CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-065

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OCT 14 1999

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA:	21-065
Drug:	FemHRT™ (Norethindrone acetate/ Ethinyl estradiol Tablets)
Sponsor:	Parke-Davis
Date of Submission:	12/16/98, 08/31/99
Type of Submission:	Original NDA, 3S
Reviewer:	Venkateswar R. Jarugula, Ph.D.
Pharmacometrics Consult:	Mike Fossler, Pharm D, Ph.D.

SYNOPSIS

FemHRT™ is a combination hormone replacement product containing norethindrone acetate (NA) and ethinyl estradiol (EE) at [redacted] 1mg NA/5 µg EE (1/5) and [redacted] The proposed indications for this product are in women with intact uterus for the I) treatment of moderate to severe vasomotor symptoms associated with menopause, ii) [redacted] and iii) prevention of osteoporosis. The recommended daily dose range is [redacted] one tablet a day. The dosage has to be titrated based on 3- and 6- month evaluation for vasomotor indications and [redacted] and dosage adjustment for prevention of osteoporosis is based on yearly evaluations.

The active ingredients of FemHRT, norethindrone acetate and ethinyl estradiol, have been widely used for over 30 years in oral contraceptive products. The usual dose of norethindrone has been 1 mg and that of ethinyl estradiol has been higher than the current product, ranging from 20 to 50 µg. Consequently, the distribution, metabolism and excretion information from literature has been summarized in the application. The Human Pharmacokinetics and Biopharmaceutics section of the NDA consists of a total six clinical pharmacology studies that were conducted to characterize pharmacokinetics of norethindrone (N) and EE in healthy postmenopausal women following administration of FemHRT™ tablets. In addition, the populations pharmacokinetics/pharmacodynamics of N and EE were assessed in a multicenter, double-blind, placebo-controlled study of FemHRT in postmenopausal women experiencing vasomotor symptoms.

The pharmacokinetic studies submitted in the NDA have shown that

- The relative bioavailability of NA and EE from FemHRT tablets in comparison to hydroalcoholic solution is 100% and 86%, respectively.

- Single dose administration of FemHRT (1/10) tablets with a high fat meal decreases the rate but not extent of EE absorption. However, the extent of N absorption is increased by 27% with high fat meal. Since, the clinical trials for FemHRT were conducted without regard to food intake, no specific dosing instructions in relation to food intake are recommended in the labeling. However, the food effect results are mentioned in the Clinical Pharmacology section of the labeling.

- The to be marketed formulation is shown to be bioequivalent to the clinical trials formulation at [redacted] and 1/5 doses.

- The drug-drug interaction study has shown that a small amount of NA, when administered alone is metabolically converted to EE such that the exposure to EE following administration of 1 mg of NA may be equivalent to oral dose of approximately 2.8 μg of EE. This conversion does not impact the labeling because the combination at the proposed dosage strengths was studied in clinical trials. However this result was mentioned in the Clinical Pharmacology section of the labeling.

- Steady state accumulation of plasma EE concentrations is predictable from single dose EE pharmacokinetics, whereas N accumulates to a greater extent than predicted due to an increase in sexual hormone binding globulin levels induced by EE.

- The results of population pharmacokinetic analysis indicated less than dose proportional increase in steady-state plasma EE concentrations for NA/EE 1/10 dose compared to 0.5/2.5 and 1/5 doses and higher than dose proportional increase of N at higher 1/5 and 1/0 doses compared to 05/2.5 dose.

- Population pharmacokinetic analysis has shown that the pharmacokinetics of EE is not affected by the covariates such as body weight, body surface area, and smoking whereas the clearance of N is affected by SHBG levels and body weight. Lower clearance values for N are associated with higher SHBG levels and lower body weight. The negative association between clearance of N and SHBG levels was also observed in the multiple dose study.

- Population PK/PD model developed by the sponsor, over estimated the efficacy at the two higher doses by the 12 week treatment period and the residual error in the model is very high (1170%).

Reviewer Comments

1. It should be noted that the clinical division is recommending nonapproval for [redacted]

2. Norethindrone acetate is completely and rapidly deacetylated to norethindrone after oral administration. Hence norethindrone plasma levels (rather than NA) were measured following oral administration of FemHRT tablets.

3. Dose proportionality could not be evaluated by traditional pharmacokinetic study because of the low EE doses (2.5, 5 and 10 μg). However, dose proportionality was evaluated in population PK analysis.

4. The drug-drug interactions observed for the NA/EE oral contraceptives (Estrostep marketed by Parke-Davis) were adapted to this product's labeling.

5. Based on the *in vitro* dissolution data presented, the proposed dissolution specifications for both NA and EE should be revised to Q = at minutes.

6. In the Dosage and Administration section of the Labeling, the phrase should be deleted.

RECOMMENDATION

The Human Pharmacokinetics and Bioavailability section of NDA 21-065 has been found to be acceptable from pharmacokinetic perspective. Reviewer Comment 5 regarding *in vitro* dissolution specification had already been agreed upon by the sponsor. Labeling comments outlined in Section VIII of the review and Reviewer Comment 6 have also been appropriately addressed by the sponsor.

/S/ 10/14/99
Venkateswar R. Jarugula, Ph.D.
Pharmacokinetic Reviewer, HFD-870

RD initialed by Ameeta Parekh, Ph.D., Team Leader /S/

FT signed by Ameeta Parekh, Ph.D., Team Leader /S/ 10/14/99

CPB briefing attendees: Drs M.Chen, A.Parekh, M.Fossler, S.Madani and M.WalKen Kamp-Barnes

cc: NDA 21-065, HFD-580 (Davis, Spell-lasane), HFD-870 (M.Chen, Parekh), B.Murphy [Drug]

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III. BACKGROUND

Menopause occurs usually at age around 50 years and is associated with low levels of estrogens. The hypoestrogenic state in menopausal women produces symptoms such as hot flashes, urinary incontinence, and urinary tract infections, which can affect the quality of life. In addition, chronic estrogen deficiency has been reported to be associated with a number of disease states such as osteoporosis, and cardiovascular disease. Estrogen replacement therapy (ERT) has been shown to alleviate or prevent many of the conditions associated with postmenopausal estrogen deficiency. However, ERT in women with intact uterus is associated with an increased risk of developing endometrial hyperplasia that can be reduced with sequential or concomitant administration of a progestin.

Currently, PremPro and PremPhase which consist of conjugated equine estrogens and medroxy progesterone acetate are available as continuous and sequential HRT in women, respectively. Activelle, consisting of norethindrone acetate and 17β-estradiol, has been recently approved for use as continuous HRT and has yet to reach the market. The active ingredients in FemHRT, norethindrone acetate and ethinyl estradiol, have been widely used in oral contraceptives at higher doses of EE (20 to 50 μg) along with 1 to 1.5 mg of norethindrone acetate compared to the doses used in FemHRT (of EE and 1 mg NA). According to the sponsor, the benefits of FemHRT include additional options for continuous combined HRT with variable doses to optimize treatment and minimal bleeding or spotting resulting in long-term compliance.

IV. PHARMACOKINETICS

Q. What is the relative bioavailability of FemHRT compared to solution?
Q. Is there any effect of food on the pharmacokinetics of FemHRT?

IV A. Relative Bioavailability and Food- Effect (Study 376-395):

This study determined the effect of food on N and EE absorption from NA/EE tablets, and the bioavailability relative to an oral solution. This open-label, single-dose, randomized, 3-way crossover study enrolled 18 healthy postmenopausal women who received the following three treatments with a one week washout period after each treatment.

Trt 1: 2 market-image NA/EE 1/10 tablets administered while fasting,
Trt 2: 2 market-image NA/EE 1/10 tablets given 15 minutes after high fat breakfast
Trt 3: 2 mg NA/20 μg EE hydroalcoholic solution administered while fasting

The formulation (WL 57184-68) used in this study was the 1mg NA/10 μg EE FemHRT tablet formulation. The mean plasma concentrations of EE and N from this study (ordinary and logarithmic axes) are illustrated in Figure 1 and the mean PK parameters are summarized in Table 1.

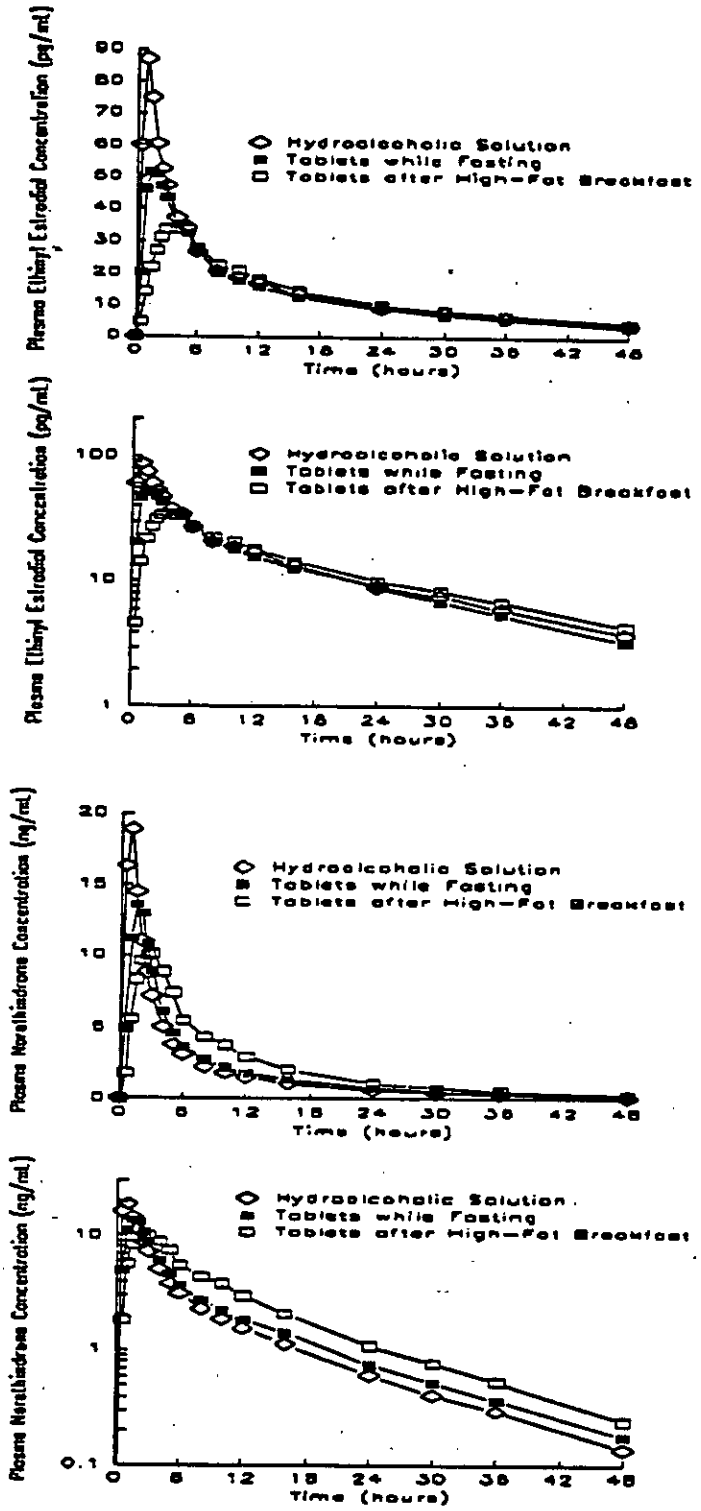


Fig 1. Mean plasma levels of EE and N from Study 376-395.

