CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-527/S-017

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA:	04-782/S-115
Name of Drug:	Premarin (conjugated estrogens, USP)
NDA:	20-527/S-017
Name of Drug:	Prempro (conjugated estrogens and medroxyprogesterone acetate combination tablets)
Applicant:	Wyeth-Ayerst Research
Indication(s):	Treatment of moderate to severe vasomotor symptoms associated with menopause
Documents Reviewed:	04-782/S-105: Volumes 1-3, 71 20-527/S-017: Volumes 1-3
Medical Reviewer:	Theresa van der Vlugt, M.D./HFD-580
Statistical Reviewer:	Shahla S. Farr, M.S./HFD-715

Introduction:

Both supplemental NDAs include the same prospective, double blind, randomized study (Protocol 0713D2-309-US, the HOPE study) and, therefore, are reviewed together in this document.

The applicant is seeking approval of a new low dose of Premarin (0.45 mg) tablets, administered alone, or in combination with either [redacted] or 1.5 mg MPA for the treatment of moderate to severe vasomotor symptoms (MSVS) associated with menopause. These requests are in the Premarin supplement.

The applicant is also seeking approval of two new lower combination doses of CE/MPA (.45 mg CE/1.5 mg MPA and .3 mg CE/1.5 mg MPA) for [redacted] and for the treatment of MSVS. CE/MPA is administered in a continuous combined regimen. These requests are in the Prempro supplement.

The treatment of MSVS is the focus of this review.

Reviewer's Comments: The sponsor has conducted only one study. In general two adequate and well-controlled Phase 3 clinical trials are needed for approval, so that the results can be reproduced. It is difficult to confirm the results and conclusions based only on one study.

Study Description:

The HOPE study is a placebo-controlled study done in postmenopausal women to evaluate the efficacy and safety of three different strengths of CE alone tablets and four different strengths of combination CE/MPA tablets in reducing the incidence of endometrial hyperplasia associated with the use of unopposed estrogen. A secondary objective is to evaluate the efficacy of CE alone and combination CE/MPA tablets, compared with placebo, in treating MSVS.

The study contains two parts, a basic study and an osteoporosis and metabolic substudy. The basic study is 1 year long (13 cycles); the substudy is 2 years long (26 cycles). The basic study is the focus of these supplemental NDAs.

HOPE is an 8-arm, double-blind, double-dummy, placebo/active-drug-controlled, multicenter outpatient study of lower-dose CE and CE/MPA tablets conducted in healthy postmenopausal women with an intact uterus. Although MSVS was not an entry criterion, the study report states "every effort was made to recruit patients who experienced an average of at least 7 to 8 MSVS per day" (page 41 of study report). All patients were required to undergo a minimum 8-week pre-study washout (women in the basic study) or 12-week week pre-study washout (women in the substudy) for prior estrogen, progestin, or androgen therapy.

A total of 2,805 women were randomized to one of eight study arms. A total of 2,673 were patients who received either active medication or placebo:

1) 0.625 CE (n=348) ("A")
2) 0.625 CE/2.5 MPA (n=331) ("B")
3) 0.45 CE (n=338) ("C")
4) 0.45 CE/2.5 MPA (n=340) ("D")
5) 0.45 CE/1.5 MPA (n=331) ("E")
6) 0.3 CE (n=326) ("F")
7) 0.3 CE/1.5 MPA (n=327) ("G")
8) Placebo (n=332) ("H")

Because MSVS was not an entry criterion, the analysis of MSVS was restricted to those women with at least 7 MSVS recorded on each of the last 7 days of the screening diary card prior to randomization, or at least 50 MSVS on the last 7 days combined. Thus a subgroup of subjects with moderate to severe vasomotor symptoms was analyzed for the MSVS indication (n=241). This group is called the "EE population".

Efficacy Endpoints:
The efficacy endpoints were **the frequency of hot flushes and severity of hot flushes.** The patients recorded each on the daily diary cards. The average daily number and average daily severity of hot flushes were evaluated by week for weeks 1 through 12, and by cycle for cycles 1 through 13. Baseline values for hot flushes were determined from the last 7 days of screening diary card data prior to study medication intake. Baseline and on-therapy averages of the number of hot flushes were calculated as the sum of the number of hot flushes on each day / number of days with data. Severity of hot flushes was recorded as mild (1), moderate (2) or severe (3). Severity was calculated as the sum of the daily severity scores / number of days with data, where the daily severity score was calculated as ((number of mild hot flushes) X 1 + (number of moderated hot flushes) X 2 + (number of severe hot flushes) X 3) / total number of hot flushes on that day. Any day with no flushes was included in the calculations, with a severity of zero. The days with all 3 categories missing were excluded from the calculations.

Vasomotor symptoms were analyzed by an analysis of covariance (ANCOVA) for comparisons between groups, and the least significant difference (LSD) procedure for pairwise comparisons. The baseline mean of VSMS was used as the covariate in the ANCOVAs.

Demographics and Baseline Characteristics:
According to the sponsor, the treatment groups were comparable in all demographic and baseline characteristics for the women evaluated for endometrial hyperplasia.

