorrhea than the approved Prempro™ 2.5 at cycle 26. The 0.45 mg CE/1.5 mg MPA dosage strength exhibited similar consecutive cycles of amenorrhea as the approved Prempro™ 2.5 at cycle 26.

2.4. Dosing, Regimen, and Administration

Prempro™ 2.5, Prempro™ 5, and Premphase® are approved for continuous oral administration, one tablet daily. Daily continuous oral administration of the 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA dosage strengths is recommended.

2.5. Labeling

The proposed labeling submitted was modified in accordance with the proposed revisions to the "Labeling Guidance for Noncontraceptive Estrogen Drug Products – Prescribing Information for Healthcare Providers and Patient Labeling" as published in the **Federal Register**, Vol. 64, No. 186, September 27, 1999, Notices.

Reviewer's Comments

A revised drug label is attached to this consultation. The revised drug label incorporates labeling modification forwarded to the Sponsor on April 13, 2001 for NDA 20-527/S-017, and proposed revisions to the "Labeling Guidance for Noncontraceptive Estrogen Drug Products – Prescribing Information for Healthcare Providers and Patient Labeling" as published in the Federal Register, Vol. 64, No. 186, September 27, 1999, Notices.

Please have the Clinical Pharmacology and Pharmacokinetics Reviewer validate the corrected numbers in Table 1 under the Pharmacokinetic subsection.

Please have the Medical Officer address the selection of the 0.45 mg CE/1.5 mg MPA dosage strength as the starting dose for the prevention of postmenopausal osteoporosis.

54 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

Theresa Van Der Vlugt
6/7/02 05:50:23 PM
MEDICAL OFFICER

Shelley Slaughter
6/10/02 11:49:30 AM
MEDICAL OFFICER
I concur.

Daniel A. Shames
6/11/02 01:53:32 PM
MEDICAL OFFICER

MEDICAL REVIEW

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

Application #: NDA#21-396 **Application Type:** NDA

Sponsor: Wyeth **Proprietary Name:** Prempro™ Premphase®

USAN Name:

Pharmaceutical Category: conjugated estrogen/progestin

Route of Administration: tablets, oral

Indication: prevention of postmenopausal osteoporosis

Dosage: CE/MPA ——— ——— 0.45mg/1.5mg, and 0.3mg/1.5mg

Reviewer: Bruce S. Schneider, MD **Dates of Review:** March 1, 2002 – June 1, 2002

Medical Safety Review: Theresa Van Der Vlugt, MD
Chemistry Review: NA
Pharmacology Review: NA
Biopharmaceutics Review: NA
Statistics Review: 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) lower than 0.625mg, combined with medroxyprogesterone acetate (MPA), 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 (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 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 (2.51% in two years). In contrast, all active-treatment groups had mean BMD increases, ranging from 1.33% to 3.48% ($p<0.001$ 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 of 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 and CE/MPA in prevention of premenopausal bone loss, while maintaining an acceptable metabolic profile. A separate safety review has been conducted by DRUDP (HFD-510).

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION: N drive location:

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

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

XXX **Approve**

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

Medical Team Leader: _____ **Date:** _____

Table of Contents

Executive Summary

I. Recommendations

A. Recommendation of Approvability: Approve
B. Recommendation on Phase 4 Studies and Risk Management Steps: None

II. Summary of Clinical Findings

A. Brief overview of clinical program

This review concentrates on the efficacy outcomes of the two-year metabolic sub-study of the sponsor's HOPE Trial. The overall purpose of the trial was to determine whether doses of conjugated estrogens (CE) lower than 0.625 mg,

[1] The safety review has been conducted by DRUDP, HFD-510

combined with MPA, are effective in reducing bone loss and the incidence of endometrial hyperplasia in postmenopausal women while maintaining efficacy in the relief of menopausal symptoms and acceptable bleeding and metabolic profiles. The results of this study will be important to clinical practice, in that they will allow physicians to use the lowest HRT doses that are effective for specific indications in individual women.

The main study consisted of two parts: a one-year basic study and a two-year osteoporosis and metabolic sub-study. The studies employed a randomized, placebo-and active-controlled, parallel group, multicenter design. Subjects were randomly assigned to one of eight treatment groups (seven active-treatment groups and placebo), 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 given 600mg elemental calcium supplementation/day. The one-year basic study enrolled 2,805 subjects, and a sub-set of 822 individuals (all postmenopausal women, 40-65 years of age) entered the two-year sub-study. The primary objectives of the basic study were to determine the efficacy of various CE and MPA regimens in reducing the incidence of estrogen-associated endometrial hyperplasia and relieving menopausal vasomotor symptoms. In addition, maturation of the vaginal epithelium was assessed as an indicator of estrogen effects on vaginal atrophy. Results for the 1-year basic study have been reviewed by DRUDP (HFD-580).

The primary objective of the metabolic sub-study was to determine the effects of various CE/MPA regimens on lumbar spine BMD over a two-year period. Doses of CE, CE/MPA, and calcium were as described above. Secondary objectives included 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.

B. Efficacy

The metabolic sub-study clearly demonstrated that all doses of CE alone and CE/MPA, 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 1.49%. In contrast, women treated with 600mg calcium plus any of the seven active treatment regimens had mean annualized lumbar spine BMD increases ranging from 0.76% in those treated with 0.3 mg CE alone to 2.03% in women treated

with CE 0.625mg/MPA 2.5mg (slope analysis). Of interest, the 0.3mg/1.5mg group had an annualized increase of 0.92%. When calculated as percent change from baseline to cycle 26, the results were similar, with BMD increases ranging from 1.33% in the lowest dose of CE alone to 3.48% in the group receiving 0.625mg/2.5mg. The placebo group lost 2.51% in this analysis. All comparisons with placebo were statistically significant ($p<0.001$ for all comparisons). All within-group changes from baseline were statistically significant ($p<0.001$ for all eight within-group comparisons, including placebo. Of note, the mean increases in BMD were generally greater for the CE/MPA combination groups than for each comparable CE-alone group.

Similar results were obtained for the BMD endpoints at the other three skeletal sites; the statistical comparisons between CE/MPA 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.

By-cycle analysis (cycles 6, 13, 19, and 26) showed clear divergence between all active-treatment groups and placebo by cycle 6 at the lumbar spine and by cycle 13 at the other three skeletal sites.

The study was not powered to detect significant differences between active-treatment groups. However, ninety-five percent confidence intervals on the differences between groups (based on annualized change in BMD derived from the slope analyses) showed no differences between a CE-alone group and the corresponding CE/MPA-combination group(s). Within the combination groups, differences favoring the 0.625 mg/2.5 mg group over both the 0.45 mg/1.5 mg and the 0.3 mg/1.5 mg groups were seen in total body and lumbar spine BMD. There was also a difference favoring the 0.45 mg/2.5 mg group over 0.3 mg/1.5 mg at the lumbar spine.

Confirming the efficacy of all doses of CE/MPA, the sponsor noted substantial and highly 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 ($p<0.001$ for all 56 comparisons with placebo).

The sponsor carried out a detailed analysis of multiple parameters related to lipid metabolism [Total-C, LDL-C, HDL-C, VLDL-C, TG, and Lp(a)]. The results of this analysis 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 and CE/MPA. There were increases in total-C in the placebo group. After two years of treatment, all active-treatment groups had increases in HDL-C

(ranging from 8.5-18.8%). All these were statistically significantly greater[2] than the 3.8% increase seen in placebo. For LDL-C, there were mean percent decreases from baseline (0.5-8.2%) that were statistically significantly different from placebo at most cycles. By two years, LDL-C increased in the placebo by 7.1%. For TG, there were statistically significant increases from baseline in all active-treatment groups, in the range 17-40% (the largest increases were in association with the highest doses) by two years, compared to an increase of 5.5% in placebo. During the trial, there were statistically significant mean percent decreases in the ratio LDL-C/HDL-C in all active-treatment groups, whereas there was no statistically significant change in placebo. These changes were all statistically significant, compared to placebo, at all cycles, and for all treatment groups.

In this trial, there was no deterioration in carbohydrate metabolism or in measured parameters relating to clotting and fibrinolysis.

Overall, the data support the efficacy of low doses of CE, with or without MPA, in preventing bone loss of bone mineral density in postmenopausal women.

C. Safety

A complete review of safety has been completed by DRUDP, HFD-580.

D. Dosing

The data support the use of CE alone and CE/MPA in this dose range for this indication. The lowest effective dose of estrogen or estrogen/progestogen should be used.

E. Special populations

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

Clinical Review[3]

I. Introduction and Background

[2] See my comments regarding use of p-values and attribution of statistical significance to lipid (and other secondary) data.

[3] Many of the tables and figures have been reproduced from the sponsor's submission. Tables and figures that are the reviewer's are so indicated. Reviewer's comments appear in **bold** text.

A. Drug: conjugated equine estrogens [CE (AY-011152)], medroxyprogesterone acetate [MPA (AY-011236)]. Product name Premarin, Prempro,

Pharmacological category: estrogen, progestin, sex steroids.

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

Proposed indication: prevention of postmenopausal osteoporosis.

Dose: CE oral tablets of 0.625 mg, 0.45 mg, and 0.3 mg. CE/MPA oral tablets of 0.625 mg/2.5 mg, 0.45 mg/2.5 mg, 0.45 mg/1.5 mg and 0.3 mg/1.5 mg.

Age groups: postmenopausal women between ages 40 and 65 years.

B. Background:

Hormone replacement therapy with estrogen effectively treats menopausal symptoms that are associated with estrogen deficiency. In addition, HRT may offer other benefits, such as prevention of loss of bone mineral. Other potential benefits include cardioprotection and maintenance of normal cognitive function, although there are no clinical data that support such actions of HRT. The major risk of HRT therapy is promotion of endometrial cancer; in addition, there is observed or potentially increased risk of gallbladder disease, breast cancer, and thromboembolic events. Although there are no definitive data linking HRT to increased breast cancer risk, use of HRT is contraindicated in women with known or suspected cancer of the breast.

In a postmenopausal woman with an intact uterus, the use of unopposed estrogen is clearly associated with an increased risk of endometrial hyperplasia and cancer. There is abundant clinical evidence that, in such women, the use of a progestin (sequentially or continuously) is effective in reducing the incidence of endometrial hyperplasia without attenuating the efficacy of the estrogen in reduction of menopausal symptoms (or, in several studies, in prevention of bone loss).

Most of the clinical safety and efficacy data related to Premarin are derived from subjects treated with 0.625 mg 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.

Comments: This issue is certainly relevant. It is important to know the least effective dose of estrogen for bone preservation as well as for relief of menopausal symptoms. There is reason to believe that lower doses of estrogen will diminish the risk of known and potential adverse events.

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 osteoporosis sub-study. The first trial enrolled 2,805 subjects. This study examined the safety and efficacy of various CE and MPA regimens in reducing postmenopausal vasomotor symptoms and preventing endometrial hyperplasia (the primary endpoint). A detailed analysis of endometrial safety was included in this trial, which has been reviewed in its entirety by DRUDP (HFD-580).

Of the 2,805 postmenopausal women who were originally enrolled, 822 remained on treatment for a second year. During this year, the sponsor investigated the safety and efficacy of the various CE and 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. The uterine and overall safety profiles associated with two years of treatment with the various CE and CE/MPA regimens are reviewed by DRUDP.

State of armamentarium for indication: Numerous estrogen and estrogen-progestin combinations have been approved for prevention of postmenopausal osteoporosis; formulations include both oral and transdermal patches. While all products have been approved for menopausal symptoms, not all products have received approval for prevention of osteoporosis. The sponsor's Premarin (CE 0.625 mg), Prempro (continuous CE 0.625 mg/MPA 2.5 mg) and Premphase (CE 0.625, with sequential MPA 0.50 mg) are among the preparations that have been approved for this indication.

Other drugs used to prevent and treat postmenopausal osteoporosis include the bisphosphonates (alendronate and risedronate), raloxifene (a SERM), and nasal salmon calcitonin. All approved drugs are anti-resorptive agents: they are anti-catabolic to bone. There are no approved bone anabolic agents at the time of this writing.

II. Clinically relevant findings from chemistry, toxicology, microbiology, biopharmaceutics, statistics, and other sources:

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 from the women who participated in the two-year sub-study were submitted in NDA#21-396 and reviewed.

V. Clinical review methods

The data were reviewed independently (by the medical officer). In addition, there were numerous meetings with the statistical reviewer, as well as with staff in DRUDP (HFD-580). The efficacy review will concentrate on the proposed labeling claims for the prevention of osteoporosis, [redacted] The review of safety has been done by HFD-580.

VI. Review of efficacy

The following is a review of clinical trial # 0713D2-309-US.

VI.1: Study design: This was a randomized, placebo- and active-controlled, prospective, parallel-group, multicenter (outpatient) study of the safety and efficacy of various doses of CE and MPA. Subjects (healthy postmenopausal women) were randomly assigned to receive one of eight regimens of CE alone, CE/MPA, or placebo over a period of 24 months (26 cycles of 28 days each).

VI.2: Objectives:

The primary objective of the osteoporosis and metabolic sub-study was *"to evaluate the safety and efficacy of lower doses of CE and MPA in preventing postmenopausal bone loss compared with placebo."* A secondary objective was *"to evaluate the possible effects of study medication on lipid and glucose/insulin metabolism and on coagulation."*

VI.3 Population:

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 ≥ 30 IU/L and 17β-estradiol ≤ 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.
- 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.

Exclusion criteria:

These are listed by the sponsor and presented verbatim:

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 . reference population database.

Comments: These are reasonable inclusion/exclusion criteria for this type of study. It should be noted that subjects who meet these criteria are very healthy, normotensive, non-diabetics, and that the adverse event profile will represent the impact of the drug(s) on this population. Mandating that a woman in the sub-study have her last menses not longer than four years prior to the trial may increase the therapeutic effect of the drug on bone loss (accelerated bone loss occurs soon after estrogen withdrawal).

VI.4 Procedures, treatments:

The sponsor provides a complete description of study procedures, treatments, diagnostic evaluation methods, and concomitant medication rules.

Comments: Methodology and quantitative data for patient recruitment (e.g., number of subjects contacted, number screened, number accepted, reasons for rejection) are not provided. This information is generally lacking from new drug applications and efficacy supplements for this therapeutic indication. Guidelines for osteoporosis studies should emphasize the importance of including recruitment data.

During the first visit, the investigators obtained a complete medical history, with special attention devoted to reproductive and obstetrical history. Subjects were given daily diary cards to record bleeding episodes and severity of hot flushes.

At Visit 2, subjects were given a complete physical examination, including breast and pelvic examinations. A mammogram was performed at this time unless the subject could provide a copy of results of mammography done within the past six months. A Pap smear with vaginal maturation index and an endometrial biopsy were also done at Visit 2. At this time a battery of screening blood tests, including hormone assays (see above), was obtained.

Subjects in the sub-study had to wait for 12 weeks between Visits 1 and 2, if there had been prior estrogen, progestin, or androgen therapy. In addition to the above procedures, all subjects in the sub-study had determination of BMD of the AP lumbar spine (L2-L4), femoral neck and trochanter, and total body. BMD was measured by dual energy x-ray absorptiometry [redacted] These pre-study scans were performed at Visits 2 and 3, not more than three weeks apart. The two pre-study scans of the lumbar spine had to differ by < 5%; otherwise a third pre-treatment scan was performed. In this case, of the three scans, the two closest to the mean of the three were reported if they were within 5% of each other. No more than three scans were done in order to meet this inclusion criterion.