Q. Is the to-be marketed formulation bioequivalent to the formulation used in clinical trials?

IV B. BIOEQUIVALENCE

The bioequivalence of clinical trial and to be marketed formulations of NA/EE tablets was investigated in studies 376-392 (0.5/2.5 tablets), 376-393 (1/5 tablets) and 376-394 (1/10 tablets). These three studies were randomized, two-period, two treatment crossover studies with 36 healthy postmenopausal women. Since the lower limit of quantitation of EE is [redacted] 6 x0/5/2.5, 3x1/5, and 2x1/10 tablets were used in these studies.

Table 3. Bioequivalence of ethinyl estradiol

Parameter	Marketed	Clinical	Ratio	90% CI
		6 x 0.5/2.5		
Cmax	46.5	48.4	96	92.5-98.9
$AUC_{(0-\infty)}$	679	699	97	94.1 – 101
		3 x 1/5		
Cmax	51.4	47.5	108	103 – 114
$AUC_{(0-\infty)}$	706	679	104	100 – 107
		2 x 1/10		
Cmax	58	54.1	107	103 –111
$AUC_{(0-\infty)}$	773	742	104	101 – 107

Table 4. Bioequivalence of norethindrone

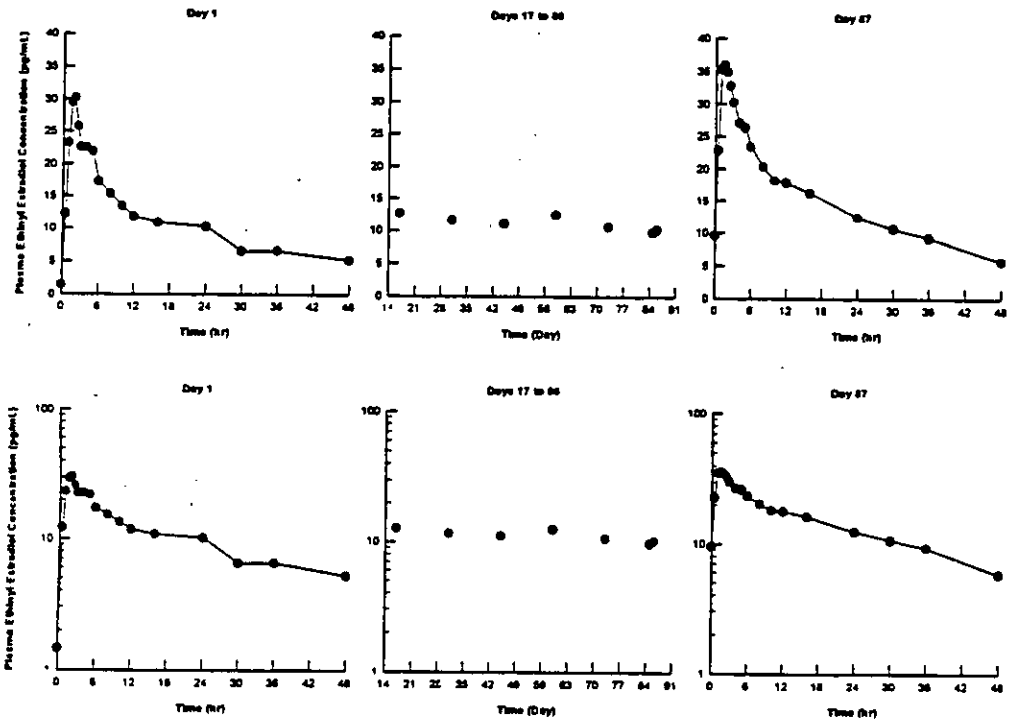
Parameter	Marketed	Clinical	Ratio	90% CI
		6 x 0.5/2.5		
Cmax	17.8	16.8	106	99.6 – 113
$AUC_{(0-\infty)}$	111	109	102	96.3 – 107
		3 x 1/5		
Cmax	19.7	17.1	115	110 – 121
$AUC_{(0-\infty)}$	132	132	100	95.7 – 104
		2 x 1/10		
Cmax	12.3	10.3	119	112 – 129
$AUC_{(0-\infty)}$	79	77.5	102	98.1 – 105

The results of BE studies show that at all three tablet strengths, both EE and N are bioequivalent except for the Cmax of N at 1/10 strength. The 90% CI for Cmax of N at this strength is slightly higher (112-129). Since the clinical division is recommending nonapproval [redacted]

Q. Can we predict steady-state accumulation plasma norethindrone and ethinyl estradiol concentrations?

IV C. Multiple Dose PK

Study 376-391 investigated the multiple dose pharmacokinetics of FemHRT at highest strength 1/10 in 18 healthy postmenopausal women who received: one NA/EE 1/10 tablet in the morning on Day1 and Days 3 to 87. Serial blood samples were collected before and for 48 hours after the dose on Days 1 and 87 and predose on Days 17, 31, 45, 59, 73, 85, and 86 for assay of N and EE. Mean plasma levels of EE and N (ordinary and logarithmic axes) from this study are illustrated in Figure 3.



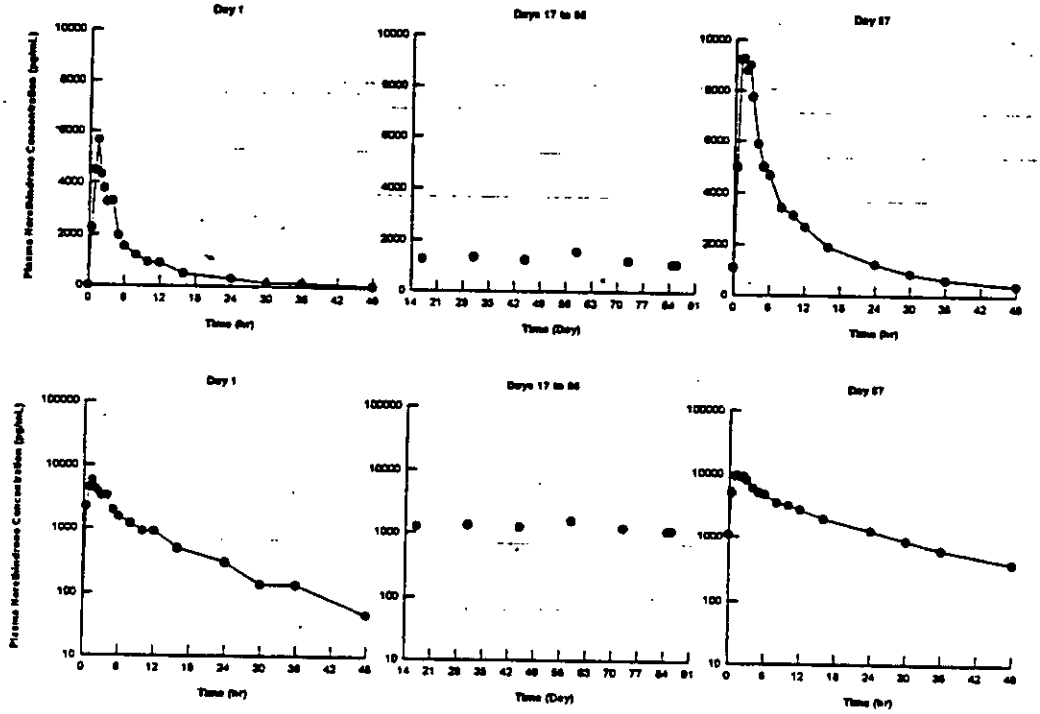


Fig 3. Plasma levels of EE and N following single and multiple dose administration of 1/10 NA/EE tablets

Table 5. Mean (SD) PK parameter of EE and N following single and multiple dosing of 1/10 NA/EE tablets

Parameter	Mean (SD)		Ratio
	Day 1	Day 87	(Day 87/Day 1)
Ethinyl Estradiol			
Cmax (pg/mL)	33.5 (13.7)	38.3 (11.9)	1.14
tmax (hr)	2.2 (1.0)	1.8 (0.7)	0.82
C(24) (pg/mL)	10.3 (7.5)	12.4 (3.6)	1.20
AUC(0-24) (pg·hr/mL)	339 (113)	471 (132)	1.39
AUC(0-tldc) (pg·hr/mL)	497 (184)	ND	ND
AUC(0-∞) (pg·hr/mL)	744[a] (477)	ND	ND
λz (1/hr)	0.027[a] (0.01)	0.03 (0.01)	1.16
t½ (hr)	30.8[a] (14.7)	23.9 (7.1)	0.78
Norethindrone			
Cmax (ng/mL)	5.97 (3.31)	10.7 (3.6)	1.80
tmax (hr)	1.8 (0.8)	1.8 (0.8)	1.00
C(24) (ng/mL)	0.297 (0.299	1.23 (0.80)	4.14
AUC(0-24) (ng·hr/mL)	29.7 (16.5)	81.8 (36.7)	2.75
AUC(0-tldc) (ng·hr/mL)	33.5 (19.2)	ND	ND
AUC(0-∞) (ng·hr/mL)	34.9 (20.1)	ND	ND
λz (1/hr)	0.077 (0.03)	0.058 (0.02)	0.76
t½ (hr)	10.3 (3.7)	13.3 (4.5)	1.29

ND = Not determined.

[a]Unreliable estimate due to high assay variability at low concentrations.

Mean Cmax, Tmax and $AUC_{(0\text{-tldc})}$ of EE following single dose of one NA/EE 1/10 tablet in this study were similar to mean dose-normalized values obtained in other single-dose studies of NA/EE 05/2.5, 1/5, and 1/10 tablets of the NDA. However, mean single-dose terminal elimination rate constant (λz) value (0.0267 hr^{-1}) was lower than the mean values obtained in other single-dose studies (0.0380 to 0.04441 hr^{-1}). This could be due to plasma EE levels during terminal portion being close to the lower limit of detection and the [redacted] used in this study was more variable at low concentrations than [redacted] assay used in other studies. Therefore, λz, t1/2 and $AUC_{(0\infty)}$ of EE following single dose administration are not reliable estimates.

EE levels reached steady state by Day 14 and the accumulation ranged from [redacted] which are slightly less than the theoretical accumulation factor of 1.65 (calculated from a mean λz values of 0.0394 hr^{-1}).

The PK parameters of N following single dose administration were similar to those seen with other studies in the NDA. Steady-state was reached by Day 17 and the plasma levels accumulated by 2.55 (based on $AUC_{0\text{-}24}$ values) which is more than the predicted accumulation (1.21 based on λz value of 0.0736 hr^{-1}). The higher accumulation of N could be due to an increase plasma SHBG concentrations induced by EE.
Norethindrone is reported to be 91% to 96% bound to plasma proteins, predominantly to SHBG. Plasma SHBG concentrations during multiple dose of NA/EE 1/10 were on average 164% higher than baseline values and reached steady state within 14 days. The steady-state plasma protein binding of norethindrone was 96.5% in this study.

Q. Is there a drug-drug interaction between norethindrone and ethinyl estradiol?

IV D. Drug- drug interaction (Study 376-396):

This is an open-label, single-dose, randomized, 3-way crossover study in 18 healthy postmenopausal women who received the following three treatments on three occasions separated by one week washout period.

Treatment 1: 1mg NA/10 µg EE hydroalcoholic solution
Treatment 2: 1 mg NA hydroalcoholic solution
Treatment 3: 10 µg EE hydroalcoholic solution

The mean plasma concentrations and PK parameters of EE and NE from this study are summarized in Figure 2 and Table 2, respectively.

