CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-843

STATISTICAL REVIEW(S)

Moore

FEB 22 1998

Statistical Review and Evaluation
Clinical Studies

Date:

NDA #: 20-843

Applicant: Schering Corp.

Name of Drug: Prometrium (Micronized Progesterone MP)

Indication: Prevention of endometrial hyperplasia in non-hysterectomized post-menopausal women who are receiving conjugated estrogens tablets

Documents Reviewed: Vol. 1.1, 1.15-1.23

Statistical Reviewer: Kate Meaker, M.S. (HFD-715)

Medical Input: Theresa van der Vlugt, M.D. (HFD-580)

Summary of Studies

The NDA submission includes only 1 clinical trial. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial is a 3-year, prospective, placebo-controlled, double-blind, multicenter study which was sponsored by NIH. Subjects were post-menopausal women, ages 45-64, who were randomly assigned to receive one of the five hormone replacement therapies (HRT) for up to 3 years of treatment. The treatment groups are listed in Table 1. The applicant for this NDA (Schering-Plough Research) provided the micronized progesterone (MP) used for one treatment group in the PEPI trial.

Table 1: Summary of Randomized, Controlled Studies

Study Number (Dates Conducted)	Number of Centers (Locations)	Total Sample Size	Type of Control	Design	Duration of Treatment
H89-117 PEPI (12/89 - 2/94)	7 (all U.S)	875 total subjects 596 total for primary effic. analysis (with uterus) CEE+MP=120 CEE only = 119 MPA+CEE cyclic =118 MPA+CEE cont. = 120 Placebo = 119	placebo and active-control treatment arms	randomized, double-blind, multicenter, parallel arms	3 years

STUDY # H89-117 (PEPI)

Background

The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial is a clinical study which was sponsored by NIH. This was a 3-year, prospective, placebo-controlled, double-blind, multicenter study. Subjects were post-menopausal women, ages 45-64, who were randomly assigned to receive one of the five hormone replacement therapies (HRT) for up to 3 years of treatment. A total of 7 centers participated in the study. The treatment groups and sample sizes are listed in Table 1.

Subjects in the CEE+MP treatment group received conjugated equine estrogen (CEE) 0.625 mg/day during days 1-28 of each 28-cycle, and Micronized Progesterone (MP) 200 mg/day during days 1-12 of each cycle. The CEE-only treatment group received conjugated equine estrogen (CEE) 0.625 mg/day during days 1-28 of each 28-cycle. The placebo group received a blinded placebo tablet during days 1-28 of each 28-cycle.

The original goal of the PEPI study was to investigate the impact of progestins in combination with conjugated equine estrogens (CEE), on lipoproteins and other cardiovascular risk factors, including glucose, insulin, fibrinogen, and blood pressure (8.G.2; V 1.15). Endometrial biopsies were scheduled at baseline and at yearly visits for safety data, not efficacy data, in the original protocol. The results of these endometrial biopsies are now the focus of the analyses for the indication of prevention of endometrial hyperplasia in non-hysterectomized post-menopausal women who are receiving conjugated estrogen tablets.

The primary objective of this data analysis is the evaluation of the effect of MP (as a component of combination estrogen-progestin HRT) on the prevention of endometrial hyperplasia in women with a uterus. The PEPI study enrolled post-menopausal women with or without a uterus. However, the intent-to-treat (ITT) population for this submission is women with an intact uterus at the time of randomization.

The only comparison of interest for this NDA is the CEE+MP treatment group with the CEE-only treatment group. The results for the placebo group are included in the label to provide background information, but are not compared to any active-treatment group because the indication specifies that the intended patient population for micronized progesterone is women also receiving conjugated estrogens.

Primary variable of interest was:

Incidence of endometrial hyperplasia at 36 months

Secondary variables of interest were:

Incidence of endometrial hyperplasia at 12 months
Incidence of endometrial hyperplasia at 24 months
Time to endometrial hyperplasia

A total of 239 patients (with an intact uterus) were randomized to the 2 treatment groups of interest. The two groups were similar with regard to the demographic characteristics at baseline, as shown in Table 2.

