CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-870

STATISTICAL REVIEW(S)

JUN 29 1998

Statistical Review and Evaluation

NDA #: 20-870

Applicant: Rhone-Poulenc Rorer Pharmaceuticals

Name of Drug: Combipatch (estradiol/norethisterone acetate transdermal system)

Indication: Treatment of Vasomotor symptoms in postmenopausal women and reduction in the incidence of endometrial hyperplasia.

Documents Reviewed: Volumes 1.1, 1.82, 1.88, 1.97, and 1.104 dated August 7, 1997, and Volume 3.1 dated October 28, 1997.

This review pertains to two clinical studies comparing three doses of combipatch with placebo for the treatment of vasomotor systems and two studies of three doses of combipatch with an estradiol patch for the prevention of endometrial hyperplasia.

The Medical Officer for this review is P. Price, M. D. (HFD-580) with whom this review was discussed.

I. Background

In a telephone conversation with the company on October 7, 1997, Dr. Lisa Kammerman (HFD-715) requested that the sponsor provide descriptive results of each of the three placebo arms (three placebo patch sizes) that were combined into the placebo comparative arm for Studies 303 and 304. The sponsor provided these in their October 28, 1997, submission. Dr. Kammerman stated in the telephone conversation that the statistical models were said to be adjusted for imbalances at baseline. Dr. Kammerman asked about the variables that were used to adjust the models. The sponsor stated that all statistical models only adjusted for treatment and center. [Treatment means were adjusted for differences among centers. This is the standard adjustment. The description in the study report led to some confusion.]

This reviewer requested a copy of the sponsor SAS program, which calculated the sponsor derived number of hot flushes per cycle. This reviewer agreed that the program calculated that response variable correctly and he found agreement with spot checks.

II. Studies for Treatment of Vasomotor Symptoms

A. Study Description and Methods of Analyses

Studies 303 and 304 were multicenter, randomized, double blind, parallel group studies comparing three different combipatch

patches with placebo over three cycles for the treatment of vasomotor symptoms in postmenopausal women.

Studies 303 and 304 were similar except that Study 304 was a continuous combined study and Study 303 was a continuous sequential study. In Study 304, the combination patches were worn the full 28-day cycle. In Study 303, a 14.5 cm^2 50mcg estradiol-only patch was worn the first 14 days of a 28-day cycle and the combination patch was worn the last 14 days of the 28-day cycle. These studies included three different patch sizes for the combipatch groups. The 9 cm^2 patch contained 50mcg E2 (17 beta-estradiol) and 140mcg NETA (norethisterone acetate). The 16cm^2 patch contained 50mcg E2 and 250mcg NETA. The 26cm^2 patch contained 50mcg E2 and 400mcg NETA. There were 4 different placebo patches: a 14.5 cm^2 patch corresponding to the E2-only patch and 9cm^2, 16 cm^2, and 26 cm^2 patches corresponding to the three E2/NETA patches.

The placebo group in Study 303 received a placebo 14.5 cm^2 patch (first 14 days) matching the E2 patch and a placebo patch matching one of the three E2/NETA patches (last 14 days). An active treatment group received an E2 patch during the first 14 days and their assigned E2/NETA size patch during the last 14 days of the cycle. All patches had to be changed every 3.5 days during the 14 day part of the 28-day cycle.

The number of hot flushes, the intensity of the hot flushes, and the presence and intensity of sweating experienced during each 24-hour period were recorded once daily in diary cards during the screening period and the randomized treatment period. The women had to have a minimum of eight moderate-to-severe hot flushes per day at baseline. The intensity of hot flushes were graded on a 10 point scale(none=0, mild=1-3, moderate=4-6, and severe=7-9). Sweating was graded on a 4 point scale (none=0, mild=1, moderate=2, and severe=3).