Other measurements included serum osteocalcin and urine calcium, creatinine, and N-telopeptide. Additionally, blood was obtained for coagulation tests, TSH levels, measures of carbohydrate metabolism, and lipid profiles.

Determination of eligibility for enrollment into the trial was based on evaluation of results from the first three visits (including evaluation of BMD by the central reading facility). Subjects meeting all criteria were randomized to receive one of eight treatment regimens (described below).

Treatment medication:

Treatment medication consisted of two tablets daily, plus calcium supplementation (600 mg elemental calcium), all taken at the same time each day. Subjects were also given daily diary cards. If a subject failed to take her study medication or calcium on a particular day, she was to record this on her diary card and take the next day's medication on schedule.

The sponsor employed a double-dummy design with eight possible regimens.

Regimen	Dose (mg)	
	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.

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Note that the dose selection was based on the 1995 FDA HRT Working Group *"Guidance for Clinical Evaluation of Combination Estrogen/Progestin-Containing Drug Products Used for Hormone Replacement Therapy of Postmenopausal Women."* The study was undertaken, in part, to satisfy a phase 4 commitment to determine the lowest effective dose of CE/MPA for prevention of osteoporosis. The 2.5 mg MPA dose is currently the lowest dose approved to reduce the incidence of endometrial hyperplasia in women with an intact uterus who receive 0.625 mg CE.

The sponsor presents a schedule of procedures in the following table:

Appears This Way On Original

	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 quality-of-life questionnaire			X				X		X		X		X	
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	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.

VI.4.1 Protocol amendments:

The protocol was amended on January 12, 1999. Preliminary summary data, by treatment group (but not by individual patients) would be provided confidentially to investigators from the NIH and others conducting the Women's Health Initiative. The information consisted of pre-study and Cycle 6 data on lipids, fibrinogen, factor VIII, and other blood parameters. No osteoporosis-related data were transmitted.

VI.4.2 Removal of patients from therapy and/or assessment:

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.

For patients in the osteoporosis sub-study group, the investigator was to obtain a serum osteocalcin level, carbohydrate coagulation, and lipid determinations, and urinary NTx/Cr. Two BMD measurements of the lumbar spine, femoral neck, and trochanter were obtained, approximately 1-2 weeks apart, if the patient had participated for 13 or more cycles.

VI.4.3 Concomitant therapy:

Patients in the sub-study were not to have taken any compounds containing estrogen, progestin, or androgen within a minimum of 12 weeks of screening. During the study, all subjects received supplementation with calcium (600 mg/day as elemental calcium). Other medications were prohibited throughout the study, without the permission of the investigator. All concomitant medications were to be recorded in the CRFs. Patients were permitted to use up to two anti-hypertensive medications. Vitamin D could be continued for those who had an established use of ≤ 400 IU/day, but higher doses of the vitamin were prohibited.

Comments: This is substandard medical therapy for postmenopausal women, who generally require 1200 mg elemental calcium plus at least 400 IU of vitamin D per day. The absence of vitamin D supplementation will in theory enhance the anti-resorptive effect of the drug, relative to placebo.

Prohibited therapies included, high doses of calcium or vitamin D, long-term use of medication that might alter mineral metabolism, the use of aspirin during two weeks prior to blood sampling, use of diuretics, calcitonin, therapeutic fluoride, anti-thyroid drugs, and bisphosphonates. Daily use of NSAIDs was also prohibited.

VI.4.4 Efficacy measurements:

For the osteoporosis sub-study, the following are listed as efficacy variables: assessment of bone loss, endometrial biopsies, vasomotor symptoms, and vaginal maturation index (VMI). The incidence of endometrial hyperplasia, which was the primary efficacy outcome variable in the one-year study, became a secondary outcome variable in the two-year sub-study.

The primary efficacy outcome variable for the two-year sub-study was change in AP lumbar spine (L2-L4) BMD. The sponsor also measured BMD changes at the femoral neck, trochanter, and total body. The primary analytical endpoint for BMD changes was cycle 26. BMD measurements were obtained at baseline, and again at cycles 6, 13, 19, and 26. At cycle 26, two BMD measurements were performed, 7-14 days apart. For patients who participated in the study for 13 or more cycles and then discontinued treatment, two final BMD measurements were to be obtained 7-14 days apart.

Quality control: The [redacted] served as the Bone Quality Control Center for BMD analysis. The BQCC evaluated scan quality and performed all scan analyses. The BQCC also monitored the quality assurance of the [redacted] densitometers, in collaboration with [redacted]

[redacted] Daily or weekly calibrations were performed at each study site using the

[redacted] was used for calibration across sites. Further details regarding quality control, including control of total body BMD measurements, are provided in the NDA.

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 were evaluated as part of the two-year sub-study. [redacted]

[redacted]

Relief of vasomotor symptoms was evaluated as in the overall study, by measuring the number and severity of hot flushes. Endpoints included the average daily number and severity of hot flushes, as recorded by the patients on their 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 vaginal maturation index (VMI), which is the proportion of vaginal superficial cells/parabasal and intermediate cells, obtained in a lateral vaginal wall smear.

The incidence of endometrial hyperplasia was assessed by endometrial biopsy, as in the overall study. All endometrial biopsies were read by two pathologists. A patient was considered to have hyperplasia if both of the primary pathologists agreed on this diagnosis. In the event that the pathologists disagreed, a third pathologist was consulted. The final decision regarding designation of hyperplasia was based on the majority opinion. An additional pathologic examination was done at cycle 26. The names and affiliations of the participating pathologists are listed in the NDA.

The analysis of metabolic profiles consisted of laboratory determination of lipids, coagulation parameters, and by an oral glucose tolerance test. As indicated in the table above, these determinations were to be done at the pre-study visits and during cycles 6, 13, 19, and 26.

The lipid profile, performed at the [redacted] consisted of total-C, HDL-C, LDL-C, very low-density lipoprotein cholesterol (VLDL-C), TG, VLDL TG, HDL2-C, HDL3-C, apolipoprotein A1, apolipoprotein B, LDL apolipoprotein B, Lp(a), and Lp(a) phenotype (pre-study only).

For the 3-hour GTT, ——————— serum glucose and insulin were measured fasting and 30 minutes, 1 hour, 2 hours, and 3 hours after oral administration of 75 grams of glucose.

Coagulation ——————— profile consisted of PT/PTT, fibrinogen activity, factor VIII activity, antithrombin III activity, protein C activity, protein S activity, plasminogen activity, PAI-1 activity, PAI-1 antigen, and tissue-type plasminogen activator (t-PA) antigen.

VI.4.5 Safety measurements:

The investigators monitored safety with medical histories, physical examinations (including gynecological examinations), and laboratory determinations.

The gynecological examinations included breast and pelvic examinations, mammography, Pap smear, and endometrial biopsy. The basic laboratory safety screen included hematology, chemistry, and urinalysis. Subjects who participated in the osteoporosis sub-study also had coagulation, carbohydrate, and lipid evaluations. The scheduling of all safety assessments is presented in the table above.

Definitions of adverse events are included in the NDA. Details regarding the conduct of laboratory tests, the central laboratories, and preparation and storage of samples are also provided.

Comments: These procedures are standard and appear to be adequate for general safety monitoring in the trial population.

Additional studies included analyses of bleeding patterns, metabolic profiles, and quality of life indicators. The methodologies for these determinations are provided in detail in the NDA (section 7, Other Analysis Methods). For analyses of bleeding and amenorrhea, the sponsor defined efficacy evaluable (EE) and intent-to-treat (ITT) populations. For the amenorrhea and vaginal bleeding analyses, the sponsor defined five different analytical populations (details in the NDA; this section is reviewed by DRUDP).

Note that assessment of endometrial hyperplasia (by endometrial biopsy) was used as a surrogate endpoint for endometrial cancer in this study. This is in accordance with above-mentioned 1995 FDA HRT Working Group "Guidance for Clinical Evaluation of Combination Estrogen/Progestin-Containing Drug Products Used for Hormone Replacement Therapy of Postmenopausal Women." This guidance provides requirements for demonstration of efficacy in preventing endometrial hyperplasia for HRT products. Endometrial hyperplasia, a condition that predicts the development of endometrial cancer, is the only accepted

surrogate endpoint for this malignancy. Endometrial biopsy is the standard method for evaluation of endometrial hyperplasia.

VI.4.6 Statistical considerations:

A separate review is provided by Biometrics.

For the two-year sub-study, the primary efficacy endpoint was the ability of lower doses of CE and MPA to prevent bone loss. Secondary endpoints included BMD at the femoral neck, trochanter, and total body; biochemical indices of bone metabolism; prevention of endometrial hyperplasia; relief of vasomotor symptoms; and changes in the vaginal maturation index. Other assessments included laboratory profiles, bleeding variables, vital signs, clinical and laboratory adverse events, and quality of life.

Analysis of primary endpoint: The primary measure of bone loss was BMD of the AP lumbar (L2 to L4) spine. In the event that one of these vertebrae was abnormal, L1 was measured in its place throughout the study.

For each patient, an estimate of the annual BMD change as a percentage of baseline was calculated by performing a linear regression on BMD values over the time of the study. The slope of the regression line (representing BMD change/day) was multiplied by 365, to yield the annual rate of change in BMD. This was then divided by the baseline BMD value to give the annual change as a percentage of baseline. The baseline BMD value was defined as the average of the pre-study measurements. If there were more than two measurements at baseline, the value was the average of the two that were within 5% of each other. and closest to the mean of all the scans at baseline. The percent annual changes were examined by analysis of covariance (ANCOVA) with time since menopause and weight included as covariates. Both treatment and investigational site were included as factors in the analysis.

In addition to the slope analysis, the sponsor analyzed the percent change from baseline at the final evaluation for each patient.

For analysis of efficacy of each CE/MPA dose, all tests of significance were 2-sided at the 0.05 level. The sponsor states that "no adjustment to the alpha-level due to multiple comparisons was necessary because of the sequential manner of testing that was done for a limited number of pairwise comparisons."

In this sequential plan, the BMD response was compared with placebo at each of the 3 CE/MPA doses. These comparisons began with the highest dose of CE (0.625) and proceeding to the next lower dose only if the comparison was significant at the 0.05 level (if the comparison of the CE/MPA combination versus placebo was significant at the 0.05 level, then CE alone was subsequently compared with placebo).

The sequence was :

1) CE 0.625 + MPA 2.5 versus Placebo
2) CE 0.45 + MPA 2.5 versus Placebo
3) CE 0.45 + MPA 1.5 versus Placebo
4) CE 0.3 + MPA 1.5 versus Placebo

The sponsor also used the same sequential rules in the analysis of the following doses of CE alone vs placebo:

1) CE 0.625 versus Placebo
2) CE 0.45 versus Placebo
3) CE 0.3 versus Placebo

Comments: The sponsor presents no justification for using the annualized BMD changes, based on regression analysis, as the primary analytical modality. The BMD responses to anti-resorptive agents are almost universally non-linear, with the maximum slope occurring early in treatment (generally within the first six months of therapy). Generally, there is very little "wobble" in BMD measurements in a treatment group over time. If a group responds to therapy, the population mean tends to rise monotonically over the period of observation, with no evidence of loss of BMD at an intermediate time point. The same is true of placebo groups that lose BMD over time, except that the BMD at any time point is generally less than that observed during the preceding time point. This response pattern is different from that observed during treatment of obesity, hypertension, or depression, in which there is much more lability inherent in the responses.

Of equal concern, this approach is not based on an ITT analysis. The primary analytical endpoint of this type of study should be the treatment-related differences at two years, using a true ITT population with LOCF. The use of the slope analysis requires a modified ITT population, which includes only those patients ("evaluable patients") who have had a baseline and at least two post-baseline measurements. This means that the analysis will include only those who have remained on study drug for at least one year. The sponsor also performed a supplemental analysis that included all subjects who had a baseline and at least one post-baseline BMD evaluation. However, this was also based on a slope analysis, using available observations for patients who dropped out.

Any labeling claims, including presentation of specific p-values, should be based on a true ITT analysis, with LOCF, using the two-year percent change in BMD as the efficacy variable.

The sponsor's treatment of the multiple dose comparisons is acceptable. If all comparisons with placebo turn out to be statistically significant, this mitigates concerns regarding this handling of multiple endpoints. However, p-values should be calculated on the basis of an ITT population, using LOCF, with the two-year time point data used as the primary comparison.

Statistical analysis plans for evaluation of biochemical indices of bone metabolism, endometrial hyperplasia, VMS, VMI, metabolic profiles, bleeding profiles, and HRQOL outcomes are also provided. For lipid profiles, the sponsor used a sequential analysis for multiple comparisons that was similar to that described above.

The sponsor also provides a power analysis for detection of BMD differences at the lumbar spine as the primary outcome variable. In addition, the sub-study was designed to have adequate power to detect statistically significant treatment-related differences in BMD at the femoral neck. There is no statement regarding power to detect treatment-related changes in total body BMD.

Comments: The description of the statistical analysis plan is often unclear and inconsistent. One may assume that all measurements with the exception of lumbar spine BMD are counted as secondary analyses. However, the order of importance of these analyses, and even the categories to which they are assigned, are inconsistent. For example, in the hierarchy of secondary endpoints, biochemical indices of bone turnover are included immediately after the BMD results,

In consultation with Biometrics, the Division has worked out an approach for dealing with these problems in labeling.

VI.5 Efficacy outcomes

VI.5.1 Populations analyzed

A total of 822 patients were randomized to receive one of the eight treatments in the two-year sub-study. Of these, 749 received at least one dose of study drug (281 received CE, 374 received CE/MPA, and 94 received placebo).

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).

In addition, 22 other patients were not included in any safety analysis because no diary cards were returned. Thus there was no documentation of receipt of study medication for these individuals. Summary data are presented for these patients in the NDA (Attachment 2 of the submission).

VI.5.1.1 Withdrawals: Of the 749 subjects randomized to one of the eight treatment groups and recorded as taking study medication, 519 completed, and 230 withdrew from the 2-year sub-study. In the following two figures, the sponsor presents the disposition of patients, by dose group.