Table 2: Demographic characteristics (Study #H89-117)

	MP+CEE (n=120)	CEE only (n=119)
	Mean (Std. Dev.) Range	Mean (Std. Dev.) Range
Age (years)	56.2 (4.1)	56.3 (4.1)
Age at Menopause (years)	50.5 (3.3)	50.6 (3.3)
Duration of Menopause (years)	5.7 (2.7)	5.6 (2.6)
Weight (kg)	67.9 (13.3)	69.9 (12.8)
	n (%)	n (%)
Race		
White	104 (86.7)	112 (94.1)
Black	3 (2.5)	3 (2.5)
Other	13 (10.8)	4 (3.4)

Source: Vol. 1.15, Table G-4

It was possible for subjects to temporarily drop from the study medication and continue in the study. It was also possible for subjects who missed a scheduled visit to continue participation in the study. Participation in the yearly study visits was similar for the 2 treatment groups (Table 3). However, the number of subjects who had endometrial biopsies declined more over time for the CEE-only treatment group than for the CEE+MP treatment group (See Tables 4). The reasons for discontinuing from the biopsy portion of the yearly visits are shown in Table 5.

Table 3: Subject participation in scheduled study visits (Study #H89-117)

	MP + CEE		CEE Only	
	n	% of rand.	n	% of rand.
Randomized	120	100.0	119	100.0
12 Month Visit	116	96.7	115	96.6
24 Month Visit	116	96.7	114	95.8
36 Month Visit	117	97.5	115	96.6

Source: Vol. 1.15, Table G-3

Table 4: Disposition of subjects at scheduled biopsy visits (Study #H89-117)

	MP + CEE			CEE Only		
	n		% of rand.	n		% of rand.
Initial Biopsy (Randomized)	120		100.0	119		100.0
12 Month Visit:						
Discontinued from biopsy portion before 12-month visit; no further biopsies		3	2.5		6	5.0
Missing 12 month biopsy		2	1.7		3	2.5
Biopsy at 12 month visit	115		95.8	110		92.4
24 Month Visit:						
Discontinued from biopsy portion before 24-month visit; no further biopsies		3	2.5		6	5.0
Missing 24 month biopsy		4	3.3		3	2.5
Biopsy at 24 month visit	110		91.7	104		87.4
36 Month Visit:						
Discontinued from biopsy portion before 36-month visit; no further biopsies		4	3.3		9	7.6
Biopsy at 36 month visit	110		91.7	98		82.4

Source: PEPI data set

Table 5: Reasons for Discontinuation from Further Biopsies (Study #H89-117)

	MP + CEE		CEE Only	
	n	% of rand.	n	% of rand.
Discontinued from biopsy portion before 12-month visit	3	2.5	6	5.0
Refused/No entry	1	0.8	3	2.5
Missed Visit	2	1.7	2	1.7
Hysterectomy	0	0.0	1	0.8
Discontinued from biopsy portion before 24-month visit	3	2.5	6	5.0
Refused/No entry	1	0.8	3	2.5
Missed Visit	2	1.7	2	1.7
Hysterectomy	0	0.0	1	0.8
Discontinued from biopsy portion before 36-month visit	4	3.3	9	7.6
Refused/No entry	2	1.7	4	3.4
Missed Visit	0		2	1.7
Hysterectomy	2	1.7	3	2.5

Source: Vol. 1.18, Appendix C-2 and PEPI data set

Applicant's Analysis

The intent-to-treat (ITT) population for this submission is not the full PEPI study patient population. Only women who had an intact uterus at baseline are considered for the analyses for the indication of prevention of endometrial hyperplasia. The ITT population for this review is all women who had an intact uterus at the time of randomization to treatment. There were 120 such subjects in the MP+CEE treatment group and 119 in the CEE-only treatment group.

The incidence of endometrial hyperplasia at each yearly endpoint was analyzed by the applicant using the Cochran-Mantel-Haenszel (CMH) test, adjusting for center. These results are shown in Table 6, and indicate a significantly higher incidence of endometrial hyperplasia in the CEE-only treatment group. Table 7 provides the frequencies of type of endometrial hyperplasia at each time point for descriptive purposes only.

Table 6: Applicant's Results (ITT) (Study #H89-117)

	MP + CEE (n=120)		CEE Only (n=119)		C-M-H test for treatment difference
	n	%	n	%	p-value
Primary Variable					
Incidence of Hyperplasia through 36-months	6	5.0	74	62.2	<0.001
Primary Variable					
Incidence of Hyperplasia through 12 months	3	2.5	43	36.1	<0.001
Incidence of Hyperplasia through 24months	4	3.3	60	50.4	<0.001

Source: Vol. 1.15, Tables G-7, G-8, and G-9.

