CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21040

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW	
NDA:	**21-040**
Compounds:	Ortho-Prefest™, 1 mg 17 β-estradiol daily for 3 days then 1 mg 17 β-estradiol + 90 μg norgestimate daily for 3 days; alternating cycles
Sponsor:	R.W. Johnson Pharmaceutical Research Institute
Type of Submission:	New Combination Drug Product
Date of Submission:	December 23, 1998
Reviewer:	S.W. Johnny Lau, R.Ph., Ph.D.

Background

NDA 21-040 for the combination of 17 β-estradiol (E_2, estrogen) and norgestimate (NGM, progestin) was submitted on December 23, 1998. Ortho-Prefest™ 1 mg E_2 alone oral tablet is to be administered daily for 3 days and then Ortho-Prefest™ 1 mg E_2 plus 90 μg NGM oral tablet is to be administered daily for another 3 days. These 3-day-off and 3-day-on norgestimate regimens are to be continuously administered. The proposed indications, in women with intact uteri, are for the treatments of: 1. moderate to severe vasomotor symptoms (VMS) associated with menopause, 2. vulvar and vaginal atrophy (VVA), and 3. prevention of osteoporosis (POO). NDA 21-040 is filed as both 505 (b)(1) and 505 (b)(2) applications. The 505 (b)(1) part of this NDA is for the proposed VMS and VVA indications. The 505 (b)(2) part of this NDA is for the proposed POO indication. The sponsor conducted 5 clinical pharmacology studies (ESTNRG-PHI-001, -004, -006, -007, and -008) to characterize the pharmacokinetics (PK) of E_2 and NGM. The formulation for E_2 alone tablet and E_2 plus NGM tablet was initially prepared

The following questions, based on the content of NDA 21-040, guided this review.

1. What is Ortho-Prefest™?

Ortho-Prefest™ is the continuous daily oral administration of alternating 3-day estrogen alone cycle and then 3-day estrogen plus progestin cycle.

2. How does Ortho-Prefest™ work?

Ortho-Prefest™ works as a continuous oral estrogen replacement therapy with intermittent oral administration of progestin to menopausal women.

3. What are the proposed indications for Ortho-Prefest™?

The proposed indications for Ortho-Prefest™, in women with intact uteri, are for the treatments of: 1. moderate to severe VMS associated with menopause, 2. VVA, and 3. POO.

4. What is the recommended dose of Ortho-Prefest™?

An Ortho-Prefest™ 1 mg E_2 alone pink oral tablet is administered daily for 3 consecutive days and then an Ortho-Prefest™ 1 mg E_2 plus 90 μg NGM white oral tablet is administered daily for another 3 consecutive days. These 3-day Ortho-Prefest™ alternating cycles are to be continuously administered.

5. How is the Ortho-Prefest™ dose determined?

E_2 Dose Selection:

In pivotal clinical study ESTNRG-CHRT-104, the relief of VMS with the 0.5 mg E_2 alone treatment group is similar to the placebo treatment group up to 8 weeks of treatment; the 1 mg E_2 alone treatment group is more efficacious than the placebo treatment group at all studied time points. However for the relief of VVA, both 0.5 and 1 mg E_2 alone treatment groups showed significant difference than placebo. Therefore, 1 mg E_2 is chosen as the estrogen dose for Ortho-Prefest™. Study ESTNRG-CHRT-104 can be classified as a dose finding study.

NGM Dose Selection:

In clinical studies ESTNRG-CHRT-102 and -103, the result of endometrial protection showed this rank order of efficacy for: 0 < 30 μg < 90 μg = 180 μg NGM dose. Therefore, 90 μg NGM is chosen as the lowest effective progestin dose for Ortho-Prefest™. Studies ESTNRG-CHRT-102 and -103 can also be classified as dose finding studies.

6. What is the rationale for intermittent oral administration of NGM in the midst of continuous E_2 administration?

Continuous E_2 administration allows uninterrupted VMS relief and treatment of VVA. The sponsor contends that intermittent administration of NGM plus a continuous E_2 administration provides effective protection for endometrial hyperplasia while minimizing the cumulative exposure to progestin.

7. What are the bioanalytical methods for E_2 and NGM used by the sponsor?

Selectivity

The selectivity for E_2 and E_2 metabolites as well as NGM and NGM metabolites were confirmed in blank human serum. Generally, endogenous steroids did not appear to adversely affect the E_2 and its metabolites assays. Additionally, the selectivity of the assay for E_1S was confirmed in serum spiked with other endogenous steroids. Generally, the assays for NGM and its metabolites demonstrate clean profiles with little endogenous interference.

Recovery

E_2 and metabolites

Extraction recoveries for E_1 and E_2 ranged from 79 to 98 and 62 to 71%, respectively in the assays. Overall mean recovery for E_1S assay was approximately 83 to 107%. Extraction recovery ranged from 115 to 128% for E_1S in assays.