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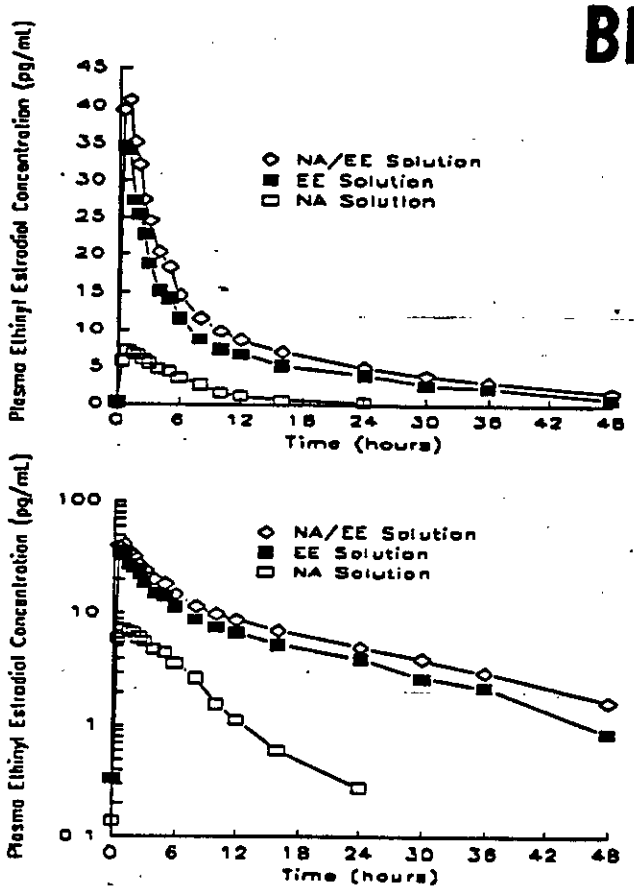

Fig 2. Mean plasma levels of EE and N from the Study 376-396.

Table 2. Mean pharmacokinetic parameters for EE and N

Parameter	10µg EE (N=17)	1/10 NA/EE (N=17)	1mg NA (N=16)	%Difference
Ethinyl Estradiol				
C_{max}[a] (pg/ml)	35.5	41.3	7.03	16.3
T_{max} (h)	0.84	0.79	1.05	-5.95
$AUC_{(0-t)}$[a] (pg.h/ml)	262	351	41.7	34.0
$AUC_{(0-\infty)}$[a] (pg.h/ml)	327	420	ND	28.4
$T_{1/2}$ (h)	18.0	17.7	ND	-1.67
CL/F (ml/min)	535	409	ND	-23.6
Norethindrone				
C_{max}[a] (ng/ml)		12.3	12.3	0.00
T_{max} (h)		0.74	0.70	-5.41
$AUC_{(0-t)}$[a] (ng.h/ml)		42.5	42.5	0.00
$AUC_{(0-\infty)}$[a] (ng.h/ml)		44.7	44.3	-0.89
$T_{1/2}$ (h)		10.7	10.6	-0.94
CL/F (ml/min)		357	356	-0.28

a parameters calculated using log-transformed data

Measurable concentrations of EE were observed following the administration 1 mg NA hydroalcoholic solution. The presence of additional EE in the dosing solutions, the assay interference and conversion during the sample preparation have been ruled out. Therefore the appearance of EE plasma levels following the administration NA solution indicates metabolic conversion of NA to EE. In vivo metabolism of N to EE via aromatization of the A-ring has been reported in the literature.

Plasma EE concentrations following single-dose administration of a 1/10 NA/EE hydroalcoholic solution were consistently higher than those following administration of 10 µg EE solution resulting in 16% higher mean C_{max} and 28% higher $AUC_{(0-\infty)}$ values. This could be mainly explained by the metabolic conversion of N to EE. However it should be noted that the mean EE $AUC_{(0\text{-}tldc)}$ value following administration of 1 mg NA solution (42 pg.hr/ml) was less than the difference between mean EE $AUC_{(0\text{-}tldc)}$ values for the 1/10 NA/EE and 10 µg EE treatments (89 pg.hr/ml). The $AUC_{(0\text{-}tldc)}$ values following 1-mg NA solution are not reliable because of low levels of EE, given the lower limit of qauntitation of [redacted]. A lower systemic clearance of EE when coadministered with NA appears unlikely because t1/2 values following NA/EE 1/10 administration were not different from values following administration of 10 µg EE. Therefore, the sponsor states that the most likely explanation for higher EE levels in 1/10 NA/EE treatment group is metabolic conversion.

Comments:

- The higher plasma EE concentrations observed following the administration of 1/10 NA/EE hydroalcoholic solution than those after 10 µg EE alone are probably due to the metabolic conversion of NA to EE. Several literature articles also reported that NA metabolically converts to EE. This observation is not likely to be of clinical significance because the safety and efficacy of FemHRT was studied in phase III clinical trials at 0.5/2.5, 1/5, and 1/10 dose combinations.

- Following single dose administration, the pharmacokinetics of N is not affected by the coadministration of EE. However, it is known that chronic administration of NA and EE together leads to accumulation of N due to the induction of SHBG synthesis by EE.

Q. Is there any effect of covariates on the pharmacokinetics of N and EE?
Q. What is the relationship between plasma concentrations of EE and its efficacy?

IV E. Population pharmacokinetics/Pharmacodynamics

The population PK/PD of three continuously administered dose combinations of NA/EE were investigated in a multicenter, double-blind, placebo-controlled study of FemHRT for the treatment of vasomotor symptoms in postmenopausal women. After a 2-week baseline period, subjects were randomly assigned to 1 of 4 double-blind parallel treatment groups (3 active and 1 placebo). A total of 266 subjects, with an entry criteria of at least

56 moderate to severe hot flashes per week were enrolled in the study. Plasma EE data was available for 187 and plasma N data was available for 189 subjects.
During the 12 week treatment period, a blood sample was collected at weeks 2, 4, and 12 for assay of plasma N and EE levels. Patients were instructed to record daily the number of mild, moderate , and severe hot flushes.

The following one-compartment open pharmacokinetic model with first order elimination and bolus input was used to fit plasma EE and N concentration versus time data.

$$C = (F*Dose/V)*e^{-(Cl/V)*t}$$

Where C is concentration of EE or N, F is relative bioavailability term, which was fixed to 1 at the lowest dose and estimated at the higher doses to help determine the dose proportionality. Because most samples were collected >8 hours after dosing, there were insufficient data to estimate a first order absorption rate constant. Hence, a one compartment open model with bolus input was chosen. It was assumed that steady state had been reached by week 2. Interindividual variability in CL and V and residual error were assumed to be lognormally distributed. Weight, body surface area, age, race, smoking status, and alcohol consumption were investigated as covariates in the model to assess their influence on variability in plasma levels. For the analysis of norethindrone PK, serum SHBG concentration at week 12 was also investigated as an additional covariate.

PK/PD relationship

The PK/PD relationship between weekly hot flash frequency (at baseline, weeks 2, 4, and 12) and EE exposure was explored using data from ITT analysis of hot flash frequency. Hot flash frequency was modeled as a function of EE dose as follows:

$$WHF = BASE * [1-PMAX * (1-e^{-KP*WEEK})-DMAX*(1-e^{-KP*WEEK})]$$

where WHF is weekly hot flash frequency; BASE is baseline hot flash frequency; PMAX is placebo response, expressed as a fraction of baseline frequency; KP is the rate constant describing the rate at which response to placebo develops; and DMAX is drug response, expressed as a fraction of baseline frequency, which was allowed to vary with dose group.

To determine whether plasma EE exposure was a better predictor of response than EE dose, the weekly hot flash data were fit to the following model:

$$WHF = BASE * [1-PMAX * (1-e^{-KP*WEEK})-DMAX* CAVG*(1-e^{-KP*WEEK})]$$

where CAVG is the predicted steady-state average EE concentration for each individual and is equal to F*DOSE/CL*24.

Results:

Table 6. Population estimates of PK parameters of EE and N

PK Parameter	Mean population estimate	Inter individual variability	Standard Error of estimate
Ethinyl estradiol			
CL (L/hr)	19.4	24%	0.956
V (L)	533	29%	94.0
F for 0.5/2.5	1		NA
F for 1/5	1.06		0.0778
F for 1/10	0.80		0.0636
Norethindrone			
CL (L/hr)	16.6	33%	1.37
V (L)	283	82%	61.5
F for 0.5/2.5	1		NA
F for 1/5	1.18		0.150
F for 1/10	1.41		0.148

Population estimates of CL and V for both N and EE were similar to those estimated from single dose studies with intensive sampling. There was no significant effect of any demographic factor on EE pharmacokinetics. There was a slight tendency for EE clearance to increase with body surface area and clearance to decrease with increased alcohol consumption. Since the improvement in model performance (based on objective function value) was marginal, the effect of these covariates was not considered strong enough to go in the label.

Population estimates of relative bioavailability (F) of EE suggested less than dose proportional increase in steady-state EE concentrations for the 1/10 strength. The drug interaction study showed that a small amount of NA is converted in vivo to EE (1 mg NA providing the equivalent of 2.8 µg oral dose of EE). Thus, the exposure to EE would be expected to reflect actual doses of 3.9, 7.8 and 12.8 µg for the 0.5/2.5, 1/5, and 1/10 combinations, respectively. When these expected dose values are normalized to nominal doses, a ratio of 1:1:0.82 (similar to the ratio of F values observed from population analysis) is obtained. Thus, it was stated by the sponsor that the observed disproportionality in EE steady state levels may be due to conversion of small amount of NA to EE and the higher ratio of EE to NA at 1/10 strength compared to lower strengths. However, it should be noted that this observation is based upon the assumption that the extent of conversion of N to EE is dose proportional.

There was no effect of any covariates on volume of distribution of norethindrone. However, there was a significant effect of both weight and serum SHBG concentration on N clearance, which was fit to the following model:

$CL = \theta_1 * SHBG^{\theta 2} * WEIGHT^{\theta 3}$

Table 7. Estimates of PK parameters from the final covariate model for N

PK Parameter	Mean population estimate	Inter individual variability	Standard Error of estimate
Norethindrone			
θ_1 (L/hr)	7.19	24%	6.88
θ_2	-0.403		0.095
θ_3	0.655		0.171
V (L)	283	82%	61.5
F for 0.5/2.5	1		NA
F for 1/5	1.21		0.153
F for 1/10	1.24		0.107

According to the model used for clearance, higher concentrations of N are associated with higher serum SHBG levels and lower body weight. Of the two factors, serum SHBG accounts for a greater proportion of the variability. The effect of SHBG on clearance is expected because of the induction effect of EE on SHBG. The weight effect was not considered significant because the observed clearances for subjects with weights greater than 90 kg are still within the range observed for patients with lower weights. Thus, the effect of weight on clearance predicted from Pop PK analysis did not lead to any dosage adjustments specifically.

PK/PD results:

The mean predicted weekly hot flash frequency (WHF) values together with observed WHF values are depicted in Figure 4.