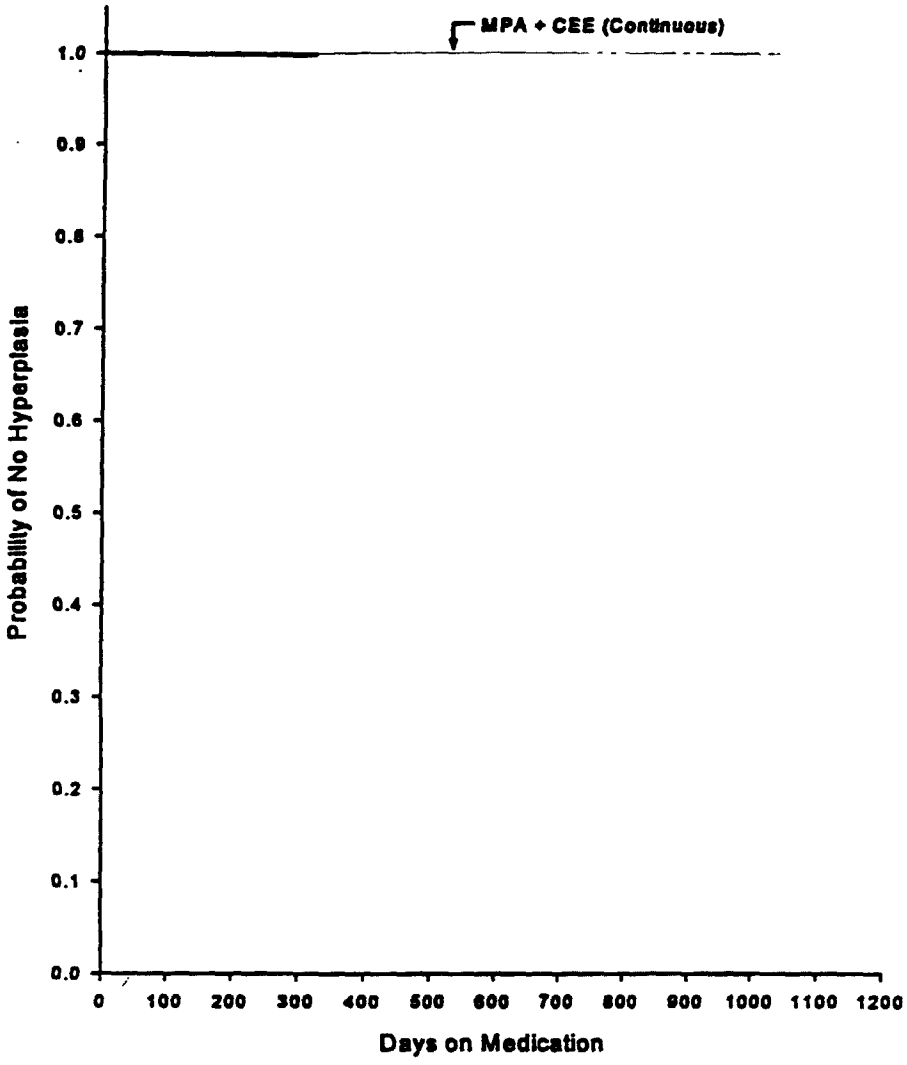
Table 7: Applicant's Results (ITT) (Study #H89-117)

	MP + CEE (n=120)			CEE Only (n=119)		
Timepoint:	12 months	24 months	36 months	12 months	24 months	36 months
Total Number Hyperplasia Cases (% of rand.)	3 (2.5)	4 (3.3)	6 (5.0)	43 (36.1)	69 (50.4)	74 (62.2)
Type of Hyperplasia						
Adenocarcinoma	0	0	0	0	0	0
Atypical Hyperplasia	0	1	1	7	10	14
Complex Hyperplasia	0	0	0	19	22	27
Simple Hyperplasia	3	3	5	17	28	33

Source: Vol. 1.15, Tables G-7, G-8, and G-9.