NGM and metabolites

The recoveries of NGM, 17d-NGM, NG, and 3-keto NGM ranged from 72 to 92%.

Accuracy and Precision

E_2 and metabolites

The accuracy of the assays for E_2 and E_1 are < 4% deviation from target concentration. The interday precision is < 12% CV for E_1 and < 18% for E_2. The showed acceptable accuracy (< 20% deviation from target concentration) with an interday bias of < 0.1% and precision of 5.8% CV over the standard curve concentration range. The accuracy of the assay for E_1S is < 3% deviation from target concentration with interday precision of < 12%.

NGM and metabolites

The accuracy and precision of the assays for NGM and metabolites are all within 15%.

8. What effects do E_2 and NGM exert on sex hormone binding globulin (SHBG)?

E_2/estrogen induces serum SHBG concentration, whereas NGM/progestin suppresses serum SHBG concentration.

9. Does the steady state PK of E_2 differ between continuous daily oral administration of 1 mg E_2 alone and continuous daily oral administration of 1 mg E_2 plus intermittent daily oral administration (every 3 days) of 90 μg NGM?

A. Theoretical Consideration

The estimated extraction ratio (ER) for E_2 is 0.48 (systemic E_2 clearance = 600 L/24 h/m^2; body surface area = 1.73 m^2; hepatic blood flow = 1.5 L/min). E_2 is an intermediate ER drug. Therefore, systemic E_2 clearance will depend on the unbound E_2 fraction. (Systemic clearances of low and intermediate ER drugs depend on the unbound fraction of these drugs. Only systemic clearances of high ER drugs depend on the blood flow of eliminating organs.) The mean ± SD% of E_2 that binds to serum SHBG and albumin is 50.3 ± 10.8% and 47.7 ± 10.5%, respectively (Langley et al. *JNCI* 75:823 1985). The unbound E_2 fraction may be changed due to changes (net effect of induction and suppression of serum SHBG concentrations via E_2 and NGM, respectively) in serum SHBG concentrations (Nilsson et al. *Br. J. Obstet. Gynecol.* 91:1031 1984; Hammond et al. *J. Bio. Chem.* 255:5023 1980) via the intermittent coadministration of NGM plus E_2. Once the unbound E_2 fraction changes, the systemic E_2 clearance and subsequent steady state serum E_2 concentrations may be different upon intermittent NGM administration

plus continuous E_2 administration versus those upon continuous E_2 alone administration. Hence theoretically, the steady state PK of E_2 may be different depending on whether or not NGM is intermittently administered with continuous E_2 administration.

B. April 5, 1999 Teleconference

In the original NDA, sponsor based studies EDMS-USRA-2348912 (simulation study for 17d-NGM; Question 19) and ESTNRG-PHI-001 to show that no drug interaction exists between E_2/E_2 metabolites and NGM/NGM metabolites. Study ESTNRG-PHI-001 is a single- and multiple-dose parallel study with 3 cyclical daily treatment groups, namely, the 1 mg E_2 - 1 mg E_2/30 µg NGM, 1 mg E_2 - 1 mg E_2/90 µg NGM, and 2 mg E_2 - 2 mg E_2/180 µg NGM treatment groups. The C_{max} and $AUC_{(0\text{-}24h)}$ ratios between Day 87 and Day 90 for E_2, E_1, and E_1S all fall within the 95% confidence interval (CI; Question 19). The results of this study show that NGM or NGM metabolites did not affect E_2, E_1, and E_1S PK within the 1 mg E_2 - 1 mg E_2/90 µg NGM treatment group between Day 87 and Day 90. However study ESTNRG-PHI-001 does not have an oral E_2 alone continuous daily treatment group, no direct assessment for the effect of intermittent administration of NGM plus continuous E_2 administration on the steady state serum E_2 concentrations can be made. This issue was discussed with the sponsor via a teleconference on April 5, 1999. The sponsor responded with an amendment on April 30, 1999.

C. Summary of the April 30, 1999 Amendment

<u>NGM counteracts the induction of SHBG by E_2</u>

Per study ESTNRG-PHI-001, serum SHBG concentrations reached steady state after about 30 days of 1 mg E_2 - 1 mg E_2/90 µg NGM Ortho-Prefest™ treatment (Attachment 1). Per study ESTNRG-CHRT-102, intermittent NGM (90 µg daily) administration in phases of 3 days off followed by 3 days on plus continuous E_2 (1 mg daily) administration shows about 20% inhibitory effect on SHBG induction as compared to continuous 1 mg E_2 alone administration (Table 1). Based on the 7th and 12th month data, the 1 mg E_2 - 1 mg E_2/30 µg NGM regimen appears to have similar effects on SHBG as compared to the E_2 alone regimen.

Table 1. Changes of serum SHBG concentrations in study ESTNRG-CHRT-102.