FIGURE 8.1A. DISPOSITION OF EVALUABLE PATIENTS IN SUBSTUDY

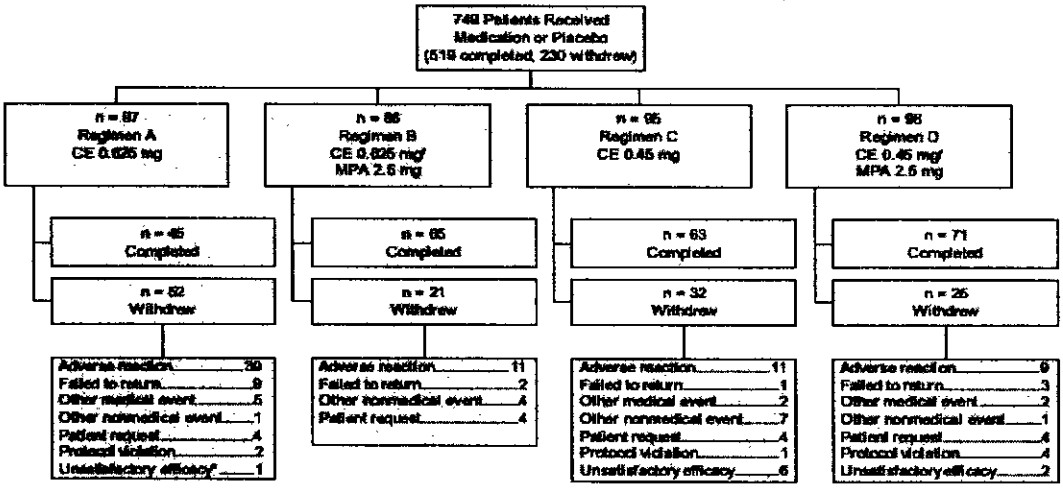
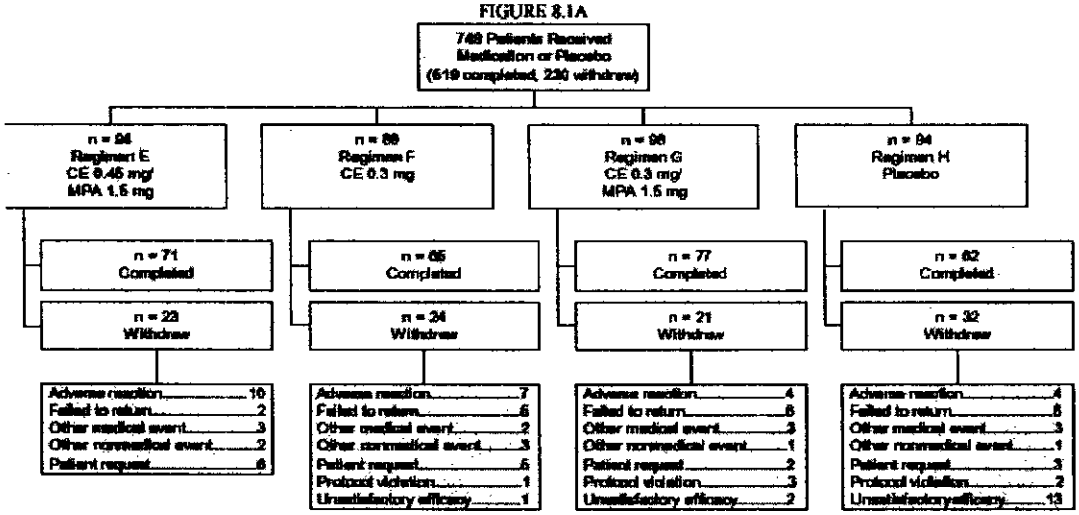


FIGURE 8.1A



*Unsatisfactory efficacy refers to development of endometrial hyperplasia, increased vasomotor symptoms, or annualized loss of > 7.5% in lumbar spine BMD.
Data from CDRs 1-6, 3-4, and 3-5.

Patients who developed endometrial hyperplasia were withdrawn from the study and given follow-up treatment. The category "unsatisfactory response - efficacy" refers to those who withdrew because of endometrial hyperplasia, increased vasomotor symptoms, or because of an annualized lumbar spine BMD loss > 7.5%[4].

As shown in the tables, 230 (31%) of the 749 subjects withdrew from the study. Adverse events were the most common reason for discontinuation, with 86 (11%) of the 749 patients withdrawing for this reason.

Statistically significant ($p < 0.001$) differences among groups were found in the numbers who withdrew for any reason, because of adverse events, and because of an unsatisfactory efficacy response.

Group A (CE alone, 0.625 mg) had the highest percentage (54%) of patients who discontinued for any reason and the highest percentage of patients (31%, 30/97).

[4] One subject, # 30918-0183, had an annualized lumbar spine BMD loss of 8.1% at cycle 13 and withdrew. This patient was in the placebo group. According to the protocol, patients with annualized loss of lumbar spine BMD > 7.5% were to be informed of the change and offered the option of withdrawing.

who withdrew because of AEs. Predictably, the highest number of patients who withdrew because of lack of efficacy was in the placebo group (14%).

The sponsor has tabulated the number of patients who discontinued, by treatment cycle, as well as all reasons for discontinuation sponsor's table below). All safety-related discontinuations are described and discussed in the section Safety-Related Discontinuations.

TABLE 8.1.1A. NUMBER (%) OF PATIENTS WITHDRAWN FROM SUBSTUDY BY TREATMENT GROUP (PRIMARY REASONS FOR WITHDRAWAL)

Primary Reason	Group A 0.625 (n = 97)	Group B 0.625/2.5 (n = 86)	Group C 0.45 (n = 95)	Group D 0.45/2.5 (n = 96)	Group E 0.45/1.5 (n = 94)	Group F 0.3 (n = 89)	Group G 0.3/1.5 (n = 98)	Group H Placebo (n = 94)	Total n = 749	Chi-square p-Value
Total	*52 (54)*	*21 (24)*	*32 (34)*	*25 (26)*	*23 (24)*	*24 (27)*	*21 (21)*	*32 (34)*	*230 (31)*	*<0.001*
Adverse events	30 (31)	11 (13)	11 (12)	9 (9)	10 (11)	7 (8)	4 (4)	4 (4)	86 (11)	<0.001
Failed to return	9 (9)	2 (2)	1 (1)	3 (3)	2 (2)	5 (6)	6 (6)	6 (6)	34 (5)	0.103
Other medical event	5 (5)	0	2 (2)	2 (2)	3 (3)	2 (2)	3 (3)	3 (3)	20 (3)	0.633
Other nonmedical event	1 (1)	4 (5)	7 (7)	1 (1)	2 (2)	3 (3)	1 (1)	1 (1)	20 (3)	0.059
Patient request	4 (4)	4 (5)	4 (4)	4 (4)	6 (6)	5 (6)	2 (2)	3 (3)	32 (4)	0.892
Protocol violation	2 (2)	0	1 (1)	4 (4)	0	1 (1)	3 (3)	2 (2)	13 (2)	0.322
Unsatisfactory response -- efficacy[a]	1 (1)	0	6 (6)	2 (2)	0	1 (1)	2 (2)	13 (14)	25 (3)	<0.001

a: Unsatisfactory response - efficacy refers to patients who withdrew because of endometrial hyperplasia, increased vasomotor symptoms, or annualized loss > 7.5% in lumbar spine bone mineral density.
Treatment groups identified by dose (mg) of CE or CE/MPA.
Data from CDRs 3-4 and 3-5.

Examination of the individual adverse events leading to discontinuation disclosed that most of these were referable to the GU system (section on Safety-Related Discontinuations). A tabulation of these is provided in the sponsor's Table 10.3.1.9 A, which is worth including here:

TABLE 10.3.1.9.A. ADVERSE EVENTS CAUSING WITHDRAWAL FROM THE STUDY: NUMBER (%) OF PATIENTS

Body System Adverse event	Group A 0.625 (n = 97)	Group B 0.625/2.5 (n = 86)	Group C 0.45 (n = 95)	Group D 0.45/2.5 (n = 96)	Group E 0.45/1.5 (n = 94)	Group F 0.3 (n = 89)	Group G 0.3/1.5 (n = 98)	Group H Placebo (n = 94)	Total (n = 749)	Pearson Chi-Square p-Value
Urogenital system										
Breast carcinoma	1 (1)	0	0	0	0	0	0	1 (1)	2 (<1)	0.556
Breast enlargement	0	1 (1)	0	0	0	0	0	0	1 (<1)	0.358
Breast neoplasm	0	0	0	0	1 (1)	0	0	0	1 (<1)	0.431
Breast pain	0	2 (2)	0	1 (1)	0	0	0	1 (1)	4 (<1)	0.275
Dyspareunia	0	0	1 (1)	0	0	0	0	0	1 (<1)	0.440
Endometrial hyperplasia	10 (10)	0	6 (6)	0	0	0	0	0	16 (2)	<0.001***
Menorrhagia	1 (1)	0	0	0	0	0	0	0	1 (<1)	0.457
Menstrual disorder	0	0	1 (1)	0	0	0	0	0	1 (<1)	0.440
Metrorrhagia	2 (2)	1 (1)	0	0	3 (3)	2 (2)	0	0	8 (1)	0.176
Urinary tract disorder	0	0	0	1 (1)	0	0	0	0	1 (<1)	0.449
Urinary urgency	1 (1)	0	0	0	0	0	0	0	1 (<1)	0.457
Uterine disorder	0	0	0	0	0	1 (1)	0	0	1 (<1)	0.386
Uterine enlargement	1 (1)	0	0	0	0	0	0	0	1 (<1)	0.457
Uterine hemorrhage	1 (1)	0	0	0	1 (1)	0	0	0	2 (<1)	0.556
Uterine spasm	1 (1)	1 (1)	0	0	0	0	0	0	2 (<1)	0.513
Vaginal dryness	0	0	0	0	0	0	0	1 (1)	1 (<1)	0.431
Vaginal hemorrhage	11 (11)	2 (2)	1 (1)	1 (1)	3 (3)	1 (1)	1 (1)	0	20 (3)	<0.001***

a: Body system totals are not necessarily the sum of the individual adverse events since a patient may report two or more different adverse events in the same body system.
b: * p<0.05, ** p<0.01, *** p<0.001
Treatment groups identified by dose (mg) of CE or CE/MPA.
Data from CDR 5-SW.

The data show that 29 of the 31 withdrawals due to AEs were referable to the GU system, with the majority due to 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).

Comments: The overall retention rate, about 70% over two years, is fairly typical of osteoporosis treatment and prevention trials. The reasons for discontinuation, by treatment group, are not unanticipated. There does not appear to be a differential rate of discontinuation, by treatment group, that would affect the analysis of bone-sparing efficacy, particularly in the lower dose groups.

VI.5.1.2 Protocol violations:

The sponsor provides summary and individual listings of protocol violations. These are divided into violations that led to withdrawal (either as primary or secondary reason for withdrawal) and those that did not.

There were violations related to entry criteria, study medication compliance, visits, procedures, and concomitant medications.

Eighteen (2.4%) patients had protocol violations either as primary or secondary reasons for withdrawal. Individual patients and treatment group assignments are presented in Tables 8.1.2.1.1A and 8.1.2.1.2A of the NDA. 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 (30925-0057 and 30940-0083) had fasting glucose levels > 6.94 mmol/L (125 mg/dL). Patient 30925-0057, and 2 other patients (30928-0021 and 30964-0054), had diabetes mellitus at study entry. Diabetes (defined as having a fasting glucose >7.77 mmol/L [140 mg/dL] or a 2-hour GTT result of >11.1

mmol/L [200 mg/dL] and at least one other value >11.1 mmol/L).

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 (30907-0001, 30907-0026, 30907-0022, 30941-0025, and 30964-0079). One (1) of these patients (30964-0079) 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.

VI.5.1.3 Data excluded from efficacy analysis:

Data excluded from the BMD analysis (the primary efficacy analysis of the two-year sub-study):

Six hundred nine patients (81%) were included in the EE population for analysis of changes in lumbar spine and total body BMD, and 608 were included in analysis of femoral neck BMD. All of the (19% of the 769) excluded patients lacked valid scans at two time points during the study. In addition, there were six patients who were excluded because they took less than 80% of the study

medication or because they received prohibited concomitant medication. All of these patients are included in the ITT analysis, however.

Examination of the data in Table 8.1.3.1B shows that the numbers of patients excluded from the EE evaluation were equally distributed across treatment groups, except that there were about twice as many in the CE 0.625 mg alone group as in the other treatment groups.

Data excluded from the analysis of secondary endpoints:

The sponsor presents an analysis of the number of patients excluded from each of the secondary analyses, by treatment group. Full details, including reasons for exclusion, are provided in the NDA and will not be presented in here. Instead, I will summarize the results:

Bone markers: There were 48, 54, and 54 patients excluded from the analyses of serum osteocalcin, urine calcium, and urine NTX, respectively. The numbers of patients were about evenly divided among the eight treatment groups, with the exception that the CE 0.625 mg and placebo groups had the greatest numbers of patients excluded from all three analyses (about 10 patients for each analysis in each of these two groups).

Endometrial hyperplasia: 518 (69%) patients were included in the EE population for analysis of endometrial hyperplasia at cycle 26. The sponsor summarizes the number of patients excluded from the EE population for this analysis at cycles 6, 13, 19, and 26 in Table 8.1.4.2A, reproduced below. Two hundred thirty-one (31%) patients were excluded at cycle 26. For these 231 patients, no valid biopsy was taken during cycles 25 to 27 and no instance of endometrial hyperplasia was diagnosed before cycle 25. Only one reason was needed to invalidate the biopsies and exclude patients from the analysis (e.g., if other HRT products were used prior to biopsy). No biopsies indicating endometrial hyperplasia were excluded from analysis. The patients excluded are listed in the NDA.

TABLE 8.1.4.2A. NUMBER (%) OF PATIENTS EXCLUDED FROM THE ENDOMETRIAL HYPERPLASIA ANALYSIS. EFFICACY-EVALUABLE POPULATION, BY TREATMENT GROUP

Reason for Exclusion[a]	Group A 0.625 (n = 97)	Group B 0.625/2.5 (n = 86)	Group C 0.45 (n = 95)	Group D 0.45/2.5 (n = 96)	Group E 0.45/1.5 (n = 94)	Group F 0.3 (n = 89)	Group G 0.3/1.5 (n = 98)	Group H Placebo (n = 94)	Total (n = 749)
Cycle 6									
No baseline biopsy	0	0	0	0	0	0	1 (1)	0	1 (<1)
No biopsy cycles 5-7 and no hyperplasia before cycle 5	12 (12)	6 (7)	7 (7)	9 (9)	10 (11)	7 (8)	8 (8)	9 (10)	68 (9)
Total patients excluded	12 (12)	6 (7)	7 (7)	9 (9)	10 (11)	7 (8)	8 (8)	9 (10)	68 (9)
Cycle 13									
No baseline biopsy	0	0	0	0	0	0	1 (1)	0	1 (<1)
No biopsy cycles 12-14 and no hyperplasia before cycle 12	30 (31)	10 (12)	19 (20)	18 (19)	19 (20)	15 (17)	15 (15)	15 (16)	141 (19)
Total patients excluded	30 (31)	10 (12)	19 (20)	18 (19)	19 (20)	15 (17)	15 (15)	15 (16)	141 (19)
Cycle 19									
No baseline biopsy	0	0	0	0	0	0	1 (1)	0	1 (<1)
No biopsy cycles 18-20 and no hyperplasia before cycle 18	37 (38)	21 (24)	24 (25)	25 (26)	24 (26)	24 (27)	22 (22)	32 (34)	209 (28)
Total patients excluded	37 (38)	21 (24)	24 (25)	25 (26)	24 (26)	24 (27)	22 (22)	32 (34)	209 (28)
Cycle 26									
No baseline biopsy	0	0	0	0	0	0	1 (1)	0	1 (<1)
No biopsy cycles 25-27 and no hyperplasia before cycle 25	42 (43)	24 (28)	28 (29)	30 (31)	25 (27)	26 (29)	23 (23)	33 (35)	231 (31)
Total patients excluded	42 (43)	24 (28)	28 (29)	30 (31)	25 (27)	26 (29)	23 (23)	33 (35)	231 (31)

a: Patients may have been excluded for more than 1 reason.
Treatment groups identified by dose (mg) of CE or CE/MPA.
Data from CDRs 2-4EB-EP6, 2-4EB-EE13, 2-4EB-EE19, and 2-4EB-EP26.

Analysis of vasomotor symptoms: Data on vasomotor symptoms were collected during 15,858 cycles. Of these, 12,640 (80%) cycles were included in the analysis. The reasons for exclusion of data and number of cycles of data excluded are summarized, by treatment group, in Table 8.1.4.3A. Examination of this table shows that the numbers of cycles excluded did not differ appreciably across groups. In addition, the reasons for exclusion were similar across treatment groups. The major reason for exclusion was absence of baseline hot flushes.