A Kaplan-Meier survival analysis was performed to investigate the time until the first (of any) diagnosis of endometrial hyperplasia. The applicant included all 5 treatment groups from the PEPI study in this analysis, and did not adjust for center. The plot of the survival curves appears on the following page. The Wilcoxon rank-sum test was used to compare the survival curve of the CEE+MP group to the CEE-only group, and the results indicate a significant difference between the survival curves ($p<.001$).

Figure G-2. Survival Plot of Time to Any Hyperplasia for the Efficacy Evaluable Population (Study No. H89-117).



Reviewer's Analysis

Each biopsy performed during the PEPI study was evaluated by at least 2 and possibly 3 raters in order to reach a final diagnosis. First a local rater at the study center made a diagnosis, then a central rater made an independent diagnosis. If the 2 agreed, that was the final result. If the local and central did not agree, the slide was sent to an arbiter for evaluation. If the arbiter's diagnosis matched either the local or central rater's, that was the final result. If all 3 disagreed, the local rater made the final decision.

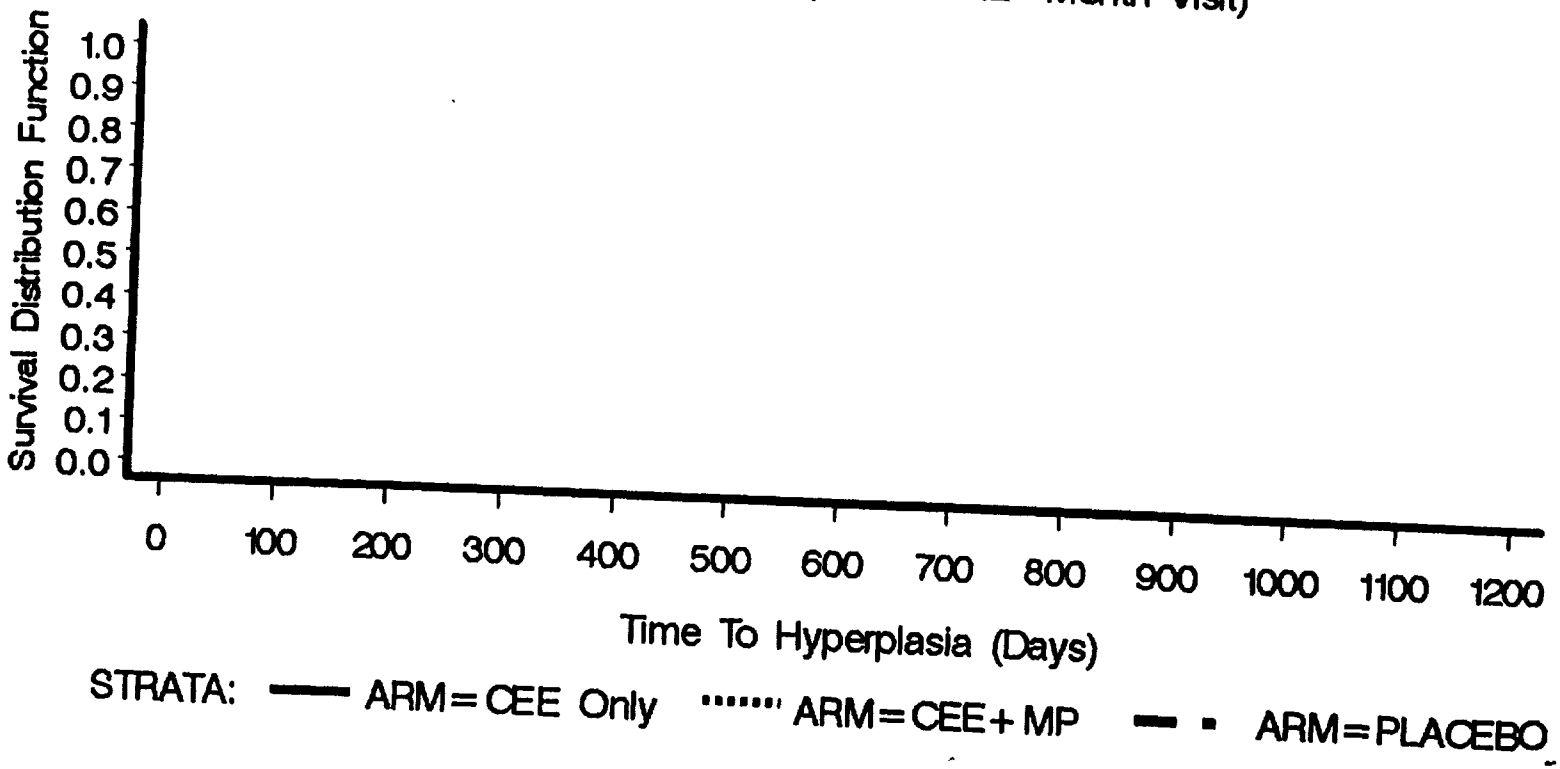
In reviewing the data from the PEPI study, the Medical Officer found one subject (PID=12; 12-month biopsy) for whom the 3 diagnoses disagreed, and the final result did not match the procedure described above from the PEPI protocol. The final result was listed as Normal, although the local rater and arbiter concluded some degree of endometrial hyperplasia. The Medical Officer felt that Normal was an incorrect final diagnosis for this subject.