There were no significant differences among the treatment groups in the number of hot flushes at baseline.

Reviewer's Comments: This comparability of the arms in regards to the demographics and baseline characteristics was assessed only for the patients evaluable for efficacy with respect to ***endometrial hyperplasia****. The demographics and baseline characteristics for the sub-population under the study for* ***vasomotor symptoms*** *were not evaluated.*

Efficacy Results:

The population that was appropriate for the indication, and that was analyzed for the VSMS endpoint was:

> *Efficacy Evaluable (EE) by Week*: All patients randomly assigned to the study, recorded taking study medication, and had at least 7 moderate to severe baseline hot flushes recorded on each of the last 7 days of the screening diary card, or at least 50 moderate to severe hot flushes on the last 7 days combined. At least 5 of 7 days' data had to be available at screening and for an on-therapy week to be included in these analyses. Weeks 1 though 12 were assessed. No procedure for imputing missing data was implemented.

The follwing table is a summary tabulation of the number of hot flushes, adjusted mean and comparisons between the active treatment groups and placebo group in the EE population for weeks 1, 4, 8 and 12:

TABLE: Summary Tabulation Of The Number Of Hot Flushes, Adjusted Mean And The P Values For The Comparisons Between The Active Treatment Groups And Placebo Group In The EE Population For Weeks 1, 4, 8 and 12

Treatment:	N	Adjusted Mean ± SE	P-Value vs. Placebo
Group A: (0.625 CE):			
Week-1	27	8.11 ± 0.82	0.26
Week-4	27	1.96 ± 0.73	<0.001
Week-8	27	0.98 ± 0.65	<0.001
Week-12	26	0.49 ± 0.54	<0.001
Group B: (0.625 CE/2.5 MPA):			
Week-1	34	9.50 ± 0.73	0.93
Week-4	33	3.38 ± 0.66	<0.001
Week-8	31	1.55 ± 0.61	<0.001
Week-12	32	1.16 ± 0.49	<0.001
Group C: (0.45 CE):			
Week-1	32	9.26 ± 0.75	0.89
Week-4	32	5.07 ± 0.67	0.002
Week-8	32	2.85 ± 0.60	<0.001
Week-12	30	2.32 ± 0.50	<0.001
Group D: (0.45 CE/2.5 MPA):			
Week-1	28	9.98 ± 0.81	0.62
Week-4	27	2.45 ± 0.73	<0.001
Week-8	27	1.19 ± 0.65	<0.001
Week-12	26	1.02 ± 0.54	<0.001
Group E: (0.45 CE/1.5 MPA):			
Week-1	29	9.99 ± 0.79	0.61
Week-4	28	3.23 ± 0.72	<0.001
Week-8	27	1.49 ± 0.65	<0.001
Week-12	27	0.94 ± 0.53	<0.001
Group F: (0.3 CE):			
Week-1	30	8.90 ± 0.78	0.65
Week-4	30	4.19 ± 0.70	<0.001
Week-8	29	2.44 ± 0.63	<0.001
Week-12	29	2.01 ± 0.52	<0.001
Group G: (0.3 CE/1.5 MPA):			
Week-1	32	10.60 ± 0.76	0.28
Week-4	32	3.84 ± 0.67	<0.001
Week-8	32	2.41 ± 0.60	<0.001
Week-12	31	1.13 ± 0.50	<0.001
Group H: (Placebo):			
Week-1	28	9.41 ± 0.81	-
Week-4	28	8.09 ± 0.72	-
Week-8	27	7.10 ± 0.65	-
Week-12	25	5.36 ± 0.55	-

*Reviewer's Comments: As seen in the Table, a decrease over time in the **frequency of hot flushes** was observed. These reductions were statistically significant as compared to placebo, at Weeks 4, 8 and 12 in all the active treatment groups. Although not presented here, significant results were observed for the **severity of hot flushes** comparing the active treatment groups to placebo) at Weeks 4, 8 and 12. These results hold after adjustment of alpha level for multiplicity of comparisons.*

Dose response analyses would have been helpful in interpreting the results of this study because of the intentions of each supplemental NDA. One intention was to establish the safety and efficacy of the new low dose of Premarin (0.45 mg) tablets administered alone, or in combination with either [redacted] or 1.5 mg MPA. A second intention was to establish the safety and efficacy of two new lower combination doses of CE/MPA (.45 mg CE/1.5 mg MPA and .3 mg CE/1.5 mg MPA).

Summary of Results:
All active treatment groups in the EE population had a significantly lower mean daily number and severity of hot flushes than the placebo group. These statistically significant differences ($p \leq 0.05$) were seen at Week 4, 8 and 12 of therapy. Differences between treatment groups were similar for each of 3 age categories (<50, 50-59, ≥60 years).

Safety Related Discontinuations:
Adverse events led to withdrawal from the study of a total of 266/2673=10% patients. They were as follows:
Groups: A: 73 (21%), B: 31 (9%), C: 36 (11%), D: 24 (7%), E: 30 (9%), F: 21 (6%), G: 30 (9%), H: 21 (6%).