To assess vasomotor symptoms, the analysis of the change in the number of hot flushes, and the intensity of hot flushes and sweating, was conducted using an Analysis of Variance model with the main effects of Treatments and Investigators. Each E2/NETA treatment group was compared to the placebo group using a one-sided test at the 0.05 significance level. [The sponsor justification for using a one-sided test was based on the clinical rationale that the E2/NETA treatments used in these studies would not worsen the vasomotor symptom relief when compared with placebo. This reviewer will report results using two tailed results.] A pairwise step-down procedure was used to maintain a family-wise error (FWE) rate of 5% following a recommendation from the FDA (memo from Dr. Rarick, January 11, 1996). The primary efficacy assessment was endpoint change in number of hot flushes(average for last 14 days). The cycle

analyses used the average from weeks 3 and 4 of the cycle. The baseline average was from the last 14 days before treatment.

B. Results

1. Study 303

There were 220 patients (53 placebo, 55 E2/NETA=50/140, 59 E2/NETA=50/250, and 53 E2/NETA=50/400) enrolled at 26 centers. Twelve patient (9 E2/NETA=50/140, and 1 each of the other 3 groups) discontinued from the study. Five of the discontinuations in the E2/NETA=50/140 group were for adverse clinical experiences.

The treatment groups were comparable at baseline in demographic and baseline efficacy variables.

Table 1 presents the adjusted treatment means and p-values comparing the 3 E2/NETA groups with placebo for the reduction in the number of hot flushes. Significant differences favoring the E2/NETA groups compared to placebo were seen at each of the 3 cycles and endpoint.

Table 2 presents the adjusted treatment means and p-values comparing the 3 E2/NETA groups with placebo for the reduction in the intensity of hot flushes. Significant differences favoring the E2/NETA groups compared to placebo were seen at each of the 3 cycles and endpoint.

Table 3 presents the adjusted treatment means and p-values comparing the 3 E2/NETA groups with placebo for the reduction in the intensity of sweating. Significant differences favoring the E2/NETA groups compared to placebo were seen at each of the 3 cycles and endpoint.

2. Study 304

There were 226 patients (54 placebo, 58 E2/NETA=50/140, 53 E2/NETA=50/250, and 61 E2/NETA=50/400) enrolled at 28 centers. Twenty-three patients (7 placebo, 6 E2/NETA=50/140, 4 E2/NETA=50/250 and 6 E2/NETA=50/400) discontinued from the study. Reasons for discontinuations were similar between the four groups.

The treatment groups were comparable at baseline in demographic variables. The treatments groups differed significantly in the number of hot flushes at baseline but not in the intensity of hot flushes or sweating. The mean number of hot flushes ranged from 11.5 for the E2/NETA=50/140 group to 9.8 for the E2/NETA=50/400 group (Table 4).

Table 4 presents the adjusted treatment means and p-values comparing the 3 E2/NETA groups with placebo for the reduction in the number of hot flushes. Significant differences favoring the E2/NETA groups compared to placebo were seen at each of the 3 cycles and endpoint.

Table 5 presents the adjusted treatment means and p-values comparing the 3 E2/NETA groups with placebo for the reduction in the intensity of hot flushes. Significant differences favoring the E2/NETA groups compared to placebo were seen at each of the 3 cycles and endpoint.

Table 6 presents the adjusted treatment means and p-values comparing the 3 E2/NETA groups with placebo for the reduction in the intensity of sweating. Significant differences favoring the E2/NETA groups compared to placebo were seen at each of the 3 cycles and endpoint.

C. Reviewer's Comments

The protocol stated that treatment by center interaction would be tested for at the 0.15 level in the analysis of reduction in the number of hot flushes. Treatment by center interaction was significant in the ITT population at this level in both studies. The sponsor did analyses pooling centers that had less than two subjects per treatment group and, in this case, the treatment by center interaction p-value > 0.15 in both studies. This reviewer thinks it is appropriate to exclude treatment by center interaction in these studies for the following reasons: there are too many degrees of freedom in the interaction term because of the large number of centers; there are four treatment groups that can cause the inconsistent orderings; more than 50% of the time the placebo group had the lowest reduction; inconsistent orderings are to be expected when sample sizes within centers are small.