Regimen	N	Period (month)	SHBG/Baseline (nmol/L)	SHBG/Treatment (nmol/L)
1 mg E_2 alone	49	7	44 ± 22	80 ± 31
	32	12	49 ± 26	84 ± 33
1 mg E_2 - 1 mg E_2/30 µg NGM	45	7	49 ± 22	80 ± 34
	35	12	48 ± 22	82 ± 29
1 mg E_2 - 1 mg E_2/90 µg NGM	41	7	44 ± 23	63 ± 28
	29	12	43 ± 21	65 ± 28

This table is extracted from Table 2 of sponsor's April 30, 1999 amendment.

<u>NGM's effect on serum SHBG concentrations as compared to other progestins</u>

No data is available on the effect of NGM alone on serum SHBG concentrations. Synthetic progestins suppress serum SHBG concentrations to different degrees, depend on their intrinsic androgenicity. The potency of NGM in counteracting/inhibiting E_2 induction of SHBG is much

less than other progestins such as levonorgestrel, gestodene, norethindrone, and 3-keto desogestrel.

Cross-study comparisons with published serum E_2 concentrations

The sponsor presented the steady state serum E_2 concentrations ± SD on Days 87 and 90 upon daily continuous oral administration of the 1 mg E_2 – 1 mg E_2/90 µg NGM regimen (study ESTNRG-PHI-001) as 36 ± 18 and 32 ± 16 pg/mL, respectively. The sponsor compared these results with Lobo et al. published mean steady state serum E_2 concentrations ± SE (30 ± 7 and 35 ± 5 pg/mL; *Obstet. & Gynecol.* 62:94 1983 and *J. Reproduct. Med.* 37:77 1992, respectively) upon daily oral administration of 1 mg E_2 alone at Day 25. The serum E_2 concentrations at Day 25 upon continuous daily 1 mg E_2 alone administration reflects the steady state serum E_2 concentrations, since the serum E_2 half-life is 15 hours and serum SHBG concentrations reaches steady state concentrations after about 30 days of E_2 treatment. 2 issues result from sponsor's cross-study comparisons. 1st, the sponsor presented average steady state serum E_2 concentrations ($C_{avg,ss}$) from study ESTNRG-PHI-001 whereas Lobo et al. presented mean minimum steady state serum E_2 concentrations (30 ± 7 pg/mL; $C_{min,ss}$). Therefore, the sponsor overestimates the steady state serum E_2 concentrations. The actually observed mean minimum steady state serum E_2 concentrations ± SD for the 1 mg E_2 – 1 mg E_2/90 µg NGM regimen on Days 87 and 90 for study ESTNRG-PHI-001 are 23.98 ± 16.0 and 23.12 ± 15.47 pg/mL, respectively (Attachment 2). 2nd, Lobo et al. published the results of 1 clinical study and a review article, therefore the 2nd cited steady state serum E_2 concentrations may not originate from a different study but may be the alteration of data from the 1st study instead. Moreover, Lobo et al. did not specify whether 35 ± 5 pg/mL is the E_2 $C_{min,ss}$ or $C_{avg,ss}$. Per cross-study comparisons (study ESTNRG-PHI-001 vs. Lobo et al. study), minimum steady state serum E_2 concentrations may be 20 - 23% lower on average with the 1 mg E_2 - 1 mg E_2/90 µg NGM Ortho-Prefest™ regimen than those with continuous daily oral 1 mg E_2 alone administration.

D. August 3, 1999 Teleconference

Based on the findings of sponsor's April 30, 1999 Amendment, the 1 mg E_2 - 1 mg E_2/30 µg NGM regimen appeared to have similar effects on SHBG as compared to the 1 mg E_2 alone regimen (Table 1). In order to get the closest estimate of steady state serum E_2 concentrations upon 1 mg E_2 alone administration, the steady state serum E_2 concentrations resulted from the 1 mg E_2 - 1 mg E_2/30 µg NGM regimen were hypothesized (per Table 1) to reflect the expected serum E_2 concentrations upon 1 mg E_2 alone administration. A teleconference was conducted with the sponsor on August 3, 1999 to request further analysis of point estimate and 90% CI for the E_2 C_{max} and $AUC_{0\text{-}24h}$ ratios between different treatment groups of the study ESTNRG-PHI-001 to assist E_2 BE assessment at steady state. The sponsor responded on August 9, 1999.