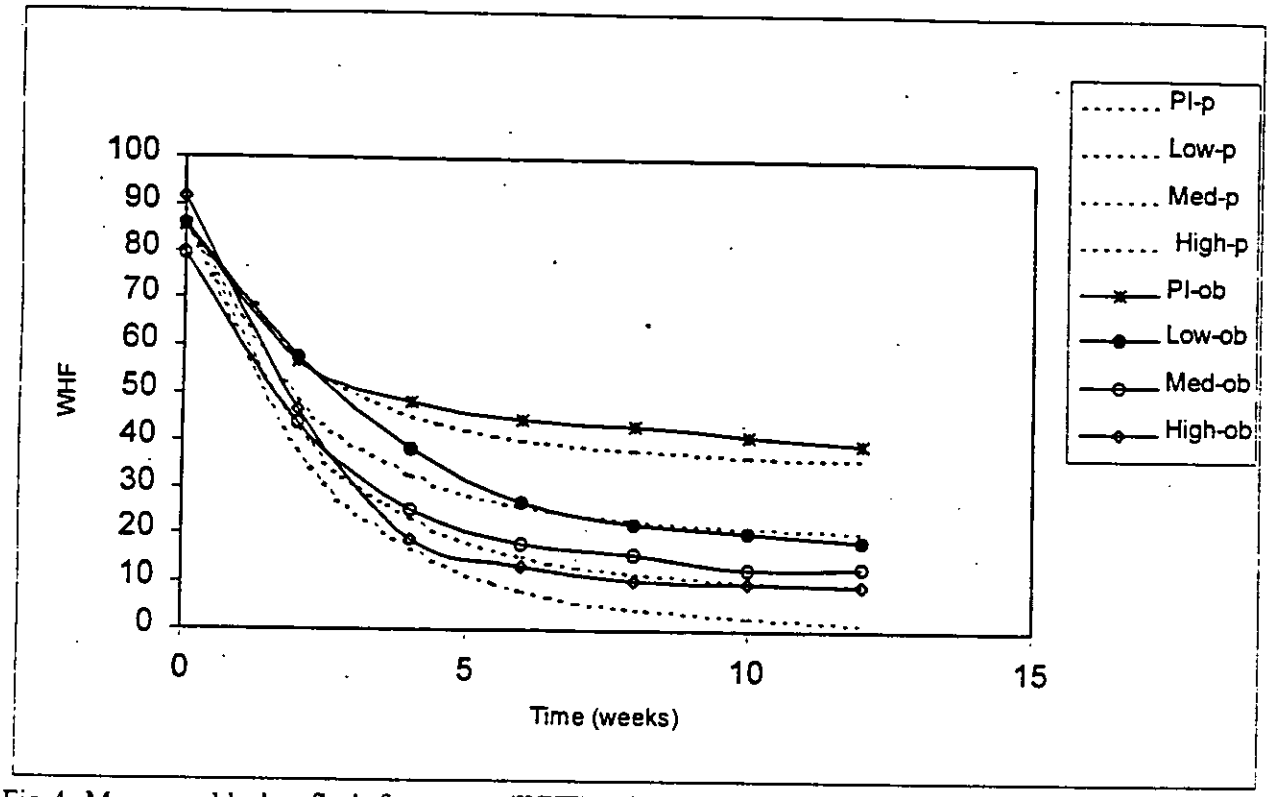

Fig 4. Mean weekly hot flash frequency (WHF) values predicted (dashed lines) by the PK/PD model along with the observed mean values (solid lines).

Table 8. Mean population parameters obtained for PK/PD model:

PK parameter	Mean population Value	Interindividual variability	Standard Error
BASE	85.5	33%	1.98
KP ($week^{-1}$)	0.425	75%	0.0523
PMAX	0.574	31%	0.0528
DMAX for 0.5/2.5	0.182		0.0651
DMAX for 1/5	0.314		0.0565
DMAX for 1/10	0.404		0.0531

BASE=baseline weekly hot flash frequency; KP=Rate constant for onset of placebo-response; PMAX=placebo response; DMAX=Drug response as a proportion of baseline.

According to the PK/PD model, the predicted baseline hot flash frequency was 86 hot flashes per week, and the half-life for onset of effect was 11 days. The maximum placebo response was a decrease of 49 hot flashes, and the additional reduction in hot flash frequency for active treatment was 16, 27, and 35 hot flashes for 0.5/2.5, 1/5, and 1/10 dose groups, respectively.

When hot flash frequency was fitted to linear or Emax models, no improvement in fit was observed. When the average plasma EE levels were incorporated in the model, no improvement in model fitting was observed. Therefore, EE exposure was not proven to be a better predictor of hot flash frequency than EE dose group.

The model predicted response along with the observed response (%reduction in WHF from baseline) at week 12 are illustrated in the following figure.

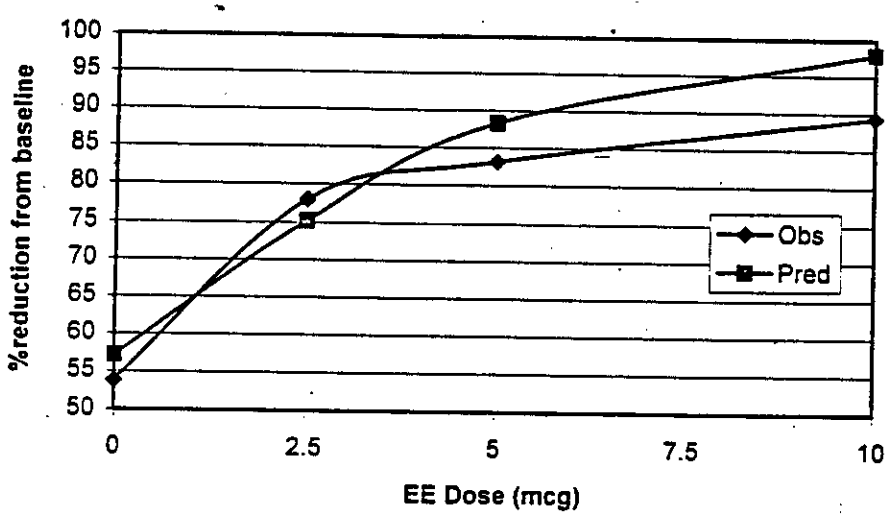

Fig 5. Observed and model predicted response (%reduction in WHF at week 12 from baseline).

From figures 4&5, it is clear that the PK/PD model over estimates the response to the active treatments particularly at the highest dose (1/10 NA/EE). Although the efficacy endpoint, WHF, was measured every week during the 12 week treatment period, only WHF at week 2, 4 and 12 were used in the PK/PD analysis (possibly because blood samples were obtained at these time points). It is possible that the model may fit the data better if additional WHF data at other time points are included in the data analysis.

Comments:

- It should be noted that the residual variability estimated by the PK/PD model is very high (1170%). This could be due to large variability in efficacy and PK and/or model mis-specification or measurement error.

- The PK/PD model over estimated the response at later time points especially at the highest dose (1/10 NA/EE dose). One of the reasons could be because the PK/PD analysis did not include any WHF data between week 4 and 12. Inclusion of all the WHF data collected at weekly intervals during 12 week treatment period instead of just week 2, 4 and 12 data in the PK/PD analysis might improve the model fitting.

- Same KP (rate at which response develops to the treatment) was used in the model for both the placebo and active treatments, which may be a questionable assumption.

Q. What is the dose –response relationship?
Q. How are the doses used in Phase III studies selected?

IV F. DOSE FINDING

The final doses to be investigated in phase III safety and efficacy studies were selected mainly based on two dose finding studies. Study 376-368 was for vasomotor symptoms and while study 376-359 investigated osteoporosis and endometrial protection.
Both these studies were randomized, double-blind, placebo-controlled, parallel group, multicenter studies. Study 376-368 investigated NA/EE 0.2/1, 0.5/2.5, 1/5, and 1/10 doses for vasomotor symptom relief with weekly hot flash frequency as a primary efficacy end point. Study 376-359 also investigated all the doses mentioned above with additional EE alone doses of 1, 2.5, 5, and 10 μg as controls for the combination doses.
The 10 μg was discontinued because of higher incidence of endometrial hyperplasia.
These studies are not formally reviewed herein (refer to Medical Officer's review). However, the results of these studies are summarized in the following table for an understanding of dose response relationship of this drug product.

Table 9. Mean weekly hot flash frequencies at primary time points (weeks 12 and 16) in study 376-368.

Time	Placebo	0.2/1	0.5/2.5	1/5	1/10
Week 12					
N	33	30	28	30	38
Baseline mean	47.0	46.7	44.0	39.8	54.4
Week 12 mean	22.3	12.5	7.3	5.3	4.7
p-value	.....	0.29	0.0001	0.0000	0.0000
%Reduction	52.5	73.2	83.4	86.7	91.3
Week 16					
N	34	29	27	30	32
Baseline Mean	48.8	44.3	44.3	44.0	53.4
Week 16 mean	26.9	9.3	11.6	4.4	3.9
p-value	.....	0.0056	0.0023	0.0000	0.0000
%Reduction	44.9	79.0	73.8	90.0	92.7

The reduction in weekly hot flash frequency at 0.2/1 dose was not significantly different from placebo group while higher doses were significantly effective than placebo. However, the relief in hot flashes does not appear to be different among the 1/5 and 1/10 doses.

Adjusted mean changes from baseline in BMD (mg/cm) from study 376-359 are included in Attachment 1. These results show that 0.5/2.5, 1/5, and 1/10 dose groups resulted in

statistically significant changes in BMD from baseline at month 12 and month 24 when compared to placebo group. However it appears that there is little difference between 1/5 and 1/10 in terms of efficacy. Similar results were also observed in Phase III studies where no significant improvement in the efficacy was noted. Please refer to Medical Officer's review for safety and efficacy questions.

Q. What is the assay method for detection of norethindrone and ethinyl estradiol in plasma? Is the assay method validated and sensitive?

V. ANALYTICAL METHODOLOGY

Two analytical methods were used to assay N and EE in plasma samples obtained from seven clinical pharmacology studies. A [redacted] method was used for samples from Study 376-391 and a [redacted] method was used from samples from all other studies. In both assay methods, concentrations of EE and N were measured simultaneously with similar lower limits of quantitation [redacted] pg/ml for EE and [redacted] pg/ml for N). The [redacted] assays were performed at [redacted] and the [redacted] assays were done at [redacted] The assay validation parameters are summarized in Table 10.

Table 10. Validation parameters for the assay of plasma EE and N concentrations

Study	Calibration range (pg/ml)	Precision (%)	Accuracy (%)
	Ethinyl Estradiol		
376-391	[redacted]	2.4 to 23.1	93.1 to 102
376-390, 376-392, 376-393, 376-394, 376-395, 376-396	[redacted]	1.3 to 9.5	97.4 to 104
	Norethindrone		
376-391	[redacted]	3.1 to 19.7	97.2 to 105
376-390, 376-392, 376-393, 376-394, 376-395, 376-396	[redacted]	1.6 to 18.2	103 to 113

For the [redacted] assay of EE, Equilin has a cross reactivity of 25.4%, and all other steroids have cross reactivity <8.4%. For norethindrone analysis by [redacted] 5α-dihydronorethindrone has cross-reactivity of 46.4%, all other steroids have cross-reactivity of <15.9%.

Comments:

- Since the doses of EE in FemHRT tablets are low (2.5 to 10 µg), multiple tablets of each dose had to be administered to characterize the PK profile following single dose, given the lower limit of quantitation for EE was [ ]pg/ml.

- The [ ]method, used in the multiple dose study, has significant cross reactivity to the related steroids. However, according to the sponsor, these potential cross-reactants were separated from EE and N during[ ]

- The precision of the[ ]assay for EE at the lower end of the calibration was inadequate to obtain reliable estimates of EE elimination rate constant after a single dose oral administration of NA/EE 1/10 in Study 376-391.