Conclusion:
The vasomotor endpoints were the average daily frequency and severity of MSVS. There was a significantly lower number and severity of hot flushes in all active treatment groups in the EE population compared with the placebo group. These differences were significant at Weeks 4, 8 and 12.

An ITT analysis of the EE subgroup was not done. However, because data were missing for at most 2 subjects in each treatment group, it is highly unlikely the results reported in this review would change with an ITT analysis.

Differences between treatment groups were similar for each of the 3 age groups (<50, 50-59, ≥60).

Reviewer's Comments: Each dose of CE and each combination of CE/MPA appear to be superior to placebo in reduction of the number and severity of moderate to severe hot flushes in healthy postmenopausal women with intact uterus.

Shahla S. Farr, M.S.
Mathematical Statistician, Biometrics II

Concur: Lisa Kammerman, Ph.D.
Team Leader, Biometrics II

Edward Nevius, Ph.D.
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This review contains 6 pages

/s/

Lisa A. Kammerman
3/18/01 06:14:36 PM
BIOMETRICS
I am signing and submitting this review on behalf of Ms. Shahla Farr, who is the author of this review. I concur with her review.

S. Edward Nevius
3/18/01 06:17:09 PM
BIOMETRICS
Concur with review.

STATISTICAL REVIEW AND EVALUATION

NDA:	04-782/S-115
Name of Drug:	Premarin (conjugated estrogens, USP)
NDA:	20-527/S-017
Name of Drug:	Prempro (conjugated estrogens and medroxyprogesterone acetate combination tablets)
Applicant:	Wyeth-Ayerst Research
Indication:	Protection of the endometrium
Documents Reviewed:	04-782/S-105: Volumes 1-3, 71 20-527/S-017: Volumes 1-3, 71
Medical Reviewer:	Theresa van der Vlugt, M.D. (HFD-580)
Statistical Reviewer:	Lisa A. Kammerman, Ph.D. (HFD-715)

Background:

Calculations of one-sided 95% confidence intervals for rates of hyperplasia, and for rates of carcinoma are the focus of this review. The medical reviewer requested these.

The data come from the HOPE study, which was submitted to both of the supplemental NDAs shown above. The supplements contain two-sided confidence intervals for hyperplasia rates. The medical reviewer reclassified one case of endometrial hyperplasia as a carcinoma. The applicant did not identify any cases of carcinoma.

The 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. Of the 2,805 women randomized, endometrial hyperplasia results for 2,153 women were analyzed. These women had biopsies positive for endometrial hyperplasia during the first 14 cycles, or had a biopsy (negative or positive) done during cycles 12 through 14.

Confidence intervals

The confidence intervals on the next page are exact Clopper-Pearson intervals, as calculated by

Table 1 shows the results for the incidence of endometrial hyperplasia at 1 year; Table 2 shows the carcinoma results.

Table 1: Incidence and one-sided 95% CIs of endometrial hyperplasia at Cycle 13

Treatment:	N	Total number of hyperplasias	One-sided 95% confidence interval
Group A: (0.625 CE)	249	20	(0, 11.5%)
Group B: (0.625 CE/2.5 MPA)	278	0	(0, 1.1%)
Group C: (0.45 CE)	279	9	(0, 5.6%)
Group D; (0.45 CE/2.5 MPA)	273	0	(0, 1.1%)
Group E: (0.45 CE/1.5 MPA)	272	0*	(0, 1.2%)
Group F: (0.3 CE)	269	1	(0, 1.8%)
Group G: (0.3 CE/1.5 MPA)	272	1	(0, 1.8%)
Group H: (Placebo)	261	0	(0, 1.2%)

Source: Columns 1, 2, and 3 are taken from Table 9.2.2.1A in the Study Report. I calculated the confidence intervals.

* The study report indicated 1 endometrial hyperplasia. The medical reviewer reclassified the case as a carcinoma.

Table 2: Incidence and one-sided 95% CIs of endometrial carcinoma at Cycle 13

Treatment:	N	Total number of Carcinomas	One-sided 95% confidence interval
Group A: (0.625 CE)	249	0	(0, 1.3%)
Group B: (0.625 CE/2.5 MPA)	278	0	(0, 1.1%
Group C: (0.45 CE):	279	0	(0, 1.1%)
Group D; (0.45 CE/2.5 MPA)	273	0	(0, 1.1%)
Group E: (0.45 CE/1.5 MPA)	272	1*	(0, 1.8%)
Group F: (0.3 CE)	269	0	(0, 1.2%)
Group G: (0.3 CE/1.5 MPA)	272	0	(0, 1.1%)
Group H: (Placebo)	261	0	(0, 1.2%)

Source: Columns 1 and 2 are taken from Table 9.2.2.1A in the Study Report. I calculated the confidence intervals.

* The medical reviewer reclassified this case as a carcinoma. The applicant originally identified it as an endometrial hyperplasia.

Lisa A. Kammerman, Ph.D.
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/s/

Lisa A. Kammerman
3/18/01 06:24:12 PM
BIOMETRICS

This is my review of the hyperplasia results.

S. Edward Nevius
3/18/01 06:32:32 PM
BIOMETRICS
Concur with review.