E. August 9, 1999 Response

Upon the August 3, 1999 request, the sponsor estimated the E_2 C_{max} and $AUC_{0\text{-}24h}$ ratios and 90% CI for Day 90 1 - 1/90 versus Day 87 1 - 1/30 regimens, Day 90 1 - 1/90 versus Day 90 1 - 1/30 regimens, and Day 87 1 - 1/90 versus Day 87 1 - 1/30 regimens for study ESTNRG-PHI-001. Day 87 is the 3rd day of the last E_2 alone cycle. Day 90 is the 3rd day of the last E_2 plus NGM cycle. Day 90 1 - 1/90 versus Day 87 1 - 1/30 comparison reveals the best estimates of the comparison between the 1 - 1/90 Ortho-Prefest™ regimen and continuous administration of 1 mg E_2 alone; therefore is the comparison of interest (Table 2). The 90% CI for E_2 C_{max} and $AUC_{0\text{-}24h}$ estimated via intrasubject variability (baseline uncorrected) did fall within the 80-125 CI and

thus pass the BE test. However, the 90% CI for E_2 C_{max} and $AUC_{0\text{-}24h}$ estimated via intersubject variability did not fall within the 80-125 CI and hence did not pass the BE test. Since these are parallel group comparisons, intersubject variability should be used to estimate the 90% CI. Based on these comparisons, the E_2 C_{max} and $AUC_{0\text{-}24h}$ upon cyclic administration of the 1 mg E_2 - 1 mg E_2/90 µg NGM regimen on Day 90 are about 12 to 18% lower than those upon cyclic administration of the 1 mg E_2 - 1 mg E_2/30 µg NGM regimen on Day 87 and is within the observation limits (20 - 23% lower in E_2 $C_{min,ss}$ than that upon 1 mg E_2 alone administration) for the cross-study comparisons above. The age, race, and height of the subjects for the 1 mg E_2 - 1 mg E_2/90 µg NGM and 1 mg E_2 - 1 mg E_2/30 µg NGM treatment groups are comparable (Attachment 3). However, the subjects' body weight of the 1 mg E_2 - 1 mg E_2/90 µg NGM treatment group may be lighter (about 6%) than the 1 mg E_2 - 1 mg E_2/30 µg NGM treatment group.

Table 2. Estimated E_2 PK parameters ratios and 90% CI for study ESTNRG-PHI-001.

Variability	Baseline	E_2	Comparison	Ratio (%)	CI Lower Limit	CI Upper Limit
Intra-subject	Uncorrected	C_{max}	D90-1/90 vs. D87-1/30	87.6	80.1	95.9
		$AUC_{0\text{-}24h}$		87.1	80.3	94.5
	Corrected	C_{max}	D90-1/90 vs. D87-1/30	85.1	77.1	93.9
		$AUC_{0\text{-}24h}$		82.0	75.1	89.5
Inter-subject	Uncorrected	C_{max}	D90-1/90 vs. D87-1/30	87.6	62.3	123.3
		$AUC_{0\text{-}24h}$		87.1	59.0	128.6
	Corrected	C_{max}	D90-1/90 vs. D87-1/30	85.1	60.0	120.7
		$AUC_{0\text{-}24h}$		82.0	53.8	124.9

This table is extracted from Tables 1 and 2 of sponsor's August 9, 1999 response.

F. Conclusions

1. Theoretically, the steady state PK of E_2 may be different depending on whether or not NGM is intermittently administered plus continuous E_2 administration.
2. Per cross-study comparisons, steady state serum E_2 concentrations may be % lower on average with the 1 mg E_2 - 1 mg E_2/90 µg NGM Ortho-Prefest™ regimen than those with continuous daily oral 1 mg E_2 alone administration. Since these are cross-study comparisons, the bioanalytical assays and demographics of subjects for the published study cannot be verified.
3. Per parallel-group comparisons within study ESTNRG-PHI-001, steady state serum E_2 C_{max} and $AUC_{0\text{-}24h}$ may be % lower on average with the 1 mg E_2 - 1 mg E_2/90 µg NGM Ortho-Prefest™ regimen than those with continuous daily oral 1 mg E_2 alone administration (as reflected via the E_2 C_{max} and $AUC_{0\text{-}24h}$ upon continuous administration of the 1 mg E_2 - 1 mg E_2/30 µg NGM regimen). These results are more reliable since these are parallel-group

comparisons within the same study and the results are within the observation limits of the cross-study comparisons above.

10. How is the POO indication claimed for Ortho-Prefest™?

A. Original NDA submission

The sponsor did not use the 1 mg E_2 - 1 mg E_2/90 µg NGM Ortho-Prefest™ regimen to conduct any clinical safety and efficacy study for the POO claim. The POO indication is claimed in the original NDA via BE to Estrace®, which has this indication. However, the lowest effective POO dose is 0.5 mg Estrace®. In single-dose studies ESTNRG-PHI-006 and -007, sponsor's 0.5 and 2 mg E_2 alone tablets (test) are bioequivalent to the 0.5 and 2 mg Estrace® tablets (reference), respectively (ratio of test to reference baseline corrected and baseline uncorrected C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$ of E_2, E_1, and E_1S for the 0.5 and 2 mg E_2 alone tablets are all within the 80 - 125 90% CI, Attachment 4). However per cross-study comparisons (ESTNRG-PHI-007 versus ESTNRG-PHI-006), the ratios of E_2 $AUC_{0\text{-}\infty}$ and C_{max} for sponsor's 1 of 2 mg E_2 alone tablets versus sponsor's 4 of 0.5 mg E_2 alone tablets are about 0.8 and 0.94, respectively. Sponsor's request for BE study waiver for their 1 mg E_2 alone tablet to 1 mg Estrace® is acceptable because:

1. the strength of sponsor's 1 mg E_2 alone tablet is bracketed within their 0.5 and 2 mg E_2 alone tablets.
2. the formulation of 1 mg E_2 alone tablet is proportionally similar to the formulation of 0.5 and 2 mg E_2 alone tablets (Attachment 5), which are shown to be bioequivalent to 0.5 and 2 mg Estrace® tablets, respectively.
3. the dissolution profiles for 1 mg E_2 alone tablet are similar to the dissolution profiles for the 0.5 and 2 mg E_2 alone tablets via the dissolution similarity factor f_2 (Attachment 5).

B. Justification

No clinical study was conducted at steady state to assess E_2 BE between the 1 mg E_2 - 1 mg E_2/90 µg NGM Ortho-Prefest™ regimen and continuous E_2 alone oral administration in order to claim the POO indication via BE study. Therefore, the following justification for the POO claim is necessary:

Per parallel treatment group comparisons within study ESTNRG-PHI-001, the steady state E_2 C_{max} and $AUC_{0\text{-}24h}$ upon cyclic administration of the 1 mg E_2 - 1 mg E_2/90 µg NGM regimen are expected to be about 12 to 18% lower than those upon continuous administration of the 1 mg E_2 alone regimen (as reflected via E_2 C_{max} and $AUC_{0\text{-}24h}$ for the Day 87 of 1 - 1/30 regimen; Question 9). Since the lowest effective dose for the POO indication is 0.5 mg Estrace®, up to 50% reduction in steady state E_2 C_{max} and $AUC_{0\text{-}24h}$ (from 1 to 0.5 mg E_2 exposure) for the 1 mg E_2 - 1 mg E_2/90 µg NGM Ortho-Prefest™ regimen may still be efficacious for POO. Therefore, the POO claim for Ortho-Prefest™ may be acceptable.

11. How are the VMS and VVA indications claimed for Ortho-Prefest™?

A. Study Description

The sponsor conducted studies ESTNRG-CHRT-104, -102, and -103 to substantiate the VMS and VVA indications claim.

Study ESTNRG-CHRT-104 is a double-blinded and randomized study, which originally compared the effect of continuous daily oral doses of 1 or 2 mg E_2 alone to placebo for the treatment of VMS and VVA. When an interim analysis in ongoing study N93-072 showed that

the 2 mg E_2 treatment group resulted in high rates of bleeding/spotting, all randomized patients to receive 2 mg E_2 were discontinued. New subjects were randomized to study the effect of continuous daily oral doses of 0.5 or 1 mg E_2 alone to placebo for the treatment of VMS and VVA. This is a pivotal study, which clearly demonstrates the efficacy of 0.5 or 1 mg E_2 alone on the treatment of VMS and VVA (August 9, 1999 sponsor's response, Attachment 6).

Studies ESTNRG-CHRT-102/103 are double-blinded, parallel group, dose-ranging, and randomized studies, which demonstrate the endometrial protection and VVA claims prospectively with continuous oral administration of 1 mg E_2 alone and cyclical oral administration of 1 mg E_2 - 1 mg E_2/30 µg NGM, 1 mg E_2 - 1 mg E_2/90 µg NGM, and 1 mg E_2 - 1 mg E_2/180 µg NGM. Treatment groups for continuous oral administration of 2 mg E_2 alone and cyclical oral administration of 2 mg E_2 - 2 mg E_2/90 µg NGM, and 2 mg E_2 - 2 mg E_2/180 µg NGM were discontinued upon interim analyses due to high rates of bleeding/spotting. Studies ESTNRG-CHRT-102/103 are not placebo controlled. Due to unacceptable inclusion and exclusion criteria of these 2 studies for VMS claims, the data were regrouped and reanalyzed. Results show that the magnitude of change in the number of moderate to severe hot flushes over the 12 study weeks was similar among all 4 treatment groups.