In Study 304, all three E2/NETA groups are significantly different from placebo if baseline number of hot flushes are included in the model to adjust for differences at baseline.

The three placebo subgroups wearing differing size placebo patches had comparable mean reductions in hot flushes. Therefore pooling of these subgroups is justifiable.

III. Endometrial Hyperplasia Studies

A. Study Description and Methods of Analyses

Studies 201 and 202 were one year, double-blind, parallel group studies comparing the three E2/NETA patch sizes with an estradiol

50mcg patch group. Studies 201 and 202 were similar except that Study 201 was a continuous sequential study whereas Study 202 was a continuous combined study. The three different E2/NETA groups also used a placebo estradiol patch whereas the estradiol group was composed of three subgroups with differing sizes of placebo E2/NETA patches in order to blind the study. In the continuous sequential trial all patients used an estradiol patch for the first 14 days of each cycle.

The primary efficacy variable was the incidence of endometrial hyperplasia in the "ITT at one year population" among the treatment groups. The "ITT at one year population" was defined to be those patients who had a biopsy during cycles 12 to 14 or developed endometrial hyperplasia any time prior to one year. If a woman dropped out before these cycles without having a biopsy indicating endometrial hyperplasia, it is impossible to know whether she would have endometrial hyperplasia or not if treated for the whole year. This patient was not included therefore in the "ITT at one year population".

Biopsy slides were read by two blinded pathologists. On patients whom the two pathologists disagreed to whether that patient had endometrial hyperplasia, a third blinded pathologist was used to judge whether that patient had endometrial hyperplasia.

The patients recorded the numbers and severity of hot flushes and the presence/severity of sweating in a daily diary. Hot flushes and sweating were graded on the following intensity scale (none=0, mild=1, moderate=2, and severe=3). [The intensity of hot flushes is different than in the vasomotor symptom trials.]

The sponsor stated that a sample size of 91 patients per treatment group would assure 90% power to detect a difference between an E2/NETA patch treatment group and the E2-only treatment group, assuming overall rates of hyperplasia of 12% for the E2-only treatment group and a 1% rate for the E2/NETA patch treatment group, and using a Bonferroni-adjustment on the=0.05 p-value which was assumed to be a one sided p-value. The sponsor used Fisher's exact test to perform the analysis. The sponsor used a one tailed test. [The sponsor's justification for using a one-sided test was based on the clinical rationale that the addition of progestin had no increased effect on the incidence of hyperplasia compared to estrogen alone.] The sponsor planned to enter 600 patients and assumed that 33% of the patients being indeterminate for analysis and hence not included in the "ITT at one year population".

As in the vasomotor studies, this review will use the two-sided Step-down multiple comparison procedure to report p-values.

The sponsor did a confirmatory analysis of the incidence of

hyperplasia stratified by investigators. First, the homogeneity of the odds ratio across investigators was verified, and then a common odds ratio was tested, stratified by investigators. These analyses excluded investigators with zero cases of hyperplasia because the odds ratio would be undefined.

An ITT analysis was done by this reviewer on the reduction at endpoint in the number of hot flushes. [The sponsor provided analyses on patients having more than three hot flushes at baseline and on patients having more than eight hot flushes at baseline. This reviewer thinks it more meaningful to do a full ITT analysis to see whether the E2/NETA patches have different effects on vasomotor symptoms than E2 alone.] Baseline was the mean of the last 14 days of baseline assessment. The mean number of hot flushes at each cycle was calculated during the 14-day window of Weeks 3 and 4 within the cycle. The sponsor used an analysis of variance with treatment and investigator as factors. The reduction in the intensity of hot flushes and sweating were analyzed similarly.

B. Results

1. Study 201

There were 646 patients at 35 centers who were randomized into the study. The table below gives the patient disposition in this study.