Amenorrhea and bleeding analysis:

For the EE1 population, 4,693 cycles of data were included and 2,367 cycles were excluded from the amenorrhea analysis for year 2. The sponsor summarizes the reasons for exclusion of cycles from the analysis of amenorrhea for the EE1 population in year 2 in Table 8.1.4.4.1A of the NDA. Examination of this table shows that the reasons for exclusion did not differ substantially across treatment groups. The major reasons for exclusion were <26 cycles of study medication completed, <28 days of bleeding data in any cycle, study medication missed for three consecutive days in any cycle, and study medication missed for any five days in any cycle.

Bleeding analysis: Ninety-four percent of all cycles (14,842/15,858) were included in the analysis of the EE population. Reasons for excluding data from the analysis of bleeding for the EE population are provided in Tables 8.1.4.4.2A of the NDA. The major reasons for exclusion of data for any given cycle were <28 days of data for the cycle and missed medication (either for three consecutive days in a cycle or for any five days in a cycle). There were no systematic

differences, across treatment groups, in the numbers of cycles dropped or in the reasons for their elimination from the analysis.

VI.5.1.3 Population demographics and other baseline characteristics

The sponsor presents these characteristics in the following table. The treatment groups were comparable in demographic and baseline characteristics. Patients were healthy (with exceptions noted above), about 51 years of age, and about 2.3 years since menopause, on average.

TABLE 8.2A. DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR WOMEN IN THE SUBSTUDY

Characteristic	Group A 0.625 (n = 97)	Group B 0.625/2.5 (n = 86)	Group C 0.45 (n = 95)	Group D 0.45/2.5 (n = 96)	Group E 0.45/1.5 (n = 94)	Group F 0.3 (n = 89)	Group G 0.3/1.5 (n = 98)	Group H Placebo (n = 94)	Total (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	5 (5)	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: This osteoporosis prevention population in this trial is predominantly white (90-98%), relatively young, healthy, of normal body weight, and only a few years past menopause. The bone-sparing efficacy of estrogen in this population, which is presumably in a period of rapid bone loss, may differ from that which might be found in older women. In addition, one can not translate the degree of efficacy into a different (especially into a non-white) population with any certainty.

VI.5.1.4 Concomitant therapy

All patients received calcium supplementation in the form of Caltrate (containing 600 mg elemental calcium). In addition, 714 (95%) patients received some other non-study medication during the trial. The sponsor presents the concomitant therapy received by 5% or more patients in any group in Table 8.3A of the NDA. The use of concomitant therapy was high and fairly evenly distributed across all treatment groups. The most common types of concomitant therapy were analgesics/antipyretics, NSAIDs, and multivitamins.

VI.5.2 Primary efficacy outcome: changes in lumbar spine BMD Secondary BMD efficacy outcomes: changes in BMD at the femoral neck, trochanter, and total body

Changes in lumbar spine BMD constituted the primary efficacy outcome of the two-year sub-study. Secondary outcomes included changes in BMD at the femoral neck, trochanter, and total body. For economy of presentation, I have included the reviews of efficacy at these skeletal sites in this section.

The sponsor presents a detailed account and analysis of treatment compliance, as well as demographics and baseline characteristics of the efficacy evaluable population for the BMD analysis.

Comments: As noted above, the sponsor's slope analysis, based on their efficacy evaluable (EE) population (patients with a baseline and at least two post-baseline BMD evaluations), is not acceptable on its own. It can not form the basis of efficacy claims for osteoporosis prevention. Analyses of BMD changes at the two-year endpoint, using an ITT population with LOCF, are required to substantiate such claims. For purposes of review, the following is a description of the EE population, plus the results of the sponsor's analysis, based on this population. Supplementary analyses including all patients who had at least 1 post-baseline visit (i.e., ITT analyses) were also done.

I have requested that the sponsor provide our Biometrics reviewer all data from the ITT set (i.e., all patients who had a baseline and at least one post-baseline visit). This should form the basis of labeling claims.

For review purposes, the following is a summary of the BMD results, based on the sponsor's slope analysis.

Treatment compliance was measured using daily diary cards. Missed study medication was returned to the investigator. Data were recorded as number and percent of cycles in which patients failed to take one or more tablets. This ranged from 22.1% in the 0.3/1.5 mg group to 31.2% in the 0.45/1.5 mg group. The rate of non-compliance in the placebo group was 28.9% (the second highest rate).

The data are presented in Table 9.1A of the NDA. There was no apparent relationship between dose and missed medication.

Population: Six hundred ten patients (81% of the total of 749 patients in the sub-study) were included in the EE population for the BMD analysis. The sponsor presents the following table of patients who completed the study, by treatment group:

TABLE 9.2A. NUMBER (PERCENT) OF PATIENTS WHO COMPLETED STUDY BY GROUP

Study Completed	Group A 0.625	Group B 0.625/2.	Group C 0.45	Group D 0.45/2.5	Group E 0.45/1.5	Group F 0.3	Group G 0.3/1.5	Group H Placebo	Total	p-Value
Yes	43 (65)	65 (86)	62 (81)	69 (87)	68 (91)	64 (83)	76 (93)	60 (77)	507 (83)	<0.001[a]
No	23 (35)	11 (14)	15 (19)	10 (13)	7 (9)	13 (17)	6 (7)	18 (23)	103 (17)	

a: Pearson chi-square test.
Treatment groups identified by dose (mg) of CE or CE/MPA
Data from CDR 1-6BMD-EE

Fewer patients Group A (0.625 mg CE) completed the study.

Demographic and baseline characteristics of patients in the BMD analysis are provided by the sponsor in Table 9.3A of the NDA. The overall characteristics of patients in this analysis are essentially the same as in the total set of patients (749) in the two-year sub-study. In addition, there were essentially no differences in these baseline characteristics across the treatment groups.

Results:

The sponsor'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 statistically 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 0.76% in group F (0.3 mg CE alone) to 2.03% in Group B (0.625/2.5 mg). In contrast, the placebo group experienced a mean decrease in lumbar spine BMD (-1.49%). All comparisons with placebo were statistically significant ($p<0.001$ for all comparisons). All within-group changes from baseline were statistically significant ($p<0.001$ for all eight within-group comparisons, including placebo, as shown in supportive Table Appendix E.3 of the NDA).

Comments: Of central importance to this study, the two lowest doses of CE and CE/MPA (groups E and G) were effective in increasing BMD compared with placebo. Also noteworthy: the mean increases in BMD were generally greater for the CE/MPA combination groups than for each comparable CE-alone group.

Similar results were obtained for the other three BMD endpoints. At the trochanter, the mean annualized 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. All comparisons were statistically significant vs placebo ($p<0.001$ for all 28 comparisons except Group F [CE 0.3 mg alone], where $p<0.003$).

Review of the data presented in the supportive Table, Appendix E.3, confirmed that all within-group comparisons (i.e., change in lumbar spine BMD vs baseline) were statistically significant ($p<0.001$). At the other skeletal sites, all within-group comparisons vs baseline were significant at the $p<0.001$ level, except: total body BMD, Group F $p=0.005$; femoral neck BMD, Group B $p=0.003$, Group F $p=0.06$, Group G $p=0.004$; trochanter Group H $p=0.60$.

The annualized mean data are presented in the sponsor's table below:

TABLE 9.4.1.1A. ANNUALIZED PERCENT CHANGE IN BONE MINERAL DENSITY FROM SLOPE ANALYSIS: COMPARISON BETWEEN ACTIVE AND PLACEBO GROUPS IN THE EFFICACY-EVALUABLE POPULATION

Region Evaluated / Treatment Group[a]	No. of Pairs	Baseline: Mean	Baseline: SD	Change from Baseline (%): Adjusted Mean[b]	Change from Baseline (%): SE	p-Values vs Placebo
L2 to L4 BMD (g/cm^2)						
Group A 0.625	66	1.16	0.15	1.68	0.24	<0.001
Group B 0.625/2.5	76	1.14	0.16	2.03	0.22	<0.001
Group C 0.45	77	1.13	0.16	1.28	0.22	<0.001
Group D 0.45/2.5	79	1.15	0.17	1.51	0.22	<0.001
Group E 0.45/1.5	75	1.15	0.14	1.14	0.22	<0.001
Group F 0.3	76	1.14	0.15	0.76	0.22	<0.001
Group G 0.3/1.5	82	1.13	0.15	0.92	0.21	<0.001
Group H Placebo	78	1.15	0.14	-1.49	0.22	
Femoral neck BMD (g/cm^2)						
Group A 0.625	66	0.90	0.14	1.11	0.30	<0.001
Group B 0.625/2.5	76	0.89	0.14	0.86	0.27	<0.001
Group C 0.45	77	0.89	0.13	1.16	0.27	<0.001
Group D 0.45/2.5	79	0.89	0.15	0.99	0.27	<0.001
Group E 0.45/1.5	74	0.88	0.10	0.80	0.28	<0.001
Group F 0.3	76	0.86	0.12	0.28	0.28	<0.001
Group G 0.3/1.5	82	0.85	0.11	0.77	0.26	<0.001
Group H Placebo	78	0.88	0.14	-1.30	0.27	

TABLE 9.4.1.1A. ANNUALIZED PERCENT CHANGE IN BONE MINERAL DENSITY FROM SLOPE ANALYSIS: COMPARISON BETWEEN ACTIVE AND PLACEBO GROUPS IN THE EFFICACY-EVALUABLE POPULATION

Region Evaluated / Treatment Group[a]	No. of Pairs	Baseline Mean	Baseline SD	Change from Baseline (%) Adjusted Mean[b]	Change from Baseline (%) SE	p-Values vs Placebo
Femoral trochanter BMD (g/cm^2)						
Group A 0.625	66	0.77	0.13	2.30	0.36	<0.001
Group B 0.625/2.5	76	0.77	0.14	2.20	0.33	<0.001
Group C 0.45	77	0.76	0.12	2.04	0.33	<0.001
Group D 0.45/2.5	79	0.76	0.14	2.60	0.33	<0.001
Group E 0.45/1.5	74	0.74	0.11	1.87	0.34	<0.001
Group F 0.3	76	0.74	0.11	1.67	0.33	0.003
Group G 0.3/1.5	82	0.75	0.12	2.23	0.32	<0.001
Group H Placebo	78	0.75	0.13	0.31	0.33	
Total body BMD (g/cm^2)						
Group A 0.625	66	1.14	0.08	0.42	0.11	<0.001
Group B 0.625/2.5	76	1.14	0.08	0.58	0.10	<0.001
Group C 0.45	77	1.14	0.08	0.47	0.10	<0.001
Group D 0.45/2.5	79	1.13	0.08	0.51	0.10	<0.001
Group E 0.45/1.5	75	1.13	0.07	0.25	0.10	<0.001
Group F 0.3	76	1.14	0.08	0.24	0.10	<0.001
Group G 0.3/1.5	82	1.13	0.08	0.30	0.10	<0.001
Group H Placebo	78	1.13	0.08	-0.85	0.10	

a: Identified by dose (mg) of CE or CE/MPA

b: Adjusted annualized mean change from baseline obtained from analysis of covariance with treatment and study site as factors and weight and years since menopause as covariates.

Data from statistical report BMD.1

The sponsor also presents an analysis of BMD data by cycle (cycles 6, 13, 19, and 26) in the supportive tables of the NDA. For changes at the lumbar spine, all seven treatment groups were statistically different from placebo by cycle 6 (and remained so), $p<0.001$ for all comparisons with placebo. The same was true for total body BMD. At the femoral neck and trochanter, statistically significant differences ($p<0.001$ for nearly all comparisons and $p<0.03$ for the remaining comparisons) were found at cycles 13, 19, and 26.

This study was not powered to show significant differences between active-treatment groups. Accordingly, no p-values were assigned to these comparisons. However, the sponsor calculated 95% confidence intervals on the differences between groups (based on annualized change in BMD derived from the slope analyses). These are presented in Supportive Table ST9-8 of the NDA.

Examination of these 95% CIs did not show any differences between a CE-alone group and the corresponding CE/MPA-combination group(s). Within the CE-alone groups, differences favoring the 0.625mg dose over 0.3 mg were seen in lumbar spine and femoral neck BMD, and differences favoring the 0.45 mg dose over 0.3 mg were seen in femoral neck BMD.

Within the combination groups, differences favoring the 0.625 mg/2.5 mg group over both the 0.45 mg/1.5 mg and the 0.3 mg/1.5 mg groups were seen in total body and lumbar spine BMD. There was also a difference favoring the 0.45 mg/2.5 mg group over 0.3 mg/1.5 mg at the lumbar spine.

The percent change from baseline to final evaluation for the efficacy evaluable population is presented in the following table. The data are in excellent agreement with those derived from the annualized (slope) analysis.

TABLE 9.4.1.1B, PERCENT CHANGE FROM BASELINE TO FINAL EVALUATION IN BONE MINERAL DENSITY: EFFICACY-EVALUABLE POPULATION

Region Evaluated / Treatment Group[a]	No. of Pairs	Baseline Mean	Baseline SD	Observed Mean	Observed SD	Change from Baseline (%) Adjusted Mean[b]	Change from Baseline (%) SE	p-Value vs Placebo
L2 to L4 BMD (g/cm^2)								
Group A 0.625	66	1.16	0.15	1.19	0.14	2.83	0.40	<0.001
Group B 0.625/2.5	76	1.14	0.16	1.18	0.17	3.77	0.37	<0.001
Group C 0.45	77	1.13	0.16	1.16	0.15	2.28	0.37	<0.001
Group D 0.45/2.5	79	1.15	0.17	1.19	0.18	3.10	0.37	<0.001
Group E 0.45/1.5	75	1.15	0.14	1.18	0.14	2.45	0.37	<0.001
Group F 0.3	76	1.14	0.15	1.16	0.15	1.51	0.37	<0.001
Group G 0.3/1.5	82	1.13	0.15	1.15	0.15	1.77	0.36	<0.001
Group H Placebo	78	1.15	0.14	1.12	0.14	-2.63	0.37	
Femoral neck BMD (g/cm^2)								
Group A 0.625	66	0.90	0.14	0.91	0.14	2.13	0.50	<0.001
Group B 0.625/2.5	76	0.89	0.14	0.90	0.14	1.67	0.46	<0.001
Group C 0.45	77	0.89	0.13	0.91	0.13	1.98	0.46	<0.001
Group D 0.45/2.5	79	0.89	0.15	0.91	0.15	1.76	0.45	<0.001
Group E 0.45/1.5	74	0.88	0.10	0.89	0.10	1.43	0.47	<0.001
Group F 0.3	76	0.86	0.12	0.87	0.12	0.80	0.46	<0.001
Group G 0.3/1.5	82	0.85	0.11	0.86	0.11	1.51	0.44	<0.001
Group H Placebo	78	0.88	0.14	0.87	0.14	-1.97	0.46	

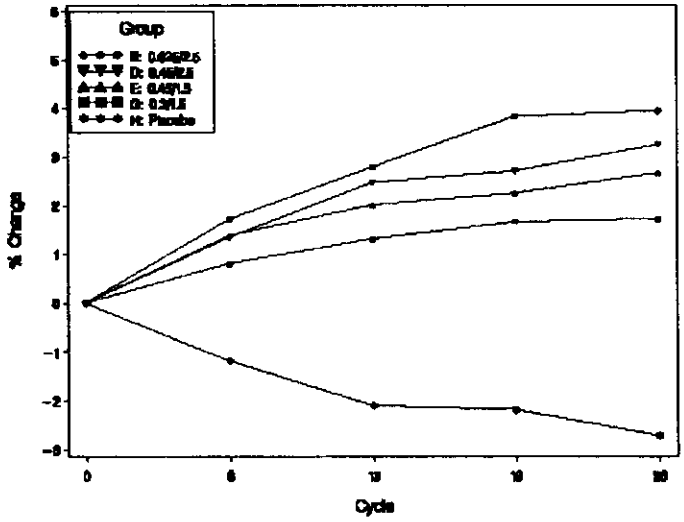
TABLE 9.4.1.1B, PERCENT CHANGE FROM BASELINE TO FINAL EVALUATION IN BONE MINERAL DENSITY: EFFICACY-EVALUABLE POPULATION