As mentioned in Question 9 above, NGM/progestin suppresses serum SHBG concentrations and in turn may affect the steady state serum E_2 concentrations. Since there is no definitive clinical safety and efficacy study as well as lack of steady state BE study to substantiate equivalence of serum E_2 concentrations upon continuous oral administration of the 1 mg E_2 - 1 mg E_2/90 µg NGM regimen versus continuous oral E_2 alone administration, the following justification for the VMS and VVA claims may be considered:

B. VMS claim:
Per studies ESTNRG-CHRT-102/103, there appears to be a trend in greater or equal improvement (not significantly different) of VMS when various intermittent oral doses of NGM are administered with continuous oral E_2 administration (1 - 1/30, 1 - 1/90, 1 - 1/180 regimens) as compared to continuous 1 mg E_2 administration at Weeks 4, 8, and 12 (August 9, 1999 sponsor's response, Attachment 6). These 2 studies are not placebo controlled. Per study ESTNRG-CHRT-104, continuous 1 mg E_2 alone administration is effective to treat VMS. Since the 1 mg E_2 - 1 mg E_2/90 µg NGM regimen showed similar efficacy to 1 mg E_2 alone regimen, it may be deduced that the 1 mg E_2 - 1 mg E_2/90 µg NGM regimen may also be effective for VMS.

C. VVA claim:
Per study ESTNRG-CHRT-104, both continuous 0.5 mg (maturation index; $p = 0.004$) and 1 mg (maturation index; $p = 0.001$) daily oral E_2 alone doses versus placebo are efficacious in relieving VVA symptoms. The same rationale as for the POO claim (Question 10) can be applied for the VVA claim. Briefly, if the intermittent administration of 90 µg NGM would lower the steady state serum E_2 concentrations (up to 50% reduction in exposure; 1 to 0.5 mg E_2), 0.5 mg E_2 alone dose may still be effective in treating VVA symptoms. Whereas E_2 C_{max} and $AUC_{0\text{-}24h}$ for the Day 90 of 1 - 1/90 regimen is estimated to be about 12 - 18% lower than those for the continuous administration of E_2 alone regimen (as reflected via E_2 C_{max} and $AUC_{0\text{-}24h}$ for the Day 87 of 1 - 1/30 regimen; Question 9). Therefore, the VVA claim for Ortho-Prefest™ may be acceptable.

12. Is the clinically-tested formulation identical to the to-be-marketed formulation? If not, what are the justifications?

The sponsor used

16. Are the doses for E_2 and NGM proportional kinetically?

Although only 1 dose strength of Ortho-Prefest™ is being sought for approval, the results of dose proportionality study (ESTNRG-PHI-001) described below are for completeness of information. Dose proportionality was shown across the range of E_2 doses (1 mg vs. 2 mg) for E_2 and E_1, but not for E_1S (Attachment 10). Dose proportionality was demonstrated across the range of NGM doses for 17d-NGM (30 µg vs. 90 µg vs. 180 µg) and across the range of NGM doses for NG (90 µg vs. 180 µg).

17. Does Ortho-Prefest™ accumulate upon multiple dose administration?

Per study ESTNRG-PHI-001, the accumulation factors after multiple doses were 1.21-2.22 for E_2, E_1, and E_1S, and 1.38-3.89 for 17d-NGM and NG (Attachment 11). The observed accumulation factors were slightly higher than the predicted accumulation factors. The predicted E_2 accumulation factor is 1.5 via serum E_2 half-life of 15 hours. The observed E_2 accumulation factor is about 2. This rise in accumulation factor might be due to the observed increases in serum SHBG concentrations, which occurred as a result of the E_2 therapy.

18. Why was only 17d- NGM simulated in study EDMS-USRA-2348912?

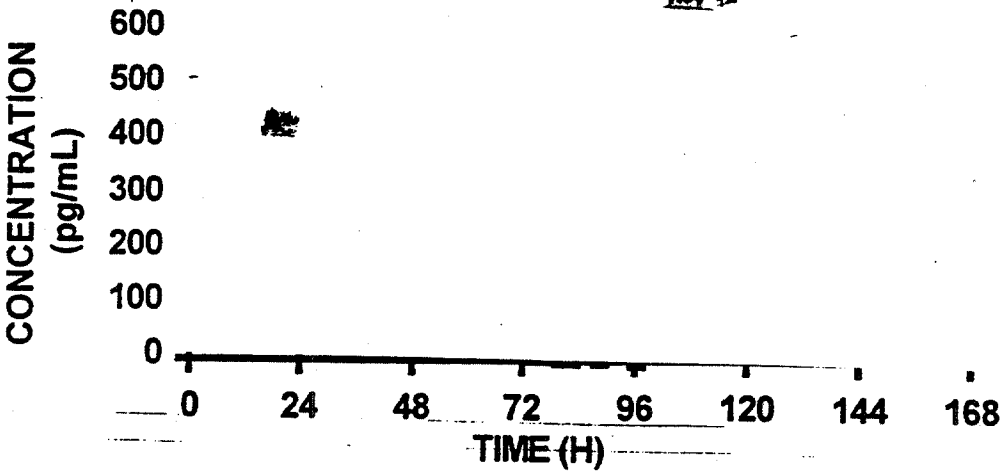
17-d NGM and NG are active metabolites of NGM. However, 17-d NGM is the primary active metabolite of NGM and therefore is simulated.