	E2 50	E2/NETA			Total
		50/140	50/250	50/400	
	n(%)	n(%)	n(%)	n(%)	n(%)
Randomized	163(100)	162(100)	163(100)	158(100)	646(100)
Completed Study	102(63)	118(73)	112(69)	120(76)	452(70)
Discontinued	61(37)	44(27)	51(31)	38(24)	194(30)
Reasons For Discontinuation					
Adverse	50(31)	19(12)	33(20)	23(15)	125(19)
Clinical Exp. Consent Withdrawn	5(3)	12(7)	8(5)	7(4)	32(5)
Lost to Follow-up	3(2)	5(3)	4(2)	5(3)	17(3)
Protocol deviation	2(1)	5(3)	3(2)	0(0)	10(2)
Other	1(1)	3(2)	3(2)	3(2)	10(2)

The "ITT at one year population" contained 462 patients [115 (71%) E2, 117(72%) E2/NETA=50/140, 113(69%) E2/NETA=50/250, 117 (74%) E2/NETA=50/400]. There were 184 (28%) not included. Of these 184, 101 had only a baseline endometrial biopsy and 80 were not included because they had a biopsy before Cycle 12 that did

not show hyperplasia and no biopsy during Cycles 12 through 14. Three patients were not included because they did not have biopsy data.

The treatment groups were comparable at baseline in demographic variables. One patient in the E2/NETA=50/140 group was determined to have complex hyperplasia with atypia at screening by two of the pathologists. This patient was included in the "ITT at one year population" as having hyperplasia; hyperplasia was found on a biopsy done on treatment. No other patient was determined to have endometrial hyperplasia at baseline.

In the "ITT at one year population", 23 (20%) on E2 were assessed to have endometrial hyperplasia compared to 1(0.85%) on both E2/NETA= 50/140 and E2/NETA=50/400, and 0(0%) on E2/NETA=50/250. The three E2/NETA comparisons with E2 were all significant at the <0.001 level using the two-sided step-down multiple comparison procedure.

If all three E2/NETA groups are combined, the 95% confidence limit on the percentage of patients having endometrial hyperplasia at one year is (0.07%, 2.07%).

The treatment groups were comparable at endpoint in changes from baseline in the number and intensity of hot flushes, and in changes from baseline in the intensity of sweating in the ITT population.

2. Study 202

There were 625 patients at 37 centers who were randomized into the study. The table below gives the patient disposition in this study.

	E2 50	E2/NETA			Total
		50/140	50/250	50/400	
	n(%)	n(%)	n(%)	n(%)	n(%)
Randomized	155(100)	163(100)	149(100)	158(100)	625(100)
Completed Study	76(49)	123(75)	99(66)	93(59)	391(63)
Discontinued	79(51)	40(25)	50(34)	65(41)	234(37)
Reasons For Discontinuation					
Adverse	59(38)	24(15)	42(28)	46(29)	171(27)
Clinical Exp. Consent Withdrawn	6(4)	7(4)	1(1)	7(4)	21(3)
Lost to Follow-up	2(1)	1(1)	4(3)	4(3)	11(2)
Protocol deviation	5(3)	4(2)	2(1)	4(3)	15(2)
Other	7(5)	4(2)	1(1)	4(3)	16(3)

The "ITT at one year population" contained 411 patients [102 (66%) E2, 123(75%) E2/NETA=50/140, 97(65%) E2/NETA=50/250, 89 (56%) E2/NETA=50/400]. There were 214 (34%) not included. Of these 99 had only a baseline endometrial biopsy and 105 were not included because they had a biopsy before Cycle 12 that did not show hyperplasia and no biopsy during Cycles 12 through 14. Nine patients had no biopsy data at all and one patient had no baseline biopsy data.

The treatment groups were comparable at baseline in demographic variables. One patient in the E2/NETA=50/250 group was determined to have hyperplasia at screening by two of the three pathologists. [The two pathologists who read all slides disagreed. One said no hyperplasia whereas the other said hyperplasia. The hyperplasia was diagnosed within the endometrium instead of within an endometrial polyp by the third pathologist.] This patient had no other biopsy and was not included in the "ITT at one year population" by the sponsor but is included in this population by this reviewer after conversations with the medical officer. No other patient was determined to have endometrial hyperplasia at baseline.