Q. **Are there any differences between to be marketed and clinical trials formulations?**
If so, did the sponsor conduct appropriate studies to support the formulation changes?

VI. FORMULATION

Four different formulations were identified by the sponsor for the development of this drug product. These are early clinical, clinical, developmental market formulation, and market formulations.

The composition of all clinical and to be marketed formulations are essentially the same both qualitatively and quantitatively except for the following differences.
Early clinical formulations (40A1, 37A1, and 38A1 representing[ ]1/5, and[ ] dosage strengths, respectively) were manufactured at Warner-Lambert's Fajardo, Puerto Rico facility using a[ ]and the[ ]process. A 5% overage of EE was added in subsequent clinical batches (40A2, 37A2, and 38A2).
The manufacturing process for the developmental market formulations (with numbers 69, 67 and 68) was same as for clinical formulations except that a[ ]processor with [ ]was used. This is considered a major change in process. Three different shapes,[ ]'D" shape for 1/5 strength, and [ ]were chosen for developmental market formulations.

[ ]was initially identified as a contract manufacture for commercial production and later changed to Duramed. The amount of EE overage was reevaluated and was reduced from 5% to 2%. The formulations with 2% overage at [ ]were identified in the NDA as 69A2, 67A2, and 68A2 for[ ]1/5, and[ ] dosage strengths, respectively. Subsequently, the manufacturing site was changed to Duramed Pharmaceuticals Inc in Cincinnati, Ohio. According to the sponsor, the entire

manufacturing equipment train and manufacturing process was physically transferred to the Duramed facility with the only difference being an overlay of [redacted] in the processor during manufacturing to improve the overall safety of the manufacturing operation. The critical manufacturing parameters (such as [redacted] established with [redacted] batches remain the same. These formulations at Duramed were identified as 69A3, 67A3, and 68A3. Based on the EE results for the Duramed stability batches, the 2% EE overage has been eliminated. The final to be marketed formulations were identified as 69A5, 67A5, and 68A5 and the composition of these formulations is listed in the table below. A table summarizing the differences among the clinical and market formulations is included in attachment 2.

Table 11. Composition of the to be marketed formulation:

Components	1/5
Norethindrone acetate	1.0 mg
Ethinyl Estradiol	5.0 µg
Lactose Monohydrate	
Corn Starch	
Microcrystalline Cellulose	
[redacted]	
Calcium stearate	
[redacted]	

Sponsor conducted three bioequivalence studies between the pivotal clinical trial formulations 40A2, 37A2, and 38A2, and commercial formulations, 69, 67, and 68 to support the major process change between the clinical and market formulations at three strengths (refer to Bioequivalence section).

In vitro dissolution comparison was made between [redacted] batches and Duramed batches to support the change in manufacturing site, and [redacted] overlay (see attached comparative dissolution data in Attachment 2).

Comment:
The changes in the formulations are adequately supported by bioequivalence study and *in vitro* dissolution comparisons.

APPEARS THIS WAY
ON ORIGINAL

Q. What are the proposed in vitro dissolution method and specifications for quality control?

VII. *IN VITRO* DISSOLUTION

The sponsor proposed the following dissolution method and specifications:

Apparatus:
Medium:

Speed:
Temperature:
Specifications:

The dissolution method including the medium and other conditions are same as the USP listed ones for NA/EE tablets. Sponsor used a different medium for early development of FemHRT tablets. Since stability of NA could not be maintained in samples for more than one hour in this medium, sponsor conducted solubility and stability investigations in different media and chose . The choice of the new medium was confirmed by comparing the dissolution profiles of four FemHRT tablet lots in both media. The new medium resulted in similar dissolution profiles to the previous medium.

In vitro dissolution data for the batches used in pivotal clinical and bioequivalence studies together with the data for the to be marked formulation are included in attachment 3.

Comments:

- Although, the USP recommended method and medium was used, the dissolution of both NA and EE from FemHRT tablets appear to be very rapid (about in minutes, the first sampling time point).

- Based on the dissolution data for the batches manufactured at and Duramed, the dissolution specification should be revised to Q= at minutes for both NA and EE.

APPEARS THIS WAY
ON ORIGINAL

VIII. LABELING

It is recommended that the Clinical Pharmacology section of the physician's labeling be revised as follows (additions are underlined and deletions are stricken out):

CLINICAL PHARMACOLOGY

Estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than [redacted] estrone and estriol at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 µg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism and estrogen replacement therapy acts to reduce the elevated levels of these hormones seen in postmenopausal women.

[redacted]

Pharmacokinetics

Absorption and Bioavailability

Norethindrone acetate (NA) is completely and rapidly deacetylated to norethindrone after oral administration, and the disposition of norethindrone acetate is indistinguishable from that of orally administered norethindrone. Norethindrone acetate and ethinyl estradiol (EE) are rapidly absorbed from FemHRT tablets, with maximum plasma concentrations of norethindrone and ethinyl estradiol generally occurring 1 to 2 hours postdose. Both are subject to first-pass metabolism after oral dosing, resulting in ~~a~~ an absolute bioavailability of approximately 64% for norethindrone and 55% for ethinyl estradiol.

[redacted]

Bioavailability of FemHRT tablets is similar to that of solution for norethindrone and slightly less for ethinyl estradiol.

Administration of [redacted] with a high fat meal decreases rate but not extent of ethinyl estradiol absorption. The extent of norethindrone absorption is increased by 27% following administration of [redacted] with food.

The full pharmacokinetic profile of femhrt (1/5) was not characterized due to assay limitations. However, the multiple dose pharmacokinetics of 1mg NA/10 ug EE was studied in 18 postmenopausal women and the Mean plasma concentrations [redacted] are shown below (Figure 1) and pharmacokinetic parameters are found in Table 1. Based on a population pharmacokinetic analysis, mean steady-state concentrations of norethindrone for the FemHRT 1 mg NA/5 mcg EE (1/5) and FemHRT 1/10 tablets are slightly more than proportional to dose when compared to the FemHRT 0.5 mg NA/2.5 mcg EE (0.5/2.5) tablet [redacted] explained by higher sex hormone binding globulin (SHBG) concentrations. Mean steady-state plasma concentrations of ethinyl estradiol for the FemHRT 0.5/2.5 and FemHRT 1/5 tablets are proportional to dose, but there is a less than proportional increase in steady state concentration for the [redacted] 1/10 tablet [redacted]

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ON ORIGINAL

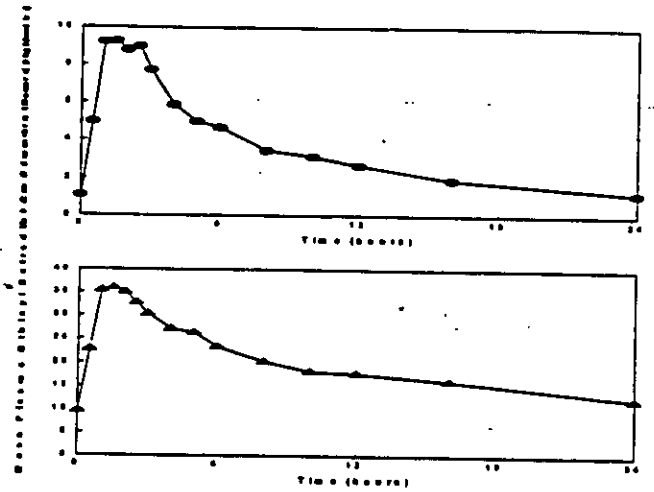

FIGURE 1. Mean Steady-State (Day 87) Plasma Norethindrone and Ethinyl Estradiol Concentrations Following [redacted] Administration of [redacted] Tablets.

TABLE 1. Mean (SD) Steady-State Pharmacokinetic Parameters[a] Following Chronic Administration of [redacted] Tablets

	Cmax	AUC(0-24)	CL/F
Norethindrone	ng/mL	ng·hr/mL	mL/min
	10.7 (3.6)	81.8 (36.7)	226 (139)
Ethinyl Estradiol	pg/mL	pg·hr/mL	mL/min
	38.3 (11.9)	471 (132)	383 (119)

[a] Cmax = Maximum plasma concentration; AUC(0-24) = Area under the plasma concentration-time curve over the dosing interval; and CL/F = Apparent oral clearance.

[Please include PK parameters from Day 1 administration and also include Tmax and t1/2 values in the above table.]

Distribution:

Volume of distribution of norethindrone and ethinyl estradiol ranges from 2 to 4 L/kg. Plasma protein binding of both steroids is extensive (>95%); norethindrone binds to both albumin and sex hormone binding globulin (SHBG), whereas ethinyl estradiol binds only to albumin. Although ethinyl estradiol does not bind to SHBG, it induces SHBG synthesis. [redacted]

Metabolism:
Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites. A small amount of norethindrone acetate is metabolically converted to ethinyl estradiol, such that exposure to ethinyl estradiol following administration of 1 mg of norethindrone acetate equivalent to oral administration of 2.8 mcg ethinyl estradiol. Ethinyl estradiol is also extensively metabolized, both by oxidation and by conjugation with sulfate and glucuronide. Sulfates are the major circulating conjugates of ethinyl estradiol and glucuronides predominate in urine. The primary oxidative metabolite is 2-hydroxy ethinyl estradiol, formed by the CYP3A4 isoform of cytochrome P450. Part of the first-pass metabolism of ethinyl estradiol is believed to occur in gastrointestinal mucosa. Ethinyl estradiol may undergo enterohepatic circulation.

Excretion:
Norethindrone and ethinyl estradiol are excreted in both urine and feces, primarily as metabolites. Plasma clearance values for norethindrone and ethinyl estradiol are similar (approximately 0.4 L/hr/kg). Steady-state elimination half-lives of norethindrone and ethinyl estradiol following administration of [redacted]1/10 tablets are approximately 13 hours and 24 hours, respectively.

Special Populations:
Patients With Renal Insufficiency:

The effect of renal disease on the disposition of FemHRT has not been evaluated. In premenopausal women with chronic renal failure undergoing peritoneal dialysis who received multiple doses of an oral contraceptive containing ethinyl estradiol and norethindrone, plasma ethinyl estradiol concentrations were higher and norethindrone concentrations were unchanged compared to concentrations in premenopausal women with normal renal function.

Patients With Hepatic Impairment:
The effect of hepatic disease on the disposition of FemHRT has not been evaluated. However, ethinyl estradiol and norethindrone may be poorly metabolized in patients with impaired liver function (see [redacted]**Precautions**).

Geriatrics:

The pharmacokinetics of FemHRT have not been studied in geriatric population.

Race:

The effect of race on pharmacokinetics of FemHRT has not been studied.

Drug Interactions

No drug-drug interaction studies have been conducted with FemHRT

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Labeling

INDIVIDUAL STUDY SUMMARIES

RELEATIVE BIOAVAILABILITY AND FOOD EFFECT (STUDY 376-395)

Title of Study: A Single-Dose Pharmacokinetic Study in Healthy Postmenopausal Women to Determine the Effect of Food on Market-Image NA/EE 1/10 (1 mg Norethindrone Acetate/10 µg Ethinyl Estradiol) Tablets and to Determine the Bioavailability of the Tablets Relative to an Oral Solution (Protocol 376-395)

Investigators:

Study Center(s):

Publication (reference): None

Studied Period (years): 12/08/95 to 12/24/95 **Clinical Phase:** 1

Objective(s): Determine the effect of administering market-image norethindrone acetate/ethinyl estradiol (NA/EE) 1/10 tablets with a high-fat breakfast on norethindrone and EE pharmacokinetics and determine the bioavailability of NA/EE 1/10 market-image tablets relative to an oral solution containing NA/EE

Methodology: An open-label, single-dose, randomized, 3-way crossover study

Number of Subjects (total and for each treatment): Planned enrollment was 18 subjects.