Region Evaluated / Treatment Group[a]	No. of Pairs	Baseline Mean	Baseline SD	Observed Mean	Observed SD	Change from Baseline (%) Adjusted Mean[b]	Change from Baseline (%) SE	p-Value vs Placebo
Femoral trochanter BMD (g/cm^2)								
Group A 0.625	66	0.77	0.13	0.80	0.13	4.17	0.63	<0.001
Group B 0.625/2.5	76	0.77	0.14	0.80	0.13	4.05	0.59	<0.001
Group C 0.45	77	0.76	0.12	0.79	0.12	3.79	0.58	<0.001
Group D 0.45/2.5	79	0.76	0.14	0.80	0.14	5.08	0.58	<0.001
Group E 0.45/1.5	74	0.74	0.11	0.77	0.11	3.60	0.59	<0.001
Group F 0.3	76	0.74	0.11	0.77	0.11	3.58	0.59	<0.001
Group G 0.3/1.5	82	0.75	0.12	0.78	0.12	4.66	0.56	<0.001
Group H Placebo	78	0.75	0.13	0.76	0.13	0.82	0.58	
Total body BMD (g/cm^2)								
Group A 0.625	66	1.14	0.08	1.15	0.08	0.78	0.19	<0.001
Group B 0.625/2.5	76	1.14	0.08	1.15	0.08	0.96	0.18	<0.001
Group C 0.45	77	1.14	0.08	1.15	0.07	0.85	0.17	<0.001
Group D 0.45/2.5	79	1.13	0.08	1.15	0.08	1.07	0.17	<0.001
Group E 0.45/1.5	75	1.13	0.07	1.14	0.07	0.56	0.18	<0.001
Group F 0.3	76	1.14	0.08	1.14	0.08	0.48	0.18	<0.001
Group G 0.3/1.5	82	1.13	0.08	1.13	0.08	0.55	0.17	<0.001
Group H Placebo	78	1.13	0.08	1.11	0.09	-1.56	0.17	

a: Identified by dose (mg) of CE or CE/MPA.
b: Adjusted mean change from baseline obtained from analysis of covariance with treatment and institutional site as factors and weight and years since menopause as covariates.

By-cycle data for lumbar spine BMD changes in the four CE/MPA combination groups and placebo are presented in the following figure:

FIGURE 9.4.1.1A. CE/MPA FOR L2 TO L4 (GROUPS B, D, E, G, AND PLACEBO): MEAN % CHANGE FROM BASELINE IN BMD IN EFFICACY-EVALUABLE POPULATION



Similar data are presented graphically for BMD changes at the femoral neck, trochanter, and total body (Figs.9.4.1.1C, E, and G of the NDA). At each skeletal site, the mean BMD values for all four active treatment groups are numerically greater than in placebo by cycle 6, and there is clear divergence between placebo and active groups by cycle 13. Of importance, the values and slopes appear to be similar among the four active treatment groups.

These results are illustrated in the following figures (for the CE/MPA combination groups and placebo):

FIGURE 9.4.1.1C. CE/MPA FOR FEMORAL NECK:
MEAN % CHANGE FROM BASELINE IN BMD IN EFFICACY-EVALUABLE POPULATION

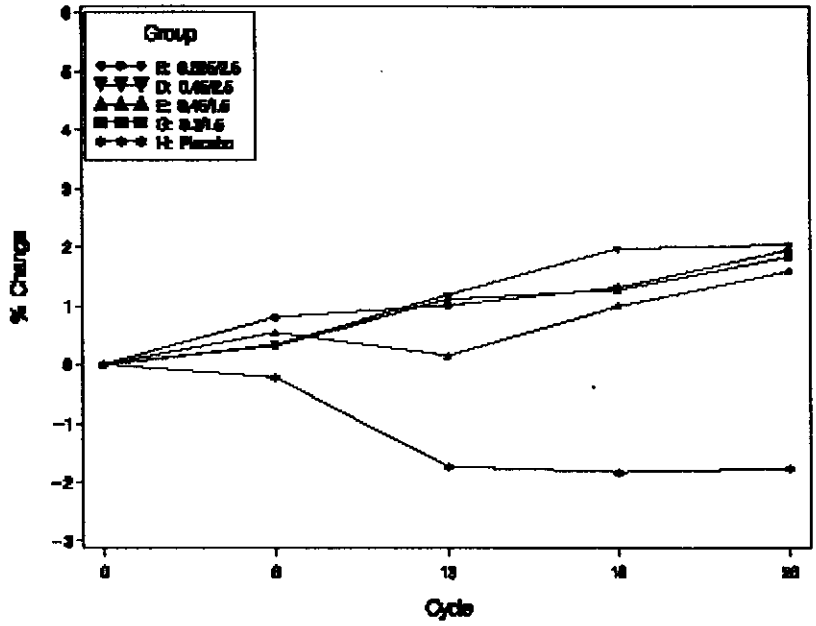


FIGURE 9.4.1.1E. CE/MPA FOR FEMORAL TROCHANTER:
MEAN % CHANGE FROM BASELINE IN BMD IN EFFICACY-EVALUABLE POPULATION

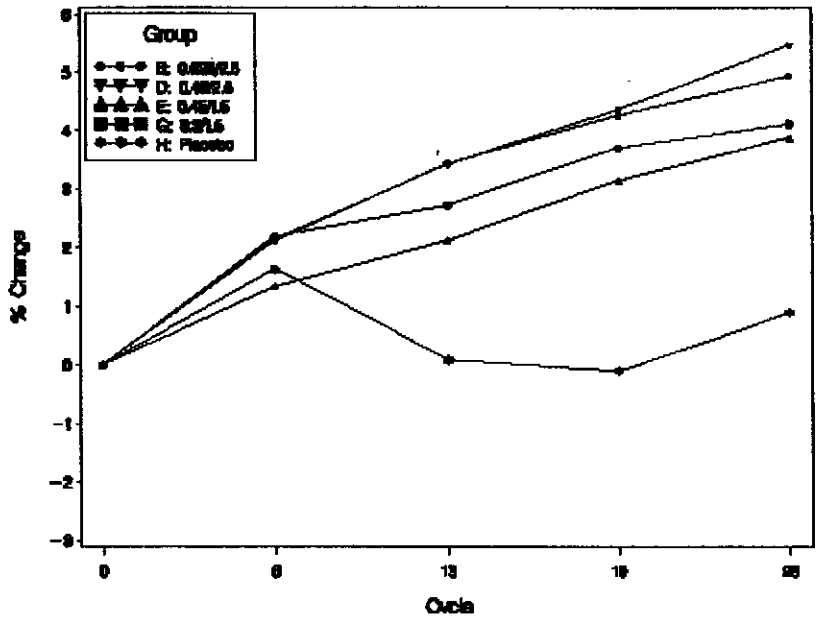
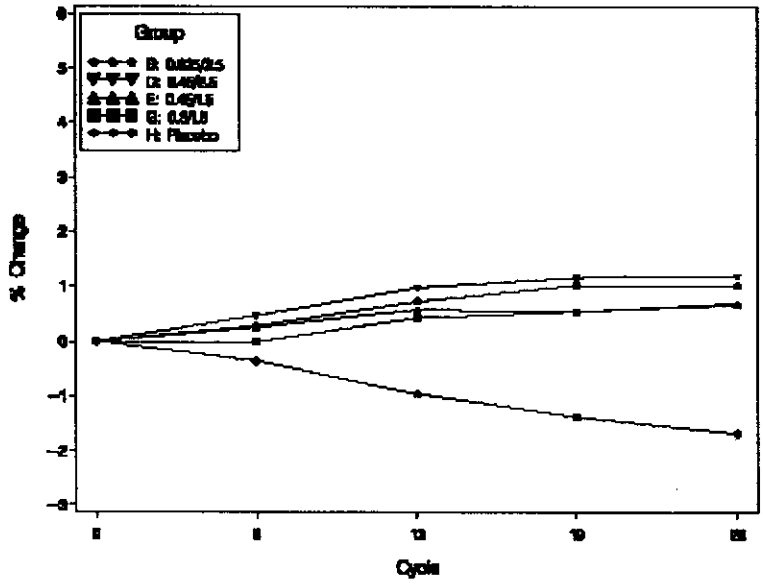


FIGURE 9.4.1.1G. CE/MPA FOR TOTAL BODY:
MEAN % CHANGE FROM BASELINE IN BMD IN EFFICACY-EVALUABLE POPULATION



Very similar results are presented for the CE-alone groups, plus placebo, in Fig. 9.4.1.1B of the NDA (not reproduced here).

Comments: These data appear to be reproducible and robust. As shown below, the results have been confirmed, for both the primary and secondary BMD efficacy objectives, by further statistical analyses (*vide infra*). In particular, the lowest doses of CE/MPA are effective in preventing bone loss at the L2-L4 lumbar spine, as well as at the three other skeletal sites. Although there appears to be a numerical trend towards a dose effect within the treatment groups, these differences appear to be small. In only a few comparisons between treatment groups did the 95% CIs on the BMD means not include 1.

As discussed above, the sponsor's primary statistical analyses should not form the basis of efficacy claims for osteoporosis drugs. Fortunately, in this case the proper analysis, using final time point data from an ITT population with LOCF, confirms the statistical significance of the relevant comparisons. This analysis is not described in the protocol or the statistical analysis plan. However, the results are provided in the Statistical Appendix of the NDA (see Biometrics Review). In my opinion, these results should provide the proper numerical data for labeling. The remaining problem concerns the appropriate endpoint --- cycle 26 or final visit. In consultation with the Biometrics reviewer, the following data are available for L2-L4 BMD, using ITT with LOCF (reviewer's table). Note that for most comparisons, the mean BMD changes are somewhat greater at

cycle 26, compared to final visit. This is most likely due to the differences in numbers of subjects who were still taking study drug.

TREATMENT GROUP	L2-L4 BMD CHANGE FROM BASELINE (%), FINAL VISIT#	L2-L4 BMD CHANGE FROM BASELINE (%), CYCLE 26*
A	2.32	2.37
B	3.39	3.48
C	2.08	2.11
D	2.91	2.98
E	2.21	2.20
F	1.24	1.33
G	1.67	1.69
H	- 2.46	- 2.51

* All individuals on study drug
# For most comparisons with cycle 26 data, means for treatment groups were slightly lower at final visit, presumably due to observations taken after treatment was stopped.

Mean BMD data for subjects at final visit, for all skeletal sites, are presented in the following tables:

APPENDIX F.3
SUMMARY TABULATION OF RESULTS FROM PARAMETRIC ANALYSIS,
AFTER CORRECTION OF ERRATA, FINAL VISITS, INTENT TO TREAT POPULATION

Protocol 719D2-309-US
Table BMD.6 : Summary Tabulation of BMD
Percent Change from Baseline, Comparison Within and Between Groups, ITT Population

Treatment Group	No. of Pairs	----Baseline---- Mean	SD	----Observed---- Mean	SD	-%Change from B/L- Adjusted Mean	SE	----P-Values---- Within Group	Versus Placebo
L2-L4 BMD (g/cm**2)									
Group A 0.625	83	1.17	0.15	1.20	0.16	2.31	0.35	<0.001	<0.001
Group B 0.625/2.5	81	1.14	0.16	1.18	0.17	3.38	0.35	<0.001	<0.001
Group C 0.45	91	1.13	0.15	1.16	0.15	2.16	0.33	<0.001	<0.001
Group D 0.45/2.5	87	1.15	0.17	1.18	0.17	2.91	0.34	<0.001	<0.001
Group E 0.45/1.5	89	1.16	0.14	1.18	0.14	2.21	0.34	<0.001	<0.001
Group F 0.3	87	1.14	0.15	1.15	0.15	1.23	0.34	<0.001	<0.001
Group G 0.3/1.5	90	1.14	0.15	1.16	0.15	1.67	0.33	<0.001	<0.001
Group H Placebo	85	1.14	0.14	1.11	0.14	-2.46	0.35	<0.001	

Note that the % BMD changes for the true ITT population are about 5-15% lower than for the sponsor's efficacy evaluable population (cf. sponsor's table, above). However, the statistical operations on the ITT data yielded essentially the same results as for the EE population. These data should be used in final labeling claims. Data from cycle 26 or final visit would be

equally representative, in my opinion. The sponsor's analysis of endpoint BMD results at the other three skeletal sites are presented in the following tables, taken from the Statistical Appendix of the NDA.

Protocol 713D2-309-US
Table BMD.6 : Summary Tabulation of BMD
Percent Change from Baseline, Comparison Within and Between Groups, ITT Population

Treatment Group	No. of Pairs	Baseline Mean	Baseline SD	Observed Mean	Observed SD	%Change from B/L Adjusted Mean	%Change from B/L SE	p-Values Within Group	p-Values Versus Placebo
TOTAL BODY BMD (g/cm**2)									
Group A 0.625	84	1.15	0.06	1.16	0.08	0.66	0.17	<0.001	<0.001
Group B 0.625/2.5	81	1.14	0.06	1.15	0.08	0.91	0.17	<0.001	<0.001
Group C 0.45	91	1.14	0.05	1.15	0.08	0.71	0.16	<0.001	<0.001
Group D 0.45/2.5	87	1.13	0.05	1.15	0.08	0.99	0.16	<0.001	<0.001
Group E 0.45/1.5	89	1.14	0.07	1.15	0.07	0.57	0.16	<0.001	<0.001
Group F 0.3	87	1.14	0.07	1.14	0.07	0.37	0.16	0.005	<0.001
Group G 0.3/1.5	91	1.13	0.05	1.14	0.08	0.51	0.16	<0.001	<0.001
Group H Placebo	85	1.13	0.05	1.11	0.08	-1.52	0.16	<0.001	

Protocol 713D2-309-US
Table BMD.6 : Summary Tabulation of BMD
Percent Change from Baseline, Comparison Within and Between Groups, ITT Population

Treatment Group	No. of Pairs	Baseline Mean	Baseline SD	Observed Mean	Observed SD	%Change from B/L Adjusted Mean	%Change from B/L SE	p-Values Within Group	p-Values Versus Placebo
FEMORAL NECK BMD (g/cm**2)									
Group A 0.625	84	0.91	0.14	0.92	0.13	1.74	0.41	<0.001	<0.001
Group B 0.625/2.5	81	0.89	0.14	0.90	0.14	1.77	0.44	<0.001	<0.001
Group C 0.45	91	0.89	0.13	0.90	0.13	1.96	0.41	<0.001	<0.001
Group D 0.45/2.5	87	0.89	0.15	0.91	0.15	1.67	0.43	<0.001	<0.001
Group E 0.45/1.5	89	0.89	0.12	0.90	0.11	1.80	0.42	0.001	<0.001
Group F 0.3	87	0.86	0.11	0.87	0.11	0.57	0.42	0.16	<0.001
Group G 0.3/1.5	91	0.86	0.11	0.87	0.12	1.41	0.41	<0.001	<0.001
Group H Placebo	85	0.88	0.14	0.87	0.13	-1.81	0.43	<0.001	

Protocol 713D2-309-US
Table BMD.4 : Summary Tabulation of BMD
Percent Change from Baseline, Comparison Within and Between Groups, ITT Population

Treatment Group	No. of Pairs	Baseline Mean	Baseline SD	Observed Mean	Observed SD	%Change from B/L Adjusted Mean	%Change from B/L SE	P-Values Within Group	P-Values Versus Placebo
FEMORAL TROCHANTER BMD (g/cm**2)									
Group A 0.625	84	0.78	0.13	0.80	0.12	3.78	0.57	<0.001	<0.001
Group B 0.625/2.5	81	0.77	0.16	0.80	0.13	3.78	0.57	<0.001	<0.001
Group C 0.45	91	0.76	0.12	0.78	0.12	3.46	0.54	<0.001	<0.001
Group D 0.45/2.5	87	0.76	0.14	0.79	0.15	4.67	0.56	<0.001	<0.001
Group E 0.45/1.5	89	0.76	0.12	0.78	0.12	3.04	0.55	<0.001	0.006
Group F 0.3	87	0.75	0.10	0.77	0.10	3.19	0.55	<0.001	0.003
Group G 0.3/1.5	91	0.76	0.12	0.79	0.12	4.17	0.54	<0.001	<0.001
Group H Placebo	85	0.75	0.12	0.76	0.12	0.93	0.56	0.12	

Subgroup analyses:

The sponsor presents analyses of subgroups based on age, years since menopause, ethnicity, and body weight at baseline. This analysis was based on the efficacy evaluable population. The results of this analysis are presented in detail in the NDA and will be reviewed briefly here. No labeling claims are made, based on this analysis.