In the "ITT at one year population", 38 (37%) were assessed to have endometrial hyperplasia on E2 compared to 1(0.81%) on E2/NETA=50/140 and 1(1.1%)on E2/NETA=50/400, and 1(1.0%) on E2/NETA=50/250. The three E2/NETA comparisons with E2 were all significant at the <0.001 level using the two-sided step-down multiple comparison procedure.

If all three E2/NETA groups are combined, the 95% confidence limit on the percentage of patients having endometrial hyperplasia at one year is (0.2%, 2.81%).

The treatment groups were comparable at endpoint in changes from baseline in the number and intensity of hot flushes, and in changes from baseline in the intensity of sweating in the ITT population.

IV. Overall Conclusions

The three combipatch patches (50/140, 50/250, 50/400) were shown to be effective in reducing vasomotor symptoms (number and intensity of hot flushes and intensity of sweating) in Studies 304 and 304 and in reducing the incidence of endometrial hyperplasia compared to estradiol alone in Studies 201 and 202. The incidence of endometrial hyperplasia at one year was about 1% on the combipatch patches.

/S/

James R. Gebert, Ph.D.
Mathematical Statistician

6/29/98

Concur: Ms. Mele

Dr. Nevius 6/29/98

This review contains 9 pages of text and 6 pages of tables.

cc:
Archival NDA 20-870
HFD-580
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TABLE 1 : Adjusted Mean Changes From Baseline In Cycles 1,2,3 and Endpoint In the Daily Number of Hot Flushes ITT Population in Study 303

	PLACEBO		E2/NETA 50/140		50/250		50/400	
	N=53		N=55		N=59		N=53	
	N	Mean ± S.E.	N	Mean ± S.E.	N	Mean ± S.E.	N	Mean ± S.E.
Cycle 1	53		53		59		53	
Baseline		11.58±0.63		11.38±0.82		10.66±0.40		10.40±0.48
Cycle Mean		8.08±0.54		4.38±0.53		4.61±0.42		3.90±0.39
Adjusted Change		-3.90±0.68		-7.38±0.69		-6.53±0.64		-6.96±0.70
P-value		NA		**<0.001**		**0.002**		**<0.001**
Cycle 2	52		48		58		52	
Baseline		11.64±0.64		11.14±0.83		10.63±0.41		10.45±0.48
Cycle Mean		6.93±0.56		1.75±0.44		2.17±0.33		1.32±0.30
Adjusted Change		-5.03±0.74		-9.78±0.78		-8.87±0.70		-9.56±0.75
P-value		NA		**<0.001**		**<0.001**		**<0.001**
Cycle 3	51		46		58		52	
Baseline		11.30±0.55		11.23±0.86		10.63±0.41		10.45±0.48
Cycle Mean		6.27±0.59		1.48±0.46		1.47±0.27		1.16±0.30
Adjusted Change		-5.32±067		-10.27±0.72		-9.48±0.63		-9.71±0.68
P-value		NA		**<0.001**		**<0.001**		**<0.001**
Endpoint	53		54		59		53	
Baseline		11.58±0.63		11.48±0.81		10.66±0.40		10.40±0.48
Mean		6.28±0.57		2.38±0.56		1.42±0.26		1.13±0.28
Adjusted Change		-5.54±0.73		-9.34±0.72		-9.51±0.68		-9.66±0.74
P-value		NA		**<0.001**		**<0.001**		**<0.001**

P-values are from two-tailed step-down multiple comparison procedure.