Diagnosis and Criteria for Inclusion: Healthy postmenopausal female volunteers

Test Product, Dose and Mode of Administration, Batch Number:
2 × market-image NA/EE 1/10 tablets (Parke-Davis Formulation WL 57184-68, Lot CX 0700695), administered orally with 8 fl oz of water

2 × market-image NA/EE 1/10 tablets (Parke-Davis Formulation WL 57184-68, Lot CX 0700695), administered orally with 4 fl oz of milk provided with a high-fat breakfast

Duration of Treatment: Single oral doses

Reference Therapy, Dose and Mode of Administration, Batch Number: 2 mg NA/20 µg EE hydroalcoholic solution (40 mL), made from bulk drug [Parke-Davis Lots M09755 (NA) and M09804 (EE)], administered orally with an additional 200 mL of water

Pharmacokinetic Sampling and Analysis: Plasma samples collected serially for 48 hours postdose were assayed for ethinyl estradiol and norethindrone by a method validated from the lower limit of quantitation, to 1000 pg/mL for ethinyl estradiol and from the lower limit of quantitation, to 25 ng/mL for norethindrone.

Criteria for Evaluation: Subjects completing all treatments and providing adequate concentration-time data were included in pharmacokinetic analysis. All subjects were included in safety analysis.

Pharmacokinetic and Statistical Methods: Noncompartmental pharmacokinetic parameters were calculated from observed plasma concentrations. Pharmacokinetic parameters and descriptive statistics (difference between least-squares treatment mean values and the associated 95% confidence intervals) were inspected for trends likely to be of clinical relevance. Analysis of variance of pharmacokinetic parameters

was used for calculation of confidence intervals using a model incorporating sequence, subject within sequence, period, and treatment effects.

SUMMARY - CONCLUSIONS:

Subject Characteristics and Disposition The 18 healthy postmenopausal women who completed this study had a mean (range) age of 59 (51-70) years, mean (range) weight of 69.6 (52.6-100.3) kg, and mean (range) height of 162.2 (148.5-172.7) cm.

Clinical Overall, single, oral doses of 2 mg NA/20 µg EE were well-tolerated by healthy postmenopausal volunteers.

Pharmacokinetics The effect of food on ethinyl estradiol and norethindrone pharmacokinetics is summarized in the following table:

Parameter	Least-Squares Mean Value[a]		Difference (%)	95% Confidence Interval
	Tablets While Fasting (N = 18)	Tablets After High-Fat Meal (N = 18)		
Ethinyl Estradiol				
Cmax[b] (pg/mL)	51.4	36.5	-29.0	-35.8 to -21.2
tmax (hr)	1.58	3.69	134	98.4 to 169
AUC(0-tldc)[b] (pg•hr/mL)	595	603	1.34	-3.0 to 5.7
AUC(0-∞)[b] (pg•hr/mL)	686	725	5.69	1.5 to 10.0
CL/F (mL/min)	506	474	-6.32	-10.6 to -2.1
λz (1/hr)	0.0441	0.0406	-7.94	-13.6 to -2.3
t½ (hr)	16.7	18.4	10.2	3.2 to 17.1
Norethindrone				
Cmax[b] (ng/mL)	13.3	11.7	-12.0	-21.9 to -1.0
tmax (hr)	1.61	2.47	53.4	21.2 to 85.7
AUC(0-tldc)[b] (ng•hr/mL)	77.8	98.5	26.6	15.9 to 38.1
AUC(0-∞)[b] (ng•hr/mL)	80.6	102	26.6	16.3 to 38.4
CL/F (mL/min)	402	309	-23.1	-36.1 to -10.1
λz (1/hr)	0.0710	0.0722	1.69	-3.2 to 6.6
t½ (hr)	10.4	10.3	-0.96	-4.8 to 2.9

a Dose = 2 mg NA/20 µg EE.
b Parameters calculated using log-transformed data.

Rate of ethinyl estradiol and norethindrone absorption from NA/EE 1/10 tablets administered with a high-fat breakfast was slower than the absorption rate when tablets were administered while fasting, based on comparisons of least-squares treatment mean Cmax and tmax values. Extent of ethinyl estradiol absorption, represented by least-squares mean AUC(0-∞) values, was essentially unaffected by administration with food, whereas extent of norethindrone absorption increased when NA/EE tablets were administered with food.

The bioavailability of ethinyl estradiol and norethindrone from NA/EE 1/10 tablets relative to that from a solution is summarized in the following table:

Parameter	Least-Squares Mean Value[a]		Difference (%)	95% Confidence Interval
	Hydroalcoholic Solution (N=18)	Tablets While Fasting (N=18)		
Ethinyl Estradiol				
Cmax[b] (pg/mL)	84.7	51.4	-39.3	-45.3 to -32.8
tmax (hr)	1.06	1.58	49.1	-3.4 to 102
AUC(0-tldc)[b] (pg•hr/mL)	692	595	-14.0	-17.6 to -10.3
AUC(0-∞)[b] (pg•hr/mL)	798	686	-14.0	-17.4 to -10.5
CL/F (mL/min)	432	506	17.1	12.2 to 22.1
λz (1/hr)	0.0419	0.0441	5.25	-0.7 to 11.2
t½ (hr)	17.6	16.7	-5.11	-11.7 to 1.5
Norethindrone				
Cmaxb (ng/mL)	18.2	13.3	-26.9	-35.2 to -18.0
tmax (hr)	0.86	1.61	87.2	26.7 to 147
AUC(0-tldc)b (ng•hr/mL)	74.6	77.8	4.29	-4.4 to 13.9
AUC(0-∞)b (ng•hr/mL)	77.0	80.6	4.68	-4.0 to 14.3
CL/F (mL/min)	430	402	-6.51	-18.7 to 5.6
λz (1/hr)	0.0739	0.0710	-3.92	-8.7 to 0.8
t½ (hr)	10.1	10.4	2.97	-1.0 to 6.9

[a] Dose = 2 mg NA/20 g EE.

[b] Parameters calculated using log-transformed data.

Ethinyl estradiol and norethindrone were absorbed more slowly from NA/EE 1/10 tablets than from solution, based on a comparison of least-squares treatment mean Cmax and tmax values. Extent of ethinyl estradiol and norethindrone absorption from tablets was similar to that from solution.

Conclusions Administration of NA/EE 1/10 tablets with a high-fat meal decreases rate but not extent of norethindrone and ethinyl estradiol absorption. NA/EE tablets can therefore be taken without regard to meals. Rate of ethinyl estradiol and norethindrone absorption is slower from NA/EE 1/10 tablets than from solution. The extent of ethinyl estradiol and norethindrone absorption from NA/EE 1/10 tablets is similar to that from NA/EE administered as a solution.

BIOEQUIVALENCE FOR NA/EE 0.5/2.5 DOSE (STUDY 376-392)

Title of the Study: A SINGLE-DOSE BIOEQUIVALENCE STUDY IN HEALTHY POSTMENOPAUSAL WOMEN COMPARING MARKET-IMAGE AND CLINICAL-TRIAL FORMULATION NA/EE 0.5/2.5 (0.5 mg NORETHINDRONE ACETATE/2.5 1g ETHINYL ESTRADIOL) TABLETS (PROTOCOL 376-392)
Investigators:
Study Center(s):
Publication (reference): None
Studied Period (years): 09/27/95 to 10/20/95 **Clinical Phase:** 1
Objective(s): Determine whether market-image and clinical-trial formulation norethindrone acetate/ethinyl estradiol (NA/EE) 0.5/2.5 tablets are bioequivalent.
Methodology: An open-label, single-dose, randomized, 2-way crossover study
Number of Subjects (total and for each treatment): Planned enrollment was 36 subjects.
Diagnosis and Criteria for Inclusion: Healthy postmenopausal female volunteers
Test Treatment, Dose and Mode of Administration, Batch Number: 6 × market-image NA/EE 0.5/2.5 tablets (Parke-Davis Formulation WL 57184-69, Lot CX 0680695), administered orally with 8 fl oz of water
Duration of Treatment: Single oral doses
Reference Treatment, Dose and Mode of Administration, Batch Number: 6 × clinical-trial NA/EE 0.5/2.5 tablets (Parke-Davis Formulation WL 57184-40A2, Lot CM 0080192), administered orally with 8 fl oz of water
Pharmacokinetic Sampling and Analysis: Plasma samples collected serially for 48 hours postdose were assayed for ethinyl estradiol and norethindrone by a method validated from the lower limit of quantitation, to 1000 pg/mL for ethinyl estradiol and from the lower limit of quantitation, to 25 ng/mL for norethindrone.
Criteria for Evaluation: Subjects completing both treatments and providing adequate concentration-time data were included in pharmacokinetic analysis. All subjects were included in safety analysis.
Pharmacokinetic and Statistical Methods: Noncompartmental pharmacokinetic parameters were calculated from observed plasma concentrations. Pharmacokinetic parameters were analyzed by ANOVA using a model incorporating sequence, subject within sequence, period, and treatment effects. Results of ANOVA were used to estimate 90% confidence intervals for ratio of treatment least-squares mean values. Bioequivalence would be concluded if estimates of the 90% confidence interval for ratio of test to reference least-squares mean values based on log-transformed Cmax data, and that based on log-transformed AUC(0-∞) data, both lay within an 80% to 125% range.

SUMMARY - CONCLUSIONS:

Subject Characteristics and Disposition: The 36 women who completed this study had a mean (range) age of 59 (51-70) years, mean (range) weight of 70.7 (53.1-102.0) kg, and mean (range) height of 161.9 (149.9-177.8) cm.

Clinical: Overall, single oral doses consisting of 6 NA/EE 0.5/2.5 (0.5 mg norethindrone acetate/2.5 1g ethinyl estradiol) tablets are well-tolerated.

Pharmacokinetics: Ethinyl estradiol and norethindrone parameter values are summarized in the following table:

Parameter	Least-Squares Mean Value[a]		Ratio (%)	90% Confidence Interval
	Market-Image (Test)	Clinical-Trial (Reference)		
Ethinyl estradiol				
Cmax[b] (pg/mL)	46.5	48.4	96	92.5-98.9
tmax (hr)	1.93	2.01	96	86.3-106
AUC(0-∞)[b] (pg+hr/mL)	679	699	97	94.1-101
Norethindrone				
Cmax[b] (ng/mL)	17.8	16.8	106	99.6-113
tmax (hr)	1.68	1.64	102	79.3-126
AUC(0-∞)[b] (ng+hr/mL)	111	109	102	96.3-107

a Dose = 3 mg NA/15 1g EE.
b Parameters calculated using log-transformed data

Rate (characterized by Cmax) and extent [characterized by AUC(0-∞)] of ethinyl estradiol and norethindrone absorption from market-image tablets were similar to rate and extent of absorption from clinical-trial tablets based on comparison of least-squares mean values. The 90% confidence intervals for the ratio of treatment least-squares mean values estimated from ln(Cmax) and ln[AUC(0-∞)] values were within the 80% to 125% interval used as a criterion of bioequivalence.

Conclusion: Market-image NA/EE 0.5/2.5 tablets are bioequivalent to clinical-trial NA/EE 0.5/2.5 tablets.