Age: The sponsor stratified the population into age tertiles (40 to < 50, 50 to < 55, and 55 to 65 years). Of importance, for the primary efficacy analysis (lumbar spine BMD), all active treatment groups were significantly greater than placebo, across the three age tertiles. Inspection of Table 9.4.1.2.1.A indicates that, within the placebo group, the youngest tertile appeared to lose lumbar spine BMD more rapidly and that the total increases in BMD in treated groups was correspondingly smaller than in the other two age tertiles. However, the placebo-subtracted differences were essentially the same among the three tertiles, with a slight tendency toward greater placebo-subtracted differences in the youngest group. The data show that estrogen treatment, in all doses studied, is effective in preventing bone loss irrespective of the age tertile, in the range 40-65 years.

For total body BMD, the increases were statistically significantly greater than placebo for all active-treatment groups, in all age categories ($p<0.001$ for all comparisons with placebo).

At the femoral neck, BMD was significantly greater than placebo in all active-treatment groups, except groups B and E at ages 55 to 65 and groups A, F, and G at ages 40 to < 50. At the trochanter, BMD in groups C, D, F, and G was significantly greater than placebo for women aged 50 to < 55 and 55 to 65 years. Results varied across ages for groups A, B, and E with no clear pattern emerging. The results of the age analysis of BMD changes for all four skeletal sites are presented in Table 9.4.1.2.1A of the NDA.

Ethnicity: The trial population was 93% white, 4% black, 2% Hispanic, and the rest Asian, Native American, and other groups. Therefore, the relationship between ethnic origin and BMD endpoints was not analyzed.

Years since menopause: The sponsor categorized years since menopause into three groups: 0 to < 2 years, 2 to < 3 years, and ≥ 3 years.

For lumbar spine and total body BMD, each treatment group showed statistically significant differences from placebo for all three subgroups of years since menopause ($p<0.001$ for all comparisons of CE/MPA vs placebo).

At the femoral neck, there were significant differences from placebo for all subgroups within each CE/MPA treatment group (for most comparisons with placebo $p<0.001$; the highest p value was 0.035 for the 0.625/2.5 mg group for subjects > 3 years since menopause). For the 0.3 mg CE alone, the comparison with placebo was not statistically significant for subjects 0 to < 2 years since menopause. For the femoral trochanter, the active treatment groups also differed significantly from placebo, with the following exceptions: group B (0.625 mg/2.5 mg CE/MPA), group E (0.45 mg/1.5 mg CE/MPA), and group G (0.3 mg/1.5 mg) at 0 to < 2 years, groups C and F for 0 to < 2 years and 2 to < 3 years. Group E did not differ statistically from the placebo group in the BMD for the femoral trochanter at > 3 years ($p = 0.062$). The sponsor summarizes the results of this analysis in Table 9.4.1.2.3A.

Body weight at baseline: The sponsor divided the subjects into three subgroups according to body weight: 40 to < 60 kg, 60 to < 70 kg and ≥ 70 kg. The primary endpoint variable, lumbar spine BMD, was significantly higher than placebo in all active treatment groups in all three body weight strata. Total body BMD was significantly higher than in the placebo group for all active-treatment groups and for all body weight strata within each active-treatment group, except for the subgroup ≥ 70 kg for group E (0.45 mg/1.5 mg).

At the femoral neck, BMD was not significantly different from placebo in the subgroup ≥ 70 kg within group B (0.625 mg/2.5 mg CE/MPA), group E (0.45 mg/1.5 mg CE/MPA), or group G (0.3 mg/1.5 mg).

At the trochanter, BMD was statistically significantly higher for all treatment groups, relative to placebo, in the 40 to < 60 kg subgroup.

This was also true for group B (0.625 mg/2.5 mg CE/MPA) in the ≥ 70 kg subgroup and for group D (0.45 mg/2.5 mg CE/MPA) in the 60 to < 70 kg subgroup. Other comparisons (active treatment vs placebo) failed to achieve statistical significance at this skeletal site.

A complete summary of BMD data by body weight for all treatment groups is presented in Table 9.4.1.2.4A of the NDA.

Comments: For the primary outcome variable (lumbar spine BMD) and for total body BMD, all CE/MPA doses produced BMD increases that were statistically significantly greater than placebo in all subgroups (age, years since menopause, and body weight) except for one (subgroup ≥ 70 kg for group E [0.45 mg/1.5 mg]). This is important because age, years since menopause, and body weight influence endogenous estrogen levels as well as the velocity of loss of BMD.

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. For body weight subgroups, the heaviest subjects failed to demonstrate efficacy of active CE/MPA at the femoral neck, with inconsistent results at the trochanter. This may have some physiological basis, since endogenous estrogen (mainly estrone) levels vary directly with adiposity in this population. Additionally, increased body weight exerts positive effects on bone via biomechanical factors. This is evidenced by the fact that, within the placebo group (Group H), the heavier subgroups gained BMD at the trochanter. This fact, plus the relatively small numbers in each subgroup, reduced the statistical significance of the comparisons. It should be noted that the BMD increases were consistently numerically greater than placebo in all active treatment groups.

Therefore, the subgroup analysis supports the conclusion that all tested doses of CE/MPA 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/MPA at other skeletal sites. The study did not test the efficacy of CE/MPA in women over age 65.

VI.5.3 Other metabolic efficacy outcomes

Biochemical markers of bone turnover:

The sponsor measured serum osteocalcin, urinary calcium, and N-telopeptide (NTX) at cycles 6, 13, 19, and 26. No labeling claims are made for these results. Nonetheless, the data are relevant and help confirm efficacy of lower doses of CE/MPA. As shown in the next tables, there were substantial and highly

statistically significant decreases in both serum osteocalcin and NTX at all cycles and in all active-treatment groups ($p < 0.001$ for all active-treatment groups at all cycles compared with placebo).

Comments: These results, with decreases of about 20-35% in osteocalcin and 35-45% in NTX, are consistent with data from other trials of estrogens as well as other anti-resorptive agents. Note that this degree of efficacy is also seen in the lowest CE/MPA group.

TABLE 9.4.2.1A. ABSOLUTE CHANGE IN BONE TURNOVER MARKERS FROM BASELINE WITHIN AND BETWEEN GROUPS - INTENT-TO-TREAT POPULATION

Treatment Group[a]	Cycle	No. of Pairs	Baseline Mean	Baseline SD	Observed Mean	Observed SD	Change from Baseline Adjusted Mean[b]	Change from Baseline SE	p-Values 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 B 0.625/2.5	6	78	11.31	3.06	7.90	2.46	-3.24	0.28	<0.001
	13	76	11.34	3.28	7.17	2.36	-3.93	0.34	<0.001
	19	65	11.42	3.21	6.77	1.77	-4.40	0.35	<0.001
	26	61	11.39	3.27	7.03	1.77	-4.14	0.38	<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 D 0.45/2.5	6	84	11.13	3.65	8.43	2.53	-2.55	0.28	<0.001
	13	78	11.15	3.74	7.30	2.26	-3.61	0.34	<0.001
	19	70	11.26	3.89	7.11	2.10	-3.87	0.34	<0.001
	26	65	11.54	3.87	7.00	1.89	-4.27	0.37	<0.001
Group E 0.45/1.5	6	83	10.91	3.18	8.11	2.37	-2.67	0.28	<0.001
	13	77	11.04	3.08	7.69	2.21	-3.15	0.33	<0.001
	19	67	11.33	3.05	7.51	2.10	-3.58	0.35	<0.001
	26	68	11.25	2.95	7.55	2.22	-3.51	0.36	<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

Appears This Way On Original

Treatment Group[a]	Cycle	No. of Pairs	Baseline Mean	Baseline SD	Observed Mean	Observed SD	Change from Baseline Adjusted Mean[b]	Change from Baseline SE	p-Value vs Placebo
Group G 0.3/1.5	6	89	11.46	4.16	9.50	3.39	-1.87	0.26	<0.001
	13	81	11.70	4.20	8.38	2.88	-3.26	0.33	<0.001
	19	76	11.85	4.26	8.39	3.12	-3.27	0.33	<0.001
	26	72	11.90	4.34	8.71	3.32	-3.03	0.35	<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/mmol 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 B 0.625/2.5	6	78	62.50	24.47	33.60	12.72	-27.93	2.23	<0.001
	13	75	61.60	24.55	28.85	11.75	-31.78	2.40	<0.001
	19	65	60.71	22.67	27.85	11.24	-31.56	2.80	<0.001
	26	61	60.54	22.72	28.54	10.60	-30.59	2.70	<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
Group D 0.45/2.5	6	84	60.86	24.86	36.24	18.62	-24.03	2.16	<0.001
	13	77	61.10	25.28	30.94	14.28	-29.30	2.40	<0.001
	19	70	59.87	25.07	29.56	12.52	-28.97	2.71	<0.001
	26	65	61.34	25.02	29.62	12.34	-30.10	2.62	<0.001
Group E 0.45/1.5	6	83	59.87	23.58	34.07	13.17	-25.22	2.17	<0.001
	13	76	60.89	23.48	32.41	15.03	-27.71	2.39	<0.001
	19	67	62.24	23.82	31.91	15.37	-29.07	2.78	<0.001
	26	67	61.37	24.07	31.28	13.15	-28.78	2.57	<0.001
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 G 0.3/1.5	6	88	56.91	25.27	37.48	16.06	-19.08	2.09	<0.001
	13	80	57.86	25.62	36.19	16.11	-20.99	2.32	<0.001
	19	75	58.84	26.06	35.91	13.45	-22.15	2.59	<0.001
	26	72	58.54	25.45	36.85	16.72	-20.47	2.48	<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	-

The sponsor also measured urinary calcium. Only groups B (0.625 mg/2.5 mg CE/MPA) and E (0.45 mg/1.5 mg CE/MPA) showed significantly larger mean decreases than placebo at 3 or more of the 4 time points.

Lipid, carbohydrate, and coagulation analyses:

This analysis is presented in Section 11 of the submission, under the heading of "other analyses." Labeling claims are made for changes in lipids alone, based on these results.

The 749 subjects who were enrolled in the two-year metabolic sub-study contributed data that were used to evaluate the possible effects of CE and CE/MPA on lipid and glucose/insulin metabolism and on coagulation. Demographic and baseline characteristics were similar among all the treatment groups in the metabolic sub-study (described above).

Lipid data were analyzed by ANOVA, based on percent change from baseline at cycles 6, 13, 19, and 26. Lipoprotein (a) phenotype was collected at screening only. For analysis by time, the average of all values at a given period was used for on-therapy data.

In the following table, the sponsor presents the minimum number of patients, by treatment group, at the pretreatment evaluation and during cycles 6, 13, 19, and 26 of treatment with study drug:

Treatment Group*	Pretreatment	6	13	19	26
Group A 0.625	97	81	65	52	40
Group B 0.625/2.5	86	79	77	65	62
Group C 0.45	95	86	69	64	59
Group D 0.45/2.5	96	85	77	71	66
Group E 0.45/1.5	93	84	77	68	69
Group F 0.3	89	79	75	65	59
Group G 0.3/1.5	98	89	80	75	72
Group H Placebo	93	83	77	62	59

The sponsor presents a summary of the number of subjects, by treatment group, with lipid values that were of "clinical importance" at each time point. These values are defined as:

Parameter	Undesirable Concentration
Total-C	> 7.7 mmol/L
HDL-C	< 0.91 mmol/L
VLDL-C	> 1.29 mmol/L
LDL-C	> 4.14 mmol/L
Total TG	> 3.39 mmol/L
Lp(a)	> 0.0072 mmol/L

The numbers of subjects, by treatment group and by cycle, with abnormal lipid values are presented in the following table. Data are presented for subjects with abnormal values at baseline and at any cycle as well as for those with normal baseline values and abnormal values on treatment.