TABLE 2 : Adjusted Mean Changes From Baseline In Cycles 1,2,3 and Endpoint In the Intensity of Hot Flushes ITT Population in Study 303

		PLACEBO		E2/NETA 50/140		50/250		50/400
		N=53		N=55		N=59		N=53
	N	Mean ± S.E.	N	Mean ± S.E.	N	Mean ± S.E.	N	Mean ± S.E.
Cycle 1	53		53		59		53	
Baseline		5.36±0.19		5.45±0.21		5.51±0.17		5.23±0.20
Cycle Mean		3.78±0.27		2.14±0.27		2.68±0.26		2.16±0.22
Adjusted Change		-1.68±0.32		-3.45±0.32		-2.93±0.30		-3.06±0.32
P-value		NA		<0.001		0.001		<0.001
Cycle 2	52		48		58		52	
Baseline		5.37±0.20		5.49±0.19		5.51±0.17		5.20±0.20
Cycle Mean		3.29±0.26		0.91±0.21		1.37±0.21		0.80±0.18
Adjusted Change		-2.08±0.29		-4.67±0.31		-4.19±0.28		-4.30±0.30
P-value		NA		<0.001		<0.001		<0.001
Cycle 3	51		46		58		52	
Baseline		5.36±0.20		5.47±0.20		5.51±0.17		5.20±0.20
Cycle Mean		3.18±0.32		0.82±0.22		0.97±0.18		0.56±0.15
Adjusted Change		-2.20±0.30		-4.84±0.32		-4.57±0.28		-4.58±0.30
P-value		NA		<0.001		<0.001		<0.001
Endpoint	53		54		59		53	
Baseline		5.36±0.19		5.50±0.21		5.51±0.17		5.23±0.20
Mean		3.24±0.32		1.24±0.29		0.92±0.17		0.64±0.17
Adjusted Change		-2.08±0.31		-4.37±0.31		-4.52±0.29		-4.53±0.31
P-value		NA		<0.001		<0.001		<0.001

Intensity of hot flushes were rated on a 10-point scale (0=none, 1-3=mild, 4-6= moderate and 7-9=severe).
P-values are from two-tailed step-down multiple comparison procedure.

TABLE 3 : Adjusted Mean Changes From Baseline In Cycles 1,2,3 and Endpoint In the Intensity of Sweating ITT Population in Study 303

	PLACEBO		E2/NETA 50/140		E2/NETA 50/250		E2/NETA 50/400	
	N=53		N=55		N=59		N=53	
	N	Mean ± S.E.	N	Mean ± S.E.	N	Mean ± S.E.	N	Mean ± S.E.
Cycle 1	53		53		59		53	
Baseline		1.79±0.09		1.95±0.07		1.95±0.09		1.96±0.09
Cycle Mean		1.36±0.11		0.88±0.11		1.00±0.11		0.85±0.09
Adjusted Change		-0.50±0.12		-1.15±0.12		-1.02±0.11		-1.13±0.12
P-value		NA		**<0.001**		**<0.001**		**<0.001**
Cycle 2	52		48		58		52	
Baseline		1.78±0.10		1.94±0.07		1.95±0.09		1.94±0.09
Cycle Mean		1.22±0.12		0.38±0.08		0.49±0.08		0.32±0.07
Adjusted Change		-0.58±0.12		-1.60±0.13		-1.53±0.11		-1.62±0.12
P-value		NA		**<0.001**		**<0.001**		**<0.001**
Cycle 3	51		46		58		52	
Baseline		1.77±0.10		1.95±0.07		1.95±0.09		1.94±0.09
Cycle Mean		1.14±0.12		0.35±0.08		0.35±0.08		0.23±0.06
Adjusted Change		-0.73±0.13		-1.76±0.14		-1.71±0.12		-1.77±0.13
P-value		NA		**<0.001**		**<0.001**		**<0.001**
Endpoint	53		54		59		53	
Baseline		1.79±0.09		1.96±0.07		1.95±0.09		1.96±0.09
Mean		1.16±0.12		0.53±0.11		0.35±0.07		0.25±0.07
Adjusted Change		-0.70±0.13		-1.53±0.13		-1.67±0.12		-1.75±0.13
P-value		NA		**<0.001**		**<0.001**		**<0.001**

Intensity of sweating were rated on a 4-point scale (0=none, 1=mild, 2= moderate and 3=severe).
P-values are from two-tailed step-down multiple comparison procedure.