BIOEQUIVALENCE FOR NA/EE 1/5 DOSE (STUDY 376-393)

Title of the Study: A SINGLE-DOSE BIOEQUIVALENCE STUDY IN HEALTHY POSTMENOPAUSAL WOMEN COMPARING MARKET-IMAGE AND CLINICAL-TRIAL FORMULATION NA/EE 1/5 (1.0 mg NORETHINDRONE ACETATE/5.0 µg ETHINYL ESTRADIOL) TABLETS (PROTOCOL 376-393)
Investigators:
Study Center(s):
Publication (reference): None
Studied Period (years): 10/07/95 to 12/20/95 — **Clinical Phase:** 1
Objective(s): Determine whether market-image and clinical-trial formulation norethindrone acetate/ethinyl estradiol (NA/EE) 1/5 tablets are bioequivalent
Methodology: An open-label, single-dose, randomized, 2-way crossover study
Number of Subjects (total and for each treatment): Planned enrollment was 36 subjects.
Diagnosis and Criteria for Inclusion: Healthy postmenopausal female volunteers
Test Treatment, Dose and Mode of Administration, Batch Number: 3 × market-image NA/EE 1/5 tablets (Parke-Davis Formulation WL 57184-67, Lot CX 0690695), administered orally with 8 fl oz of water
Duration of Treatment: Single oral doses
Reference Treatment, Dose and Mode of Administration, Batch Number: 3 × clinical-trial NA/EE 1/5 tablets (Parke-Davis Formulation WL 57184-37A2, Lot CM 0090192), administered orally with 8 fl oz of water
Pharmacokinetic Sampling and Analysis: Plasma samples collected serially for 48 hours postdose were assayed for ethinyl estradiol and norethindrone by a method validated from the lower limit of quantitation, to 1000 pg/mL for ethinyl estradiol and from the lower limit of quantitation, to 25 ng/mL for norethindrone.
Criteria for Evaluation: Subjects completing both treatments and providing adequate concentration-time data were included in pharmacokinetic analysis. All subjects were included in safety analysis.
Pharmacokinetic and Statistical Methods: Noncompartmental pharmacokinetic parameters were calculated from observed plasma concentrations. Pharmacokinetic parameters were analyzed by ANOVA using a model incorporating sequence, subject within sequence, period, and treatment effects. Results of ANOVA were used to estimate 90% confidence intervals for ratio of treatment least-squares mean values. Bioequivalence would be concluded if estimates of the 90% confidence interval for ratio of test to reference least-squares mean values based on log-transformed Cmax data, and that based on log-transformed AUC(0-∞) data, both lay within an 80% to 125% range.
SUMMARY - CONCLUSIONS:
Subject Characteristics and Disposition: The 36 women who completed this study had a mean (range) age of 59 (50-70) years, mean (range) weight of 64.7 (46.2-91.5) kg, and mean (range) height of 164.1 (147.3-180.3) cm.
Clinical: Overall, single oral doses consisting of 3 NA/EE 1/5 (1.0 mg norethindrone acetate/5.0 µg ethinyl estradiol) market-image and clinical-trial tablets are well-tolerated.

Pharmacokinetics: Ethinyl estradiol and norethindrone parameter values are summarized in the following table:

Parameter	Least-Squares Mean Value[a]		Ratio (%)	90% Confidence Interval
	Market-Image (Test)	Clinical-Trial (Reference)		
Ethinyl Estradiol				
Cmax[b] (pg/mL)	51.4	47.5	108	103 - 114
tmax (hr)	1.58	1.78	89	76.4 - 101
AUC(0-∞)[b] (pg hr/mL)	706	679	104	100 - 107
Norethindrone				
Cmax[b] (ng/mL)	19.7	17.1	115	110 - 121
tmax (hr)	1.49	1.88	79	65.7 - 92.8
AUC(0-∞)[b] (ng hr/mL)	132	132	100	95.7 - 104

a Dose = 3 mg NA/15 μg EE.

b Parameters calculated using log-transformed data.

Rate (characterized by Cmax) and extent [characterized by AUC(0-∞)] of ethinyl estradiol and norethindrone absorption from market-image tablets were similar to rate and extent of absorption from clinical-trial tablets based on comparison of least-squares mean values. The 90% confidence intervals for the ratio of treatment least-squares mean values estimated from ln(Cmax) and ln[AUC(0-∞)] values were within the 80% to 125% interval used as a criterion of bioequivalence.

Conclusion: Market-image NA/EE 1/5 tablets are bioequivalent to clinical-trial NA/EE 1/5 tablets.

BIOEQUIVALENCE FOR NA/EE 1/10 DOSE (STUDY 376-394)

Title of the Study: A SINGLE-DOSE BIOEQUIVALENCE STUDY IN HEALTHY POSTMENOPAUSAL WOMEN COMPARING MARKET-IMAGE AND CLINICAL-TRIAL FORMULATION NA/EE 1/10 (1.0 mg NORETHINDRONE ACETATE/10 µg ETHINYL ESTRADIOL) TABLETS (PROTOCOL 376-394)
Investigators:
Study Center(s):
Publication (reference): None
Studied Period (years): 11/11/95 to 12/20/95 — **Clinical Phase:** 1
Objective(s): Determine whether market-image and clinical-trial formulation norethindrone acetate/ethinyl estradiol (NA/EE) 1/10 tablets are bioequivalent
Methodology: An open-label, single-dose, randomized, 2-way crossover study
Number of Patients (total and for each treatment): Planned enrollment was 36 subjects.
Diagnosis and Criteria for Inclusion: Healthy postmenopausal female volunteers
Test Treatment, Dose and Mode of Administration, Batch Number: 2 × market-image NA/EE 1/10 tablets (Parke-Davis Formulation WL 57184-68, Lot CX 0700695), administered orally with 8 fl oz of water
Duration of Treatment: Single oral doses
Reference Treatment, Dose and Mode of Administration, Batch Number: 2 × clinical-trial NA/EE 1/10 tablets (Parke-Davis Formulation WL 57184-38A2, Lot CM 0100192), administered orally with 8 fl oz of water
Pharmacokinetic Sampling and Analysis: Plasma samples collected serially for 48 hours postdose were assayed for ethinyl estradiol and norethindrone by a method validated from the lower limit of quantitation, to 1000 pg/mL for ethinyl estradiol and from the lower limit of quantitation, to 25 ng/mL for norethindrone.
Criteria for Evaluation: Subjects completing both treatments and providing adequate concentration-time data were included in pharmacokinetic analysis. All subjects were included in safety analysis.
Pharmacokinetic and Statistical Methods: Noncompartmental pharmacokinetic parameters were calculated from observed plasma concentrations. Pharmacokinetic parameters were analyzed by ANOVA using a model incorporating sequence, subject within sequence, period, and treatment effects. Results of ANOVA were used to estimate 90% confidence intervals for ratio of treatment least-squares mean values. Bioequivalence would be concluded if estimates of the 90% confidence interval for ratio of test to reference least-squares mean values based on log-transformed Cmax data, and that based on log-transformed AUC(0-∞) data, both lay within an 80% to 125% range for both ethinyl estradiol and norethindrone.
SUMMARY – CONCLUSIONS: **Subject Characteristics and Disposition:** The 36 women who completed this study had a mean (range) age of 61 (50-70) years, mean (range) weight of 69.7 (50.0-99.0) kg, and mean (range) height of 164.7 (155.5-176.5) cm. **Clinical:** Overall, single oral doses consisting of 2 NA/EE 1/10 (1.0 mg norethindrone acetate/10 µg ethinyl estradiol) tablets are well-tolerated.

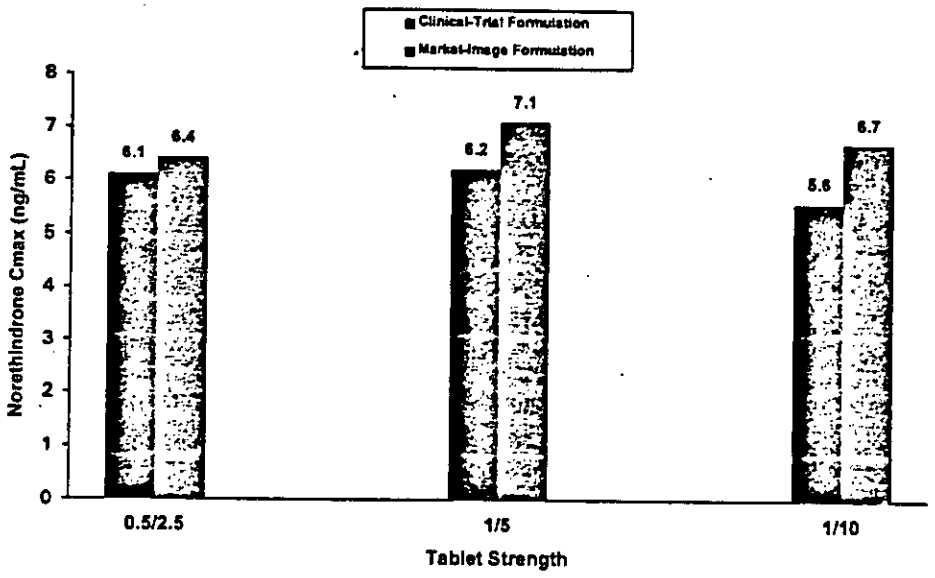
Pharmacokinetics: Ethinyl estradiol and norethindrone parameter values are summarized in the following table:

Parameter	Least-Squares Mean Value[a]		Ratio (%)	90% Confidence Interval
	Market-Image (Test)	Clinical-Trial (Reference)		
Ethinyl Estradiol				
Cmax[b] (pg/mL)	58.0	54.1	107	103 - 111
tmax (hr)	1.44	1.58	91	83.8 - 98.5
AUC(0-∞)[b] (pg·hr/mL)	773	742	104	101 - 107
Norethindrone				
Cmax[b] (ng/mL)	12.3	10.3	119	112 - 129
tmax (hr)	1.58	1.71	92	75.5 - 109
AUC(0-∞)[b] (ng·hr/mL)	79.0	77.5	102	98.1 - 105

[a] Dose = 2 mg NA/20 µg EE.
[b] Parameters calculated using log-transformed data.

Pharmacokinetics: (continued)

Rate (characterized by Cmax) and extent [characterized by AUC(0-∞)] of ethinyl estradiol absorption from market-image tablets were similar to rate and extent of absorption from clinical-trial tablets based on comparison of least-squares mean values. The 90% confidence intervals for the ratio of treatment least-squares mean values estimated from ln(Cmax) and ln[AUC(0-∞)] values were within the 80% to 125% interval used as a criterion of bioequivalence. Norethindrone absorption rate from the market-image tablets was slightly higher than that from the clinical-trial tablets based on comparison of least-squares mean ln(Cmax) values. The upper limit of the 90% confidence interval for the ratio of treatment mean values estimated from ln(Cmax) values fell just outside the 80% to 125% interval used as a criterion of bioequivalence. Extent of norethindrone absorption from the market-image tablets was similar to that from the clinical-trial tablets based on comparison of least-squares mean ln[AUC(0-∞)] values. The 90% confidence interval for the ratio of treatment mean values estimated from ln[AUC(0-∞)] values was within the 80% to 125% interval used as a criterion of bioequivalence.



Pharmacokinetics: (continued)

A comparison of mean dose-normalized norethindrone Cmax values for 3 dose combinations of NA/EE (0.5/2.5, 1/5, 1/10) revealed that the Cmax value for the 1/10 clinical-trial tablet was lower than values for the 0.5/2.5 and 1/5 clinical-trial tablets, and that the Cmax value for the 1/10 market-image tablet was similar to values for the 0.5/2.5 and 1/5 market-image tablets (see figure). No significant safety concerns were associated with the slightly higher norethindrone absorption rate from market-image 1/10 tablets, and since the extent of norethindrone absorption was not different between the 2 formulations, it is not considered to be clinically important.