The Cochran-Mantel-Haenszel (CMH) and survival analyses performed by the applicant were appropriate methods, and the correct ITT patient group was used. The only concern of this reviewer is the possible impact on the results due to patient 12. This reviewer reanalyzed the PEPI study data with patient 12 as having a result of endometrial hyperplasia at the 12-month time point instead of a normal result. As shown in Table 8 and in the survival curve plot on the next page, the results of this reanalysis concur with those of the applicant. The conclusion is that there is a significantly lower incidence of endometrial hyperplasia in the CEE+MP treatment group than in the CEE-only treatment group (CMH; $p<.001$) and there is a significant difference between the survival curves of the CEE+MP group and the CEE-only group (Wilcoxon; $p<.001$).

Table 8: Reviewer's Results (ITT; Changed result for Patient 12 at 12-month) (Study #H89-117)

	MP + CEE (n=120)		CEE Only (n=119)		C-M-H test for treatment difference
	n	%	n	%	p-value
Primary Variable					
Incidence of Hyperplasia through 36-months	7	5.8	74	62.2	<0.001
Primary Variable					
Incidence of Hyperplasia through 12 months	4	3.3	43	36.1	<0.001
Incidence of Hyperplasia through 24months	5	4.2	60	50.4	<0.001

NDA 20–843 Prometrium
Survival Analysis
(Patient ● coded as Hyperplasia at 12–Month Visit)



Additional Analyses

The results of the placebo treatment group were not considered in the efficacy analyses because no comparison of the active-treatment groups to placebo was desired. The Medical Officer decided that the label should include the information from the placebo group to provide background information on the incidence of endometrial hyperplasia in women with an intact uterus who are not receiving any HRT treatment. The results reported by the applicant were confirmed by this reviewer, and are given in Table 9.

Table 9: Reviewer's Results (Placebo Group; ITT) (Study #H89-117)

	Placebo (n=119)		
Timepoint:	12 months	24 months	36 months
Total Number Hyperplasia Cases (% of rand.)	0 (0.0)	1 (0.8)	3 (2.5)
Type of Hyperplasia			
Adenocarcinoma	0	0	1
Atypical Hyperplasia	0	1	0
Complex Hyperplasia	0	0	1
Simple Hyperplasia	0	0	1

Source: Vol. 1.15, Tables G-7, G-8, and G-9.

Conclusions - PEPI Study (Study #H89-117)

The goal of the analyses for this NDA submission was to evaluate the effect of micronized progesterone (as a component of combination estrogen-progestin HRT) on the prevention of endometrial hyperplasia in women with a uterus. The results indicate that there is a significantly lower incidence of endometrial hyperplasia in the CEE+MP treatment group than in the CEE-only treatment group. Also, there is a significant difference between the survival curves for the time until occurrence of endometrial hyperplasia for the CEE+MP group and the CEE-only group (Wilcoxon; $p<.001$), with the CEE-only group showing earlier onset. These results support the conclusion that micronized progesterone provides protection from endometrial hyperplasia in women with an intact uterus who are receiving CEE hormone replacement therapy.

/S/

Katherine B Meaker, M.S.
Mathematical Statistician

Concur: Dr. Nevius KM 2/22/98

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cc:
Archival NDA 20-843
HFD-580
HFD-580/TvanderVlugt, LRarick
HFD-580/DMoore
HFD-715/ENevius, LKammerman, KMeaker, Division File, Chron

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