TABLE 4 : Adjusted Mean Changes From Baseline In Cycles 1,2,3 and Endpoint In the Daily Number of Hot Flushes ITT Population in Study 304

	PLACEBO		E2/NETA 50/140		E2/NETA 50/250		E2/NETA 50/400	
	N=54		N=58		N=53		N=61	
	N	Mean ± S.E.	N	Mean ± S.E.	N	Mean ± S.E.	N	Mean ± S.E.
Cycle 1	51		56		50		61	
Baseline		10.56±0.56		11.21±0.49		10.28±0.37		9.81±0.29
Cycle Mean		6.65±0.72		5.20±0.66		3.07±0.55		3.20±0.55
Adjusted Change		-4.43±0.63		-6.40±0.60		-7.64±0.62		-7.06±0.58
P-value		NA		0.014		<0.001		0.001
Cycle 2	50		54		49		58	
Baseline		10.61±0.57		11.11±0.48		10.16±0.36		9.91±0.28
Cycle Mean		5.29±0.63		3.03±0.66		1.55±0.40		1.81±0.50
Adjusted Change		-5.77±0.57		-8.53±0.55		-8.94±0.56		-8.51±0.53
P-value		NA		<0.001		<0.001		<0.001
Cycle 3	47		51		49		55	
Baseline		10.42±0.51		11.15±0.50		10.16±0.36		9.84±0.29
Cycle Mean		4.93±0.69		2.13±0.58		1.12±0.33		0.61±0.20
Adjusted Change		-5.83±0.51		-9.46±0.49		-9.22±0.49		-9.65±0.48
P-value		NA		<0.001		<0.001		<0.001
Endpoint	51		57		52		61	
Baseline		10.56±0.56		11.45±0.53		10.37±0.38		9.81±0.29
Mean		4.80±0.66		2.63±0.65		1.78±0.52		1.33±0.43
Adjusted Change		-6.20±0.58		-9.29±0.56		-8.86±0.57		-8.98±0.54
P-value		NA		<0.001		0.001		<0.001

P-values are from two-tailed step-down multiple comparison procedure.

TABLE 5 : Adjusted Mean Changes From Baseline In Cycles 1,2,3 and Endpoint In the Daily Intensity of Hot Flushes ITT Population in Study 304

	PLACEBO		E2/NETA 50/140		E2/NETA 50/250		E2/NETA 50/400	
	N=54		N=58		N=53		N=61	
	N	Mean ± S.E.	N	Mean ± S.E.	N	Mean ± S.E.	N	Mean ± S.E.
Cycle 1	51		55		49		61	
Baseline		5.49±0.17		6.00±0.22		5.95±0.22		5.59±0.17
Cycle Mean		3.36±0.32		2.88±0.35		1.75±0.30		1.86±0.29
Adjusted Change		-2.30±0.34		-3.22±0.33		-4.33±0.34		-3.84±0.32
P-value		NA		0.036		<0.001		<0.001
Cycle 2	50		53		49		58	
Baseline		5.50±0.17		5.99±0.23		5.87±0.21		5.60±0.17
Cycle Mean		3.06±0.33		1.72±0.32		0.89±0.23		1.04±0.26
Adjusted Change		-2.45±0.34		-4.32±0.33		-5.08±0.33		-4.56±0.32
P-value		NA		<0.001		<0.001		<0.001
Cycle 3	46		50		49		55	
Baseline		5.58±0.18		6.08±0.23		5.87±0.21		5.58±0.16
Cycle Mean		2.76±0.35		1.26±0.30		0.72±0.21		0.38±0.12
Adjusted Change		-2.60±0.32		-4.78±0.31		-5.11±0.30		-5.13±0.29
P-value		NA		<0.001		<0.001		<0.001
Endpoint	50		56		52		61	
Baseline		5.48±0.17		6.02±0.22		5.98±0.21		5.59±0.17
Mean		2.63±0.33		1.44±0.31		1.03±0.27		0.79±0.24
Adjusted Change		-2.79±0.35		-4.58±0.33		-4.96±0.34		-4.79±0.32
P-value		NA		<0.001		<0.001		<0.001

Intensity of hot flushes were rated on a 10-point scale (0=none, 1-3=mild, 4-6= moderate and 7-9=severe).
P-values are from two-tailed step-down multiple comparison procedure.