TABLE 11.2.1C. NUMBER OF SUBSTUDY PATIENTS WITH LIPID VALUES OF CLINICAL IMPORTANCE

Variable Limit Treatment Group	Abnormal Pretreatment Only	Values Abnormal[a]						Values Abnormal[c]				
		Pretreatment	Cycle 6	Cycle 13	Cycle 19	Cycle 26	Direction of Change[b]	Normal Values Pretreatment	Cycle 6	Cycle 13	Cycle 19	Cycle 26
Total-C > 7.7 mmol/L												
Group A 0.625	1	--	--	--	--	--		2	1	--	1	--
Group B 0.625/2.5	2	--	--	--	--	--		--	--	--	--	--
Group C 0.45	2	1	1	1	1	1	1U	3	1	--	3	2
Group D 0.45/2.5	1	--	--	--	--	--		--	--	--	--	--
Group E 0.45/1.5	2	--	--	1	1	1		2	--	1	2	1
Group F 0.3	1	2	2	--	--	--	1E, 1U	1	1	--	--	--
Group G 0.3/1.5	4	2	2	1	1	--	2E	1	--	1	--	--
Group H Placebo	1	1	--	1	1	1	1E	7	1	2	2	4
HDL-C < 0.91 mmol/L												
Group A 0.625	2	--	--	--	--	--		--	--	--	--	--
Group B 0.625/2.5	1	--	--	--	--	--		--	--	--	--	--
Group C 0.45	--	--	--	--	--	--		--	--	--	--	--
Group D 0.45/2.5	2	1	1	--	--	1	1E	2	--	1	1	--
Group E 0.45/1.5	--	--	--	--	--	--		--	--	--	--	--
Group F 0.3	2	--	--	--	--	--		--	--	--	--	--
Group G 0.3/1.5	2	2	1	1	--	--	2U	1	1	--	--	--
Group H Placebo	2	--	--	--	--	--		--	--	--	--	--
VLDL-C > 1.29 mmol/L												
Group A 0.625	2	1	1	1	1	1	1E	3	2	2	2	2
Group B 0.625/2.5	1	3	1	2	1	1	1D, 2E	2	--	2	1	1
Group C 0.45	--	--	--	--	--	--		2	2	--	2	2
Group D 0.45/2.5	3	1	--	--	1	--	1E	--	--	--	--	--
Group E 0.45/1.5	5	--	--	--	--	--		1	--	--	1	--
Group F 0.3	3	1	1	1	--	--	1U	6	5	3	2	1
Group G 0.3/1.5	1	8	6	4	4	5	5E, 3D	2	1	1	--	--
Group H Placebo	2	4	3	3	1	1	1D, 2E, 1U	3	3	--	1	1

TABLE 11.2.1C. NUMBER OF SUBSTUDY PATIENTS WITH LIPID VALUES OF CLINICAL IMPORTANCE

Variable Limit Treatment Group	Abnormal Pretreatment Only	Values Abnormal[a]						Values Abnormal[c]				
		Pretreatment	Cycle 6	Cycle 13	Cycle 19	Cycle 26	Direction of Change[b]	Normal Values Pretreatment	Cycle 6	Cycle 13	Cycle 19	Cycle 26
LDL-C > 4.14 mmol/L												
Group A 0.625	18	17	12	11	8	7	8D, 8E, 1U	2	2	2	--	1
Group B 0.625/2.5	14	10	5	4	4	5	7D, 3E	4	2	3	1	--
Group C 0.45	14	22	16	11	11	8	11D, 9E, 2U	2	1	--	1	1
Group D 0.45/2.5	18	17	12	11	8	13	6D, 8E, 3U	4	2	1	1	3
Group E 0.45/1.5	16	16	12	11	10	12	3D, 10E, 3U	4	--	3	--	2
Group F 0.3	6	29	21	17	18	26	9D, 14E, 6U	5	2	--	3	2
Group G 0.3/1.5	7	22	18	15	12	15	6D, 11E, 5U	7	3	1	--	4
Group H Placebo	7	27	17	19	15	17	4D, 12E, 11U	11	4	6	3	2
TG > 3.39 mmol/L												
Group A 0.625	--	1	1	--	1	1	1E	4	3	2	4	2
Group B 0.625/2.5	1	2	--	2	1	1	1D, 1E	4	1	3	2	1
Group C 0.45	--	--	--	--	--	--		5	4	--	3	2
Group D 0.45/2.5	--	--	--	--	--	--		1	--	--	1	1
Group E 0.45/1.5	1	--	--	--	--	--		1	1	--	--	--
Group F 0.3	1	--	--	--	--	--		4	2	3	1	--
Group G 0.3/1.5	1	4	3	2	1	1	4E	1	1	--	1	1
Group H Placebo	1	1	1	--	1	--	1E	5	4	1	3	--
Lp(a) > 1.29 mmol/L												
Group A 0.625	11	18	17	16	14	9	9D, 7E, 2U	2	--	1	2	1
Group B 0.625/2.5	5	29	25	23	19	20	15D, 11E, 3U	--	--	--	--	--
Group C 0.45	6	30	25	20	18	17	10D, 8E, 12U	5	--	3	1	2
Group D 0.45/2.5	2	18	17	14	13	14	13D, 5E	1	1	--	--	--
Group E 0.45/1.5	4	24	22	23	17	17	11D, 6E, 7U	--	--	--	--	--
Group F 0.3	5	29	24	25	24	20	10D, 11E, 8U	--	--	--	--	--
Group G 0.3/1.5	4	28	24	23	20	19	9D, 14E, 5U	--	--	--	--	--
Group H Placebo	4	27	25	23	20	17	10D, 11E, 6U	1	1	1	1	--

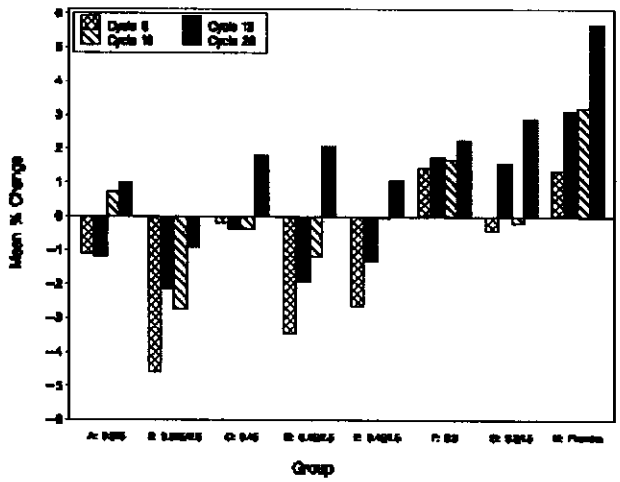
a: Patient with abnormal values before and during treatment.
b: For patients with abnormal values before treatment, the number of patients and the direction of change by any amount was noted as U: increased, d: decreased, E: equivocal (up or down) or no change.
c: Patient with normal values before treatment and abnormal values during treatment.
For patients with more than 1 determination at prescreening or any cycle, any abnormal value was counted.

Comments: This analysis demonstrates that, for all measured parameters and irrespective of treatment group, there was no tendency towards deterioration in lipid levels during the two years of the study. It is known that HRT with estrogen alone exerts beneficial effects on cardiovascular risk factors (fall in total and LDL-C, rise in HDL-C), with variable effects on concentrations of plasma triglycerides (tendency to increase). These effects tend to be diminished by addition of progestogens, although this is probably dose-dependent. The long-term effects of lower doses of progestogens on plasma lipids have not been established. In particular, it is important to establish the effects of adding low doses of progestational agents to varying doses of estrogen. Therefore, the data presented in this section provide valuable information to clinicians.

Individual lipid parameters: The sponsor presents an analysis of mean changes, by treatment group and by cycle, in each of the following: total-C, HDL-C, VLDL-C, LDL-C, TG, and Lp(a).

For total cholesterol, there were small reductions in the groups receiving the two highest doses of CE/MPA, with statistically significant differences from placebo at all time points in the highest combination group (Group B) only. Mean total-C levels rose in the placebo group during the trial. The mean percent changes from baseline during cycles 6, 13, 19, and 26 are shown in the next figure.

FIGURE 11.2.1.1A. TOTAL CHOLESTEROL

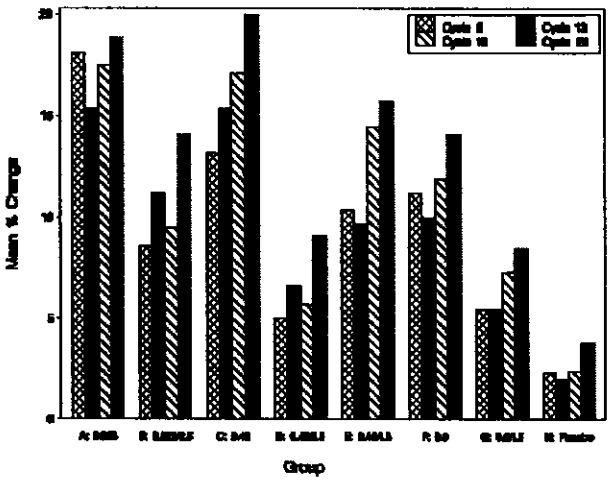


Comments: In my review of this section, I have used the term "statistically significant" in only a nominal sense. Although the analysis of plasma lipids was pre-specified, the results represent a secondary outcome with multiple comparisons. To the best of my knowledge, appropriate adjustments were not part of a statistical analysis plan for these metabolic outcomes. On the other hand, and complicating this issue further, many of the metabolic

outcomes have considerable supporting evidence from prior studies, as well as biological plausibility, based on the known effects of estrogens and the interrelationships among these parameters. I recommend that the outcomes be retained in labeling, with the omission of p-values. Confidence intervals may be permitted, depending on the opinion of Biometrics.

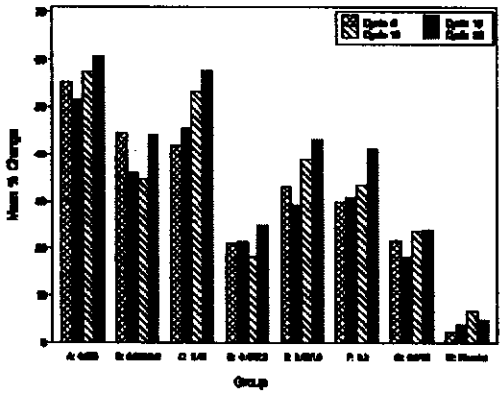
For HDL-C, during the two years of treatment, all active-treatment groups had statistically significant increases from baseline, ranging from 5-20%. These were greater than the 2-4% increases that were found in the placebo group. The data are presented in the following figure:

FIGURE 11.2.1.2A. HDL-CHOLESTEROL



For HDL_2–C, the results are essentially the same:

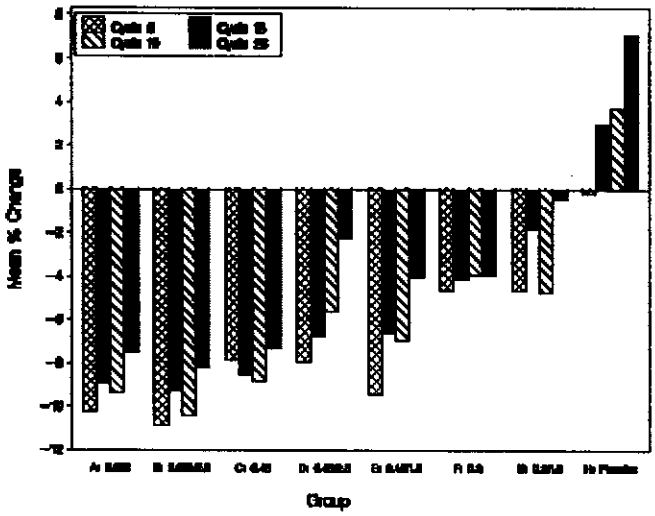
FIGURE 11.2.1.3A. HDL_2-CHOLESTEROL



The results for HDL_3–C were similar(data in NDA).

For LDL-C, there were mean percent decreases from baseline that were statistically significantly different from placebo at most cycles. The levels in the placebo group increased during the trial. The data are shown in the next figure:

FIGURE 11.2.1.5A. LDL-CHOLESTEROL

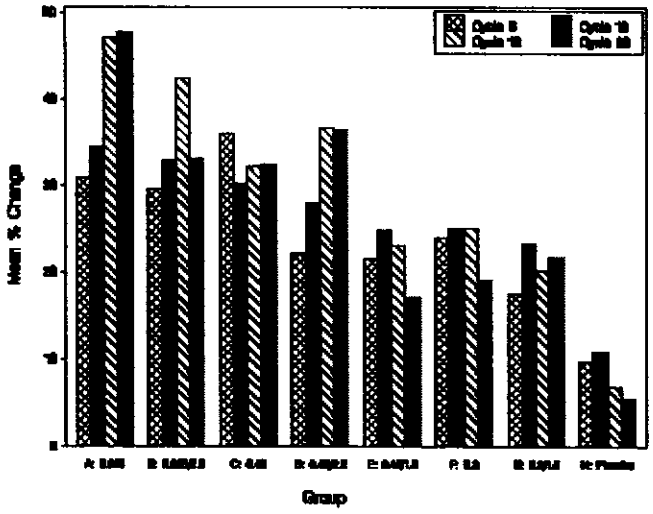


For VLDL-C, there were no statistically significant differences between mean changes in subjects who were in any of the active treatment groups and those who received placebo. There were numerical increases in this parameter in all treatment groups at all cycles.

For TG, there were statistically significant increases from baseline in all active-treatment groups. Treatment with the two highest doses of CE/MPA resulted in changes in TG levels that were statistically significantly different from placebo. Treatment with the lowest doses were associated with somewhat smaller increases in TG levels that were not statistically significantly different from placebo. The data are presented in the next figure:

Appears This Way
On Original

FIGURE 11.2.1.8A. TRIGLYCERIDES



Similar results are presented for VLDL-TG (data presented in NDA).

The sponsor has also analyzed changes in the LDL-C/HDL-C ratio, by study group and by cycle. At baseline, the ratio LDL-C/HDL-C was <3.0 in all groups. During the trial, there were statistically significant mean percent decreases in the ratio in all active-treatment groups, whereas there was no statistically significant change in placebo. These changes were all highly significant, compared to placebo, at all cycles, and for all treatment groups. The data are presented in the sponsor's table 11.2.1.13A. Since the proposed label change includes claims for this ratio, the data are reproduced here.

TABLE 11.2.1.13A. RATIO OF LDL-CHOLESTEROL TO HDL-CHOLESTEROL

Treatment Group[a] Cycle	No. of Pairs	Baseline Mean ± SD	Observed Mean ± SD	% Change From Baseline Mean ± SE	p-Value Within Group	p-Value Versus Placebo	p-Value Versus CE Alone[b]
Group A 0.625							
6	82	2.61 ± 1.01	1.99 ± 0.81	-23.24 ± 1.61	<0.001	<0.001	
13	66	2.56 ± 1.00	2.01 ± 0.84	-19.93 ± 1.88	<0.001	<0.001	
19	53	2.52 ± 0.95	1.94 ± 0.80	-21.51 ± 2.07	<0.001	<0.001	
26	41	2.60 ± 1.02	2.01 ± 0.82	-20.74 ± 2.45	<0.001	<0.001	
Group B 0.625/2.5							
6	79	2.55 ± 0.84	2.07 ± 0.63	-16.64 ± 1.64	<0.001	<0.001	0.004
13	77	2.50 ± 0.80	2.02 ± 0.62	-17.11 ± 1.74	<0.001	<0.001	0.26
19	65	2.45 ± 0.79	1.99 ± 0.63	-17.06 ± 1.86	<0.001	<0.001	0.1
26	62	2.47 ± 0.82	1.96 ± 0.58	-18.58 ± 2.01	<0.001	<0.001	0.49
Group C 0.45							
6	87	2.57 ± 0.88	2.08 ± 0.72	-17.67 ± 1.56	<0.001	<0.001	
13	73	2.54 ± 0.86	1.99 ± 0.68	-20.09 ± 1.79	<0.001	<0.001	
19	64	2.61 ± 0.87	2.02 ± 0.67	-21.58 ± 1.87	<0.001	<0.001	
26	59	2.60 ± 0.90	2.00 ± 0.70	-21.43 ± 2.06	<0.001	<0.001	
Group D 0.45/2.5							
6	86	2.61 ± 0.75	2.29 ± 0.72	-11.30 ± 1.58	<0.001	<0.001	0.003
13	80	2.59 ± 0.77	2.27 ± 0.75	-11.28 ± 1.72	<0.001	<0.001	<0.001
19	71	2.60 ± 0.79	2.33 ± 0.78	-9.29 ± 1.79	<0.001	<0.001	<0.001
26	67	2.59 ± 0.81	2.35 ± 0.83	-9.25 ± 1.94	<0.001	<0.001	<0.001
Group E 0.45/1.5							
6	84	2.44 ± 0.88	2.04 ± 0.82	-16.24 ± 1.59	<0.001	<0.001	0.51
13	77	2.46 ± 0.87	2.09 ± 0.81	-13.51 ± 1.74	<0.001	<0.001	0.007
19	69	2.48 ± 0.86	2.02 ± 0.75	-17.56 ± 1.81	<0.001	<0.001	0.12
26	69	2.51 ± 0.87	2.09 ± 0.78	-16.17 ± 1.90	<0.001	<0.001	0.056
Group F 0.3							
6	80	2.59 ± 0.73	2.23 ± 0.71	-13.78 ± 1.63	<0.001	<0.001	
13	75	2.56 ± 0.75	2.24 ± 0.74	-12.21 ± 1.77	<0.001	<0.001	
19	65	2.56 ± 0.69	2.22 ± 0.67	-13.36 ± 1.87	<0.001	<0.001	
26	60	2.58 ± 0.70	2.20 ± 0.69	-15.35 ± 2.05	<0.001	<0.001	
Group G 0.3/1.5							
6	89	2.65 ± 0.91	2.41 ± 0.91	-9.06 ± 1.54	<0.001	0.001	0.032
13	81	2.60 ± 0.91	2.44 ± 0.89	-5.95 ± 1.69	<0.001	0.002	0.009
19	75	2.58 ± 0.93	2.31 ± 0.94	-10.70 ± 1.73	<0.001	<0.001	0.29
26	74	2.54 ± 0.88	2.33 ± 0.84	-7.57 ± 1.85	<0.001	<0.001	0.004
Group H Placebo							
6	84	2.62 ± 0.82	2.55 ± 0.83	-2.03 ± 1.60	0.16		
13	78	2.63 ± 0.83	2.66 ± 0.87	1.57 ± 1.73	0.44		
19	63	2.64 ± 0.87	2.67 ± 0.87	2.22 ± 1.88	0.22		
26	60	2.62 ± 0.88	2.69 ± 0.92	3.28 ± 2.03	0.087		

a: Identified by dose (mg) of CE or CE/MPA.
b: Comparison with CE alone at same dose.
Data from statistical report LIP.1.