Conclusions: Market-image NA/EE 1/10 tablets are bioequivalent to clinical-trial NA/EE 1/10 tablets with respect to rate and extent of ethinyl estradiol absorption and extent of norethindrone absorption. Rate of norethindrone absorption from market-image NA/EE 1/10 tablets is slightly higher than that from clinical-trial tablets. This difference is not considered to be clinically important.

DRUG – DRUG INTERACTION (STUDY 376-396)

Title of the Study: A SINGLE-DOSE STUDY IN HEALTHY POSTMENOPAUSAL WOMEN COMPARING THE PHARMACOKINETICS OF NORETHINDRONE ACETATE/ETHINYL ESTRADIOL (NA/EE) ADMINISTERED ALONE AND IN COMBINATION (PROTOCOL 376-396)	
Investigators:	
Study Center(s): Parke-Davis Community Research Clinic, Ann Arbor, Michigan USA	
Publication (reference): None	
Studied Period (years): 09/06/95 to 09/26/95	**Clinical Phase:** 1
Objective(s): Determine whether a pharmacokinetic interaction between norethindrone acetate and ethinyl estradiol occurs at doses used for hormone replacement therapy (1 mg and 10 µg, respectively)	
Methodology: An open-label, single-dose, randomized, 3-way crossover study	
Number of Subjects (total and for each treatment): Planned enrollment was 18 subjects.	
Diagnosis and Criteria for Inclusion: Healthy postmenopausal female volunteers	
Test Treatment, Dose and Mode of Administration, Batch Number: 1-mg NA/10-µg EE hydroalcoholic solution (20 mL), made from bulk drug [Parke-Davis Lots M09755 (NA) and M09804 (EE)], administered orally with an additional 220 mL of water	
Duration of Treatment: Single oral doses	
Reference Treatment, Dose and Mode of Administration, Batch Number: 1-mg NA hydroalcoholic solution (20 mL), made from bulk drug (Parke-Davis Lot M09755), administered orally with an additional 220 mL of water	
Reference Treatment, Dose and Mode of Administration, Batch Number: 10-µg EE hydroalcoholic solution (20 mL), made from bulk drug (Parke-Davis Lot M09804), administered orally with an additional 220 mL of water	
Pharmacokinetic Sampling and Analysis: Plasma samples collected serially for 48 hours postdose were assayed for ethinyl estradiol and norethindrone by a method validated from the lower limit of quantitation, to 1000 pg/mL for ethinyl estradiol and from the lower limit of quantitation, to 25 ng/mL for norethindrone.	
Criteria for Evaluation: Subjects completing all treatments and providing adequate concentration-time data were included in pharmacokinetic analysis. All subjects were included in safety analysis.	
Pharmacokinetic and Statistical Methods: Noncompartmental pharmacokinetic parameters were calculated from observed plasma concentrations. Pharmacokinetic parameters and descriptive statistics (difference between least-squares treatment mean values and associated 95% confidence intervals) were inspected for trends likely to be of clinical relevance. Analysis of variance of pharmacokinetic parameters was used for calculation of confidence intervals using a model incorporating sequence, subject within sequence, period, and treatment effects.	
SUMMARY - CONCLUSIONS:	
Subject Characteristics and Disposition: The 17 women who completed at least one treatment in this study had a mean (range) age of 58 (50-68) years, mean (range) weight of 68.4 (50.4-94.0) kg, and mean (range) height of 163.5 (158.0-174.0) cm. **Clinical:** Norethindrone acetate and ethinyl estradiol administered alone and together were well-tolerated by healthy subjects.	

Pharmacokinetics: Ethinyl estradiol and norethindrone parameter values are summarized in the following tables:

Parameter	Ethinyl Estradiol Least-Squares Mean Value			Difference[b] (%)	95% Confidence Interval[b]
	10-µg EE Solution (N = 17)	1/10 NA/EE Solution (N = 17)	1-mg NA Solution (N = 16)		
Cmax[a] (pg/mL)	35.5	41.3	7.03	16.3	0.2 to 33.6
tmax (hr)	0.84	0.79	1.05	-5.95	-42.8 to 30.5
AUC(0-tldc)[a] (pg·hr/mL)	262	351	41.7	34.0	8.1 to 65.2
AUC(0-∞)[a] (pg·hr/mL)	327	420	ND	28.4	16.6 to 40.1
CL/F (mL/min)	535	409	ND	-23.6	-33.1 to -14.0
λz (1/hr)	0.0432	0.0411	ND	-4.86	-17.4 to 7.7
t½ (hr)	18.0	17.7	ND	-1.67	-14.2 to 10.9

ND = Not determined.

[a] Parameters calculated using log-transformed data

[b] Comparison of 1/10 NA/EE solution and 10-µg EE solution

Parameter	Norethindrone Least-Squares Mean Value		Difference (%)	95% Confidence Interval
	1-mg NA Solution (N = 16)	1/10 NA/EE Solution (N = 17)		
Cmax[a] (ng/mL)	12.3	12.3	0.00	-8.3 to 10.1
tmax (hr)	0.74	0.70	-5.41	-32.4 to 21.1
AUC(0-tldc)[a] (ng·hr/mL)	42.5	42.5	0.00	-4.9 to 4.7
AUC(0-∞)[a] (ng·hr/mL)	44.7	44.3	-0.895	-6.6 to 4.6
CL/F (mL/min)	357	356	-0.280	-7.2 to 6.6
λz (1/hr)	0.0698	0.0676	-3.15	-12.6 to 6.3
t½ (hr)	10.7	10.6	-0.935	-14.2 to 12.3

[a] Parameters calculated using log-transformed data

Plasma ethinyl estradiol concentrations following single-dose administration of a 1/10 NA/EE hydroalcoholic solution were consistently higher than those following administration of a 10-µg EE solution, whereas no differences in plasma norethindrone concentrations were observed. Measurable plasma concentrations of ethinyl estradiol were obtained following administration of a 1-mg NA solution (see figure below). The most likely explanation for higher ethinyl estradiol concentrations in the 1/10 NA/EE treatment group, given the appearance of ethinyl estradiol after administration of the 1-mg NA solution, was metabolic conversion of norethindrone to ethinyl estradiol. Alternative explanations for both observations, such as the presence of additional ethinyl estradiol in the dosing solutions and assay interference, were ruled out. Inhibition of ethinyl estradiol metabolism by norethindrone could have contributed to the higher ethinyl estradiol concentrations in the 1/10 NA/EE treatment group, but there is little support for such an interaction. Thus, the results support conversion of norethindrone to ethinyl estradiol to a small extent, with 1 mg norethindrone acetate producing plasma ethinyl estradiol concentrations equivalent to those expected following a 2.8-µg oral ethinyl estradiol dose.

SUMMARY - CONCLUSIONS:

Patient Characteristics and Disposition: 19 healthy female subjects entered and 17 subjects completed the study. The mean (range) age was 30.8 (20-39) years and the mean (range) weight was 79.9 (52.6-141.2) kg. Two subjects withdrew from the study due to pregnancy.

Clinical: Overall, Estrostep was well-tolerated by healthy female volunteers.

Pharmacokinetics: Mean ethinyl estradiol and norethindrone pharmacokinetic parameter values are summarized in the following table:

Parameter	Mean (SD)			
	Single Dose	Steady State		
	1/35 (N = 19)	1/20 (N = 17)	1/30 (N = 17)	1/35 (N = 16)
Ethinyl Estradiol				
Cmax (pg/mL)	77.7 (21.8)	61.0 (16.8)	92.4 (26.9)	113 (44)
tmax (hr)	1.5 (0.4)	1.5 (0.3)	1.5 (0.3)	1.4 (0.3)
C(24) (pg/mL)	10.5 (3.5)	13.5 (5.7)	19.8 (9.3)	22.4 (9.1)
AUC(0-24) (pg·hr/mL)	666 (194)	661 (190)	973 (293)	1149 (372)
AUC(0-tldc) (pg·hr/mL)	826 (249)	ND	ND	ND
AUC(0-∞) (pg·hr/mL)	937 (272)	ND	ND	ND
λz (1/hr)	0.0461 (0.0129)	ND	ND	0.0399 (0.0126)
t½ (hr)	16.3 (4.8)	ND	ND	19.3 (6.9)
CL/F (mL/min)	672 (195)	549 (171)	567 (199)	568 (219)
Vd/F (L)	931 (334)	ND	ND	905 (314)
Norethindrone				
Cmax (ng/mL)	5.45 (2.61)	10.8 (3.9)	12.7 (4.1)	12.7 (4.1)
tmax (hr)	1.7 (0.8)	1.7 (0.8)	1.6 (0.8)	2.1 (1.4)
C(24) (ng/mL)	0.220 (0.176)	1.16 (0.59)	1.64 (0.83)	1.81 (0.74)
AUC(0-24) (ng·hr/mL)	27.6 (15.1)	81.1 (28.5)	102 (32)	109 (32)
AUC(0-tldc) (ng·hr/mL)	30.2 (17.3)	ND	ND	ND
AUC(0-∞) (ng·hr/mL)	31.7 (17.9)	ND	ND	ND
λz (1/hr)	0.0763 (0.0225)	ND	ND	0.0588 (0.0179)
t½ (hr)	9.98 (3.52)	ND	ND	12.8 (3.6)
CL/F (mL/min)	708 (547)	220 (137)	166 (85)	152 (73)
Vd/F (L)	632 (619)	ND	ND	167 (82)

ND = Not determined.

Mean steady-state ethinyl estradiol AUC(0-24) value for the 1/35 dose was 25% higher than the mean single-dose AUC(0-∞) value, indicating that with chronic administration of Estrostep, ethinyl estradiol accumulated to a slightly greater extent than would be predicted from single-dose pharmacokinetics. Mean steady-state norethindrone AUC(0-24) value for the 1/35 dose was 3.4 times higher than the single-dose AUC(0-∞) value. This is consistent with nonlinear pharmacokinetics due to the increase in serum SHBG concentrations induced by ethinyl estradiol. Mean serum SHBG concentrations during chronic administration of Estrostep were approximately 2 to 3 times higher than baseline values.

Mean steady-state concentrations of norethindrone for the 1/20, 1/30, and 1/35 tablet strengths increased as ethinyl estradiol dose increased over the 21-day dose regimen, due to dose-dependent effects of ethinyl estradiol on serum SHBG concentrations. Mean steady-state plasma concentrations of ethinyl estradiol for the 1/20, 1/30, and 1/35 tablet strengths were proportional to ethinyl estradiol dose.

Conclusions: Steady-state accumulation in plasma ethinyl estradiol concentrations is slightly greater than predicted from single-dose pharmacokinetics following administration of Estrostep. Norethindrone accumulates considerably more than predicted from single-dose pharmacokinetics due to the 2- to 3-fold

increase in serum SHBG concentrations during treatment with Estrostep. Mean steady-state plasma concentrations of ethinyl estradiol for the 1/20, 1/30, and 1/35 tablet strengths are proportional to ethinyl estradiol dose. Mean steady-state plasma concentrations of norethindrone for the 1/20, 1/30, and 1/35 tablet strengths increase as ethinyl estradiol dose increases; this is attributed to the dose-dependent increases in serum SHBG concentrations.