TABLE 6 : Adjusted Mean Changes From Baseline In Cycles 1,2,3 and Endpoint In the Daily Intensity of Sweating ITT Population in Study 304

	PLACEBO	E2/NETA 50/140	E2/NETA 50/250	E2/NETA 50/400
	N=54	N=58	N=53	N=61
	N Mean ± S.E.	N Mean ± S.E.	N Mean ± S.E.	N Mean ± S.E.
Cycle 1	51	55	49	61
Baseline	1.91±0.08	2.08±0.10	2.01±0.12	1.92±0.08
Cycle Mean	1.27±0.12	1.07±0.12	0.57±0.11	0.72±0.11
Adjusted Change	-0.71±0.13	-1.08±0.13	-1.53±0.14	-1.26±0.13
P-value	NA	**0.035**	**<0.001**	**0.001**
Cycle 2	50	52	49	58
Baseline	1.91±0.09	2.07±0.10	1.99±0.11	1.90±0.08
Cycle Mean	1.11±0.12	0.71±0.13	0.25±0.07	0.40±0.09
Adjusted Change	-0.83±0.13	-1.43±0.13	-1.81±0.13	-1.55±0.13
P-value	NA	**0.001**	**<0.001**	**<0.001**
Cycle 3	47	49	49	55
Baseline	1.95±0.09	2.12±0.10	1.99±0.11	1.88±0.09
Cycle Mean	1.12±0.13	0.42±0.11	0.24±0.07	0.18±0.05
Adjusted Change	-0.81±0.12	-1.78±0.12	-1.79±0.12	-1.77±0.12
P-value	NA	**<0.001**	**<0.001**	**<0.001**
Endpoint	51	55	52	61
Baseline	1.91±0.08	2.09±0.10	2.01±0.11	1.92±0.08
Mean	1.07±0.13	0.52±0.12	0.37±0.10	0.32±0.08
Adjusted Change	-0.88±0.14	-1.65±0.13	-1.70±0.13	-1.65±0.13
P-value	NA	**<0.001**	**<0.001**	**<0.001**

Intensity of sweating were rated on a 4-point scale (0=none, 1=mild, 2= moderate and 3=severe).
P-values are from two-tailed step-down multiple comparison procedure.

JUL 7 1998

Addendum to Statistical Review Dated June 29,1998

NDA #: 20-870

Applicant: Rhone-Poulenc Rorer Pharmaceuticals

Name of Drug: Combipatch (estradiol/norethisterone acetate transdermal system)

In working with Dr. Price on the label for combipatch, it was agreed that 2 endrometrial hyperplasia called focal hyperplasias by the sponsor should be included as endometrial hyperplasias in our reports and in the label. The sponsor agreed with this assessment.

In Study 202 there was one focal hyperplasia in the E2 group making the total number of hyperplasias in this group 39 not 38 as listed in the original review. This change does not have any effect on the significance mentioned or the confidence limits for endometrial hyperplasia pooling all three combipatch groups.

In Study 201, there was an additional focal hyperplasia, which occurred in the E2/NETA (50/250) group making 1 hyperplasia in this group. (This hyperplasia was not mentioned in the sponsor's report and primary tables.) This changes the 95% confidence limit for endometrial hyperplasia in the combined combipatch groups to be (0.18%,2.52%) in Study 201.

/S/

James R. Gebert, Ph.D.
Mathematical Statistician

Concur: Ms. Mele J Mele 7/7/98

Dr. Nevius 7-7-98

cc:
Archival NDA 20-870
HFD-580
HFD-580/Dr. Price
HFD-580/Mr. Markow
HFD-715/Div. File, Chron
HFD-715/Dr. Gebert
HFD-715/Ms. Mele