19. Does E_2 and NGM interact with each other kinetically upon administration of Ortho-Prefest™ regimen?

A simulation (study EDMS-USRA-2348912) of serum 17d-NGM concentrations via the superposition method was conducted to estimate the concentration vs. time profile during the 3-day NGM off-and-on treatment phases.

Mean serum 17d-NGM concentrations obtained from study ESTNRG-PHI-001 were used for the simulation. Figure 1 shows the simulated serum 17d-NGM concentrations, during the E_2-alone and the E_2/NGM treatments, upon oral administration of the 1 mg E_2 - 1 mg E_2/90 µg NGM regimen.

Figure 1: Simulated serum 17d-NGM concentrations upon oral administration of the 1 mg E_2 - 1 mg E_2/90 µg NGM regimen.



In Figure 1, the 1st segment of the graph (0-24 hours) contains the actual study ESTNRG-PHI-001 Day 90 data; namely, the last day of the last 3-day E_2/NGM treatment. The next segment (24-96 hours) is an extrapolation from the Day 90 data; this segment shows the simulated 17d-NGM data during the 3-day E_2-alone treatment. The 3rd segment (96-120 hours) contains the actual study ESTNRG-PHI-001 Day 4 data; namely, the 1st day of the 1st 3-day E_2/NGM treatment phase. The last segment (120-168 hours) represents the simulated 2nd and the 3rd days of the 1st 3-day E_2/NGM treatment.

Per Figure 1, the results of the simulated 17d-NGM concentrations at the 3rd day of the 1st 3-day E_2/NGM treatment phase (Segment 4, 144-168 hours) is very close to the Day 90 data (Segment 1, 0-24 hours; the 3rd day of the last 3-day E_2/NGM treatment). The simulated profiles showed that minimum serum 17d-NGM concentrations were always above 100 pg/mL during the 3-day 1 mg/90 µg E_2/NGM treatment. Serum 17d-NGM concentrations gradually declined to approximately 100 pg/mL at 24 hours after the last E_2/NGM dose, i.e., right before the 1st E_2-alone dose. The assay LLOQ for 17d-NGM is 100 pg/mL.

Per study ESTNRG-PHI-001, the C_{max} and $AUC_{(0\text{-}24h)}$ ratios between Day 87 and Day 90 for E_2, E_1, and E_1S all fall within the 95% CI (Attachment 12). The results of this study showed that NGM or NGM metabolites did not affect E_2, E_1, and E_1S PK upon oral administration of the 1 mg E_2 - 1 mg E_2/90 µg NGM regimen at Day 87 and Day 90.

Per in vitro studies XT070796 and DM95334, E_2, NGM, 17-d NGM, NG, and 3-keto NGM (NG acetate) can inhibit cytochrome P450 (CYP) 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, 3A4/5, 4A9/11 in human liver microsome systems. However, the inhibitory constants (K_i) for E_2, NGM, 17-d NGM, NG, and 3-keto NGM are in the order of 10^3 to 10^4 times higher than the C_{max} of E_2, NGM, 17-d NGM, NG, and 3-keto NGM (Attachment 13). Thus, the potential for E_2, NGM, 17-d NGM, NG, and 3-keto NGM to interact with each other via inhibition of CYP isoenzymes is minimal.

20. Does high fat meal affect the Ortho-Prefest™ PK?

The effect of food on the PK of E_2, E_1, E_1S, 17d-NGM, and NG was evaluated in the ESTNRG-PHI-004 study. The study results show that the ratios of high fat meal versus fasted

state for the $AUC_{0\text{-last}}$ of E_2, E_1, E_1S, 17d-NGM, and NG as well as the ratios for the C_{max} of E_2 and NG fall within the 90% CI (Attachment 14). High fat meal increased the C_{max} of E_1 and E_1S (14 and 24%, respectively), and decreased the C_{max} of 17d-NGM by 16%. Since subjects in pivotal clinical studies ESTNRG-CHRT-104, -102, and –103 were instructed to take 1 tablet by mouth daily at bedtime, preferably between 9 p.m. and 12 midnight, these differences may not be clinically significant.

21. What are the covariates for Ortho-Prefest™ PK?

In study EDMS-USRA-2277684, E_2 and E_2 metabolites as well as NGM and NGM metabolites C_{max} and $AUC_{0\text{-last}}$ from 5 data-rich, single-dose, PK studies (ESTNRG-PHI-008, ESTNRG-PHI-006, ESTNRG-PHI-007, ESTNRG-PHI-004, and ESTNRG-PHI-002) were pooled as dependent variables to evaluate the relationship to the demographic covariates (race, age, and body weight). The correlation between PK and demographic covariates (race, age, and body weight) was evaluated via regression models (Attachment 15).