Carbohydrate metabolism:

No labeling claims are made for changes in carbohydrate metabolism. The results of these analyses are briefly reviewed here.

The number of subjects with glucose and insulin data, by treatment group and by cycle, are presented in Table 11.2.2A of the NDA. These are essentially the same as for the lipid analyses. The sponsor presents data, for all treatment groups and at each cycle, for glucose and insulin responses during OGTT. Values are presented at times 0, 30 minutes, 60 minutes, 120 minutes, and 180 minutes (Figures 11.2.2 A, B, C, D, and E of the NDA). The glucose curves were

very similar for all treatment groups at all cycles. Similar data are presented for insulin levels during the OGTT at each cycle. (Figures 11.2.2 F, G, H, I, and J).

The sponsor has also calculated AUCs for glucose and insulin excursion curves and presented the data as mean changes among treatment groups and at each cycle. The AUCs were somewhat variable, both within and between treatment groups. Some of the comparisons (between active-treatment groups and placebo, as well as a few of the within-group changes from baseline) achieved nominal statistical significance. In the placebo group, the glucose AUC declined significantly from baseline at 6 weeks, but not at other times. In the active-treatment groups, there were a few statistically significant within-group increases from baseline. However, with one exception (Group D, 0.45mg/2.5mg) these were not consistent across cycles. Moreover, there was no apparent dose effect.

Comments: None of the increases were considered to be clinically significant by the sponsor. I concur in this conclusion.

There were no statistically significant mean changes in insulin AUC, with the following exceptions:

There were within-group increases in Group A at cycles 19 and 26; in Group B at cycle 19, in Group D (0.45mg/2.5mg) at all cycles, in Group E at cycle 19. There were no within-group changes in the placebo group. Statistically significant differences from placebo were found in Group A at cycle 19, Group B at cycle 19, Group D at cycles 6, 13, and 19, and Group E at cycle 19.

Comments: It is interesting that Group D (CE 0.45mg/MPA 2.5mg) had the highest and most consistent glucose and insulin AUCs. This pattern would suggest increased peripheral resistance to insulin action. The responses were not seen in the CE 0.45mg group alone, nor was the pattern found with any other dose combination. It is most likely that this was a chance finding; further analyses would be required to confirm this. Of interest, neither the insulin nor the glucose AUCs were increased at baseline in this treatment group. In fact, this group had the (numerically) lowest glucose AUC at baseline and the second lowest insulin AUC at that time point. Perhaps this contributed to the increases in both parameters, within this treatment group. The data are presented in Table 11.2.2B of the NDA.

Six subjects were found to have diabetes by standard criteria, and 43 individuals were identified as having impaired glucose tolerance. All were included in the analysis. Of those with diabetes, two were in Group A, two in Group B, one in Group E, and one in Group G. All were identified by OGTT at pre-treatment. The diabetic glucose curves recurred once in three of the subjects (in Groups A and B) and at all four cycles in the other three individuals. The distribution of the 43 with IGTT, by cycle and treatment group, is presented in the following table:

TABLE 11.2.2E. NUMBER OF PATIENTS DIAGNOSED WITH IMPAIRED GLUCOSE METABOLISM

Treatment Group[a]	Pretreatment	During Treatment	Total
Group A 0.625	3	5	6
Group B 0.625/2.5	1	7	7
Group C 0.45	0	5	5
Group D 0.45/2.5	1	5	5
Group E 0.45/1.5	1	4	5
Group F 0.3	3	6	6
Group G 0.3/1.5	2	6	7
Group H placebo	1	1	2

a: Identified by dose (mg) of CE or CE/MPA.

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

Coagulation studies: The sponsor 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. No labeling claims are made for coagulation factor outcomes, and these are reviewed briefly here.

Comments: The effects of estrogen on coagulation factors vary with dose and route of administration. Oral estrogens increase levels of factors VII, IX, X, and X complex. The concentrations of fibrinogen and antithrombin III are reduced by oral estrogens.

The numbers of subjects who contributed data to this analysis are presented by treatment group and by cycle in Table 11.2.3A of the NDA. These did not differ appreciably from the other metabolic analyses.

The following is a brief summary of results of this analysis:

PT: There were no statistically significant changes in PT 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.

PTT: 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 in

PTT between subjects given CE alone and the corresponding CE/MPA group. These differences were neither clinically significant nor consistent.

Factor VIII: There were no statistically significant within-group changes from baseline in Factor VIII levels in any treatment group during cycles 6 and 13, except for a slight increase in Group G. Following cycles 19 and 26, there was a small decrease in mean Factor VIII levels in all treatment groups. There were no differences between the placebo group and any active treatment group.

Fibrinogen Activity: Small but statistically significant mean decreases from baseline were found in all active-treatment groups except 0.3 mg/1.5 mg CE/MPA and placebo during cycles 6 and 13. These changes were significantly different from placebo at cycle 6 for all treatment groups and at cycle 13 for all groups except 0.45 mg CE-alone and the 0.45 mg/2.5 mg and 0.3 mg/1.5 mg CE/MPA groups. In the active-treatment groups, the only significant mean increase from baseline occurred during cycle 19 in the 0.45 mg/2.5 mg CE/MPA group. In the placebo group, there were significant mean increases from baseline during cycles 19 and 26. There were no significant differences in fibrinogen activity between CE alone and comparable CE/MPA treatment groups at any measurement time.

TPA antigen: Levels of TPA antigen were statistically significantly decreased from baseline in all active-treatment groups, with the following exceptions: during cycle 13 with 0.625 mg/2.5 mg CE/MPA and 0.45 mg CE with either 2.5 mg or 1.5 mg MPA and during cycles 13, 19, and 26 with 0.3 mg CE with or without MPA. In the placebo group, there was a small increase that was significant only during cycle 26. There were no differences between CE alone and the comparable CE/MPA. Most changes with active treatment were statistically significantly different from placebo.

Plasminogen Activity: There were statistically significant mean increases over baseline in all active-treatment groups at all measured time points. In placebo, there were significant increases only during cycle 13. All increases associated with active treatment were significantly greater than in placebo. There were no significant differences in PA between CE alone and the comparable CE/MPA treatments at any cycle.

Plasminogen Activator Inhibitor 1 (PAI-1) Activity: There were statistically significant mean decreases in nearly all active-treatment groups. Most of these decreases were significantly different from the changes (mean increases) found in the placebo group. There were no significant differences between the CE and comparable CE/MPA groups.

PAI-1 Antigen: There were statistically significant mean decreases from baseline during cycles 6, 13, 19, and 26 of treatment with 0.625 mg CE alone, during cycles 6, 19, and 26 with 0.45 mg CE alone, and during cycle 19 with 0.625

mg/2.5 mg, 0.45 mg/2.5 mg, and 0.45 mg/1.5 mg CE/MPA. In the placebo group, there were no statistically significant mean differences from baseline. There were sporadic statistically significant differences between mean change with placebo and that with two of the active-treatment groups at one or more cycles. There were no significant differences between CE alone and comparable CE/MPA treatment groups that were consistent across all cycles.

Antithrombin III Activity: For this anticoagulant factor, there were slight but statistically significant mean decreases in all treatment groups at nearly all cycles. There were very few, sporadic, statistically significant differences between the placebo group and the 0.625 mg/2.5 mg and 0.3 mg/1.5 mg CE/MPA groups and the 0.45 mg and 0.3 mg CE-alone groups. There were no significant differences between the CE-alone and the comparable CE/MPA treatment groups.

Protein C: There were a few, sporadic, statistically significant differences from baseline (both increases and decreases), with no consistent changes that could be attributed to treatment.

Protein S Activity: There were statistically significant decreases in all treatment groups except 0.3 mg/1.5 mg CE/MPA and placebo. These decreases were significantly different from placebo group for all treatment groups at most cycles. With a few exceptions, there were no significant differences between the CE-alone and comparable CE/MPA treatment groups.

Comments: Overall, the pattern of mean changes in procoagulant, fibrinolytic, and anticoagulant factors did not suggest any clinically significant alterations in hemostasis that could be attributed to treatment with any of the CE/MPA or CE-alone regimens.

Other efficacy endpoints: The sponsor also evaluated the treatment-related effects of CE and CE/MPA on the incidence of endometrial hyperplasia, the incidence of hot flushes, and vaginal maturation index. In addition, an analysis of vaginal bleeding and amenorrhea was conducted for the two-year sub-study. These are reviewed by DRUDP (HFD-580).

VII. Review of safety

Methodologies for analysis of clinical and laboratory safety, including statistical considerations, are described above, in **Sections VI.4.4, VI.4.5, and VI.4.6.** A complete review of safety has been conducted by the Medical Officer in DRUDP, HFD-580.

VIII. Dosing, regimen, and administration issues

As of this writing, the known benefits of HRT in postmenopausal women are prevention of osteoporosis and treatment of postmenopausal symptoms. HRT undoubtedly improves lipid parameters that are associated with increased cardiovascular risk. However, a beneficial effect on clinical cardiovascular outcomes has not been demonstrated. Risks of HRT include increased incidence of endometrial cancer (largely eliminated by concurrent administration of a progestogen) and breast cancer. The degree to which chronic administration of Premarin 0.625 mg/day increases the risk of breast cancer in a woman with no prior risk factors is not known, but the consensus of epidemiologists is that the relative risk is < 2. It is likely that the lower doses of estrogen will pose even lower risks.

For these reasons, if a woman is to be treated with HRT, the wisest course is to administer the lowest dose of CE/MPA that will be effective for the specific indication or indications. Based on the present study, we know that the lowest available dose of CE/MPA (0.3mg/1.5mg) is effective in preventing bone loss. Although there were trends towards increased effectiveness with the higher doses, the differences between active treatment groups were not statistically significant, using the ITT analysis. It is unclear whether small differences in BMD will ultimately translate into fracture prevention efficacy.

A given patient may require a higher dose of HRT for alleviation of menopausal symptoms, and her response to therapy should guide the choice of dose regimen. Nonetheless, based on results of the present study, the lowest dose preparations (CE 0.3mg/ MPA 1.5mg) should be available for use in this population.

IX. Use in special populations

Combination HRT with CE/MPA is indicated for postmenopausal women with an intact uterus.

X. Conclusions and recommendations

The following conclusions and recommendations apply to bone-sparing and metabolic efficacy parameters only. Furthermore, these comments are limited to efficacy outcomes for which labeling claims are proposed by the sponsor.

The metabolic sub-study was adequately designed to test the safety and efficacy of two years of treatment with various doses of CE/MPA and CE alone. 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/MPA 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 trial clearly demonstrated that all doses of this hormone replacement combination, including the lowest, were effective in preventing loss of BMD in postmenopausal women. This was true irrespective of the statistical approach used in the analysis. At the lumbar spine (the primary efficacy endpoint), women treated with 600mg calcium alone (the placebo group) had a mean annualized BMD decrease of 1.49%. In contrast, women treated with 600mg calcium plus any of the seven active treatment regimens had mean annualized lumbar spine BMD increases ranging from 0.76% in those treated with 0.3 mg CE alone to 2.03% in women treated with CE 0.625mg/MPA 2.5mg (slope analysis). The 0.3mg/1.5mg group had an annualized increase of 0.92%. When calculated as percent change from baseline to cycle 26, the results were similar, with BMD increases ranging from 1.33% in the lowest dose of CE alone to 3.48% in the group receiving 0.625mg/2.5mg. The placebo group lost 2.51% in this analysis. All comparisons with placebo were statistically significant ($p<0.001$ for all comparisons). All within-group changes from baseline were statistically significant ($p<0.001$ for all eight within-group comparisons, including placebo. Of note, the mean increases in BMD were generally greater for the CE/MPA combination groups than for each comparable CE-alone group.

Similar results were obtained for the BMD endpoints at the other three skeletal sites; the statistical comparisons between CE/MPA 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.

By-cycle analysis (cycles 6, 13, 19, and 26) showed clear divergence between all active-treatment groups and placebo by cycle 6 at the lumbar spine and by cycle 13 at the other three skeletal sites.

The study was not powered to detect significant differences between active-treatment groups, and no p-values were assigned to these comparisons. Ninety-five percent confidence intervals on the differences between groups (based on annualized change in BMD derived from the slope analyses) showed no differences between a CE-alone group and the corresponding CE/MPA-combination group(s). Within the combination groups, differences favoring the 0.625 mg/2.5 mg group over both the 0.45 mg/1.5 mg and the 0.3 mg/1.5 mg groups were seen in total body and lumbar spine BMD. There was also a difference favoring the 0.45 mg/2.5 mg group over 0.3 mg/1.5 mg at the lumbar spine.

Confirming the efficacy of all doses of CE/MPA, the sponsor noted substantial and highly 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 ($p<0.001$ for all 56

comparisons with placebo [7 active treatment groups x 4 cycles x 2 bone markers]).

The sponsor carried out a detailed analysis of multiple parameters related to lipid metabolism [Total-C, LDL-C, HDL-C, VLDL-C, TG, and Lp(a)]. The results of this analysis 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 and CE/MPA. 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 statistically significantly greater than the 2-4% increases seen in placebo. For LDL-C, there were mean percent decreases from baseline that were statistically significantly different from placebo at most cycles. The levels of LDL-C increased during the trial. For TG, there were statistically 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 statistically significant mean percent decreases in this ratio in all active-treatment groups, whereas there was no statistically significant change in placebo. These changes were all highly significant, compared to placebo, at all cycles, and for all treatment groups.

Recommendations: I recommend approval of the sponsor's labeling claims for efficacy in prevention of osteoporosis, based on the two-year sub-study, with modifications in the proposed labeling. [redacted] The final recommendation of approval is, of course, contingent on the results of the safety review.

Regarding labeling:

1. **The BMD efficacy data should be based on the ITT approach, with LOCF.**
2. **The sponsor should include an additional cumulative response curve (see Biometrics Review) that depicts BMD changes throughout the population for all four CE/MPA doses and placebo. These curves provide the practitioner with far more information than is obtained through presentation of population means alone. Although this approach is new for estrogens, we have recently used it for other agents. Judging from the appearance of these curves, I see no reason why the sponsor should object to their inclusion.**
3. [redacted]

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DMEDP, HFD-510

XI. Appendix

Review of financial disclosure data:

The sponsor has submitted the names of all clinical investigators whose sites enrolled patients in the 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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