Due to inadequate number of Black and Asian subjects in the pooled data (the 164 subjects participating in these studies included 100 Caucasians, 61 Hispanics, 2 Blacks, and 1 Asian), the race effect could only be evaluated between the Caucasian and the Hispanic postmenopausal women. No significant PK difference was found between these 2 groups. Postmenopausal women in age groups 40-50, 51-55, 56-60, 61-66 years showed no significant difference in the PK of E_2, NGM, and their metabolites. Postmenopausal women of body weight <60, 60-80, and >80 kg also showed no significant difference in the PK of E_2 and its metabolites. The PK of 17d-NGM and NG were not significantly different between women weighing <60 and 60-80 kg. Women with a body weight higher than 80 kg showed the following significant correlations:

Table 3. Significant body weight covariate with 17d-NGM and NG PK parameters.

Analyte	Parameter	Reference	Comparison	Geometric Mean of Reference	Geometric Mean of Test	Ratio (%)	p –values
17d-NGM	$AUC_{0\text{-last}}$	60-80 kg	>80 kg vs. 60-80 kg	8231.99	5800.63	70	0.0454
	C_{max}	60-80 kg	>80 kg vs. 60-80 kg	964.61	591.19	61	<0.001
NG	C_{max}	60-80 kg	>80 kg vs. 60-80 kg	252.68	175.68	70	<0.001

This table is extracted from Attachment 15.

22. What are the clinical PK of E_2 and NGM?

See the Suggested Labeling Statements for Clinical Pharmacology section below.

23. What are the sponsor's proposed dissolution methods and specifications for Ortho-Prefest™?

The proposed in vitro dissolution method is the USP Apparatus 2 (paddle), 50 rpm, 500 mL of % sodium lauryl sulfate in water for both E_2 and NGM (Attachment 16). The sponsor proposed the following specifications:

Table 4. Sponsor's proposed dissolution specification for E_2 and NGM.

Time (min)	E_2		NGM	
30	Not less than in min	% (Q) of label claim	Not less than in min	% (Q) of label claim

This table is extracted from Attachment 16.

24. What is the sponsor's proposed Clinical Pharmacology Section of the labeling for Ortho-Prefest™?

Comments

1. No data are available for the direct comparison of E_2 PK upon oral administration of the 1 mg E_2 - 1 mg E_2/90 µg NGM Ortho-Prefest™ regimen versus that of 1 mg E_2 alone oral administration. In the future, the E_2 alone treatment group should be included in the multiple dose PK studies for E_2 plus progestin products up to serum SHBG concentrations reach steady state.
2. Per cross-study comparisons (between study ESTNRG-PHI-001 and Lobo et al. *Obstet. & Gynecol.* 62:94 1983), minimum steady state serum E_2 concentrations may be 20 - 23% lower on average with the 1 mg E_2 - 1 mg E_2/90 µg NGM Ortho-Prefest™ regimen than those with continuous daily oral 1 mg E_2 alone administration.
3. Per parallel-group comparisons within study ESTNRG-PHI-001, steady state serum E_2 C_{max} and $AUC_{0\text{-}24h}$ concentrations are expected to be 12 - 18% lower on average with the 1 mg E_2 - 1 mg E_2/90 µg NGM Ortho-Prefest™ regimen than those with the continuous daily oral 1 mg E_2 - 1 mg E_2/30 µg NGM regimen.
4. Sponsor's BE study waiver request for the 1 mg E_2 alone Ortho-Prefest™ tablet is acceptable.
5. Sponsor needs to specify the temperature of the proposed in vitro dissolution method. The in vitro dissolution specification should be "not less than % or Q = % of label claim in minutes" for E_2 and "not less thar % or Q = % of label claim in minutes" for NGM.
6. The statements "Food has no clinically significant effect on the pharmacokinetics of estradiol, norgestimate, and their metabolites. ORTHO-PREFEST™ can be given without regard to food." in the Absorption section of the labeling should be removed. The statements "High fat meal does not significantly affect the $AUC_{0\text{-}last}$ for estradiol, estrone, estrone sulfate, 17-deacetylnorgestimate, and norgestrel as well as the C_{max} for estradiol and norgestrel as compared to fasted state. High fat meal resulted in a 14% and 24% increase in C_{max} for estrone and estrone sulfate, respectively, as compared to fasted state. High fat meal resulted in a 16% decrease in C_{max} for 17-deacetylnorgestimate as compared to fasted state. ORTHO-PREFEST™ was dosed in the clinical safety and efficacy studies without regard to food." should be stated in the Absorption section of the labeling instead.
7. The statements "Animal studies indicate that norgestimate and/or metabolite(s) are distributed to skin, muscles, liver, adrenals, and adipose tissue. There is no significant retention, of either estradiol or norgestimate and/or metabolites(s), in these tissues." in the Distribution section of the labeling should be removed.
8. The statement "Estradiol and other naturally occurring estrogens are bound mainly to sex hormone binding globulin (SHBG), and to a lesser degree to albumin." in the Distribution section of the labeling should be removed. The statement "Estradiol is mainly bound to sex

hormone binding globulin (SHBG) and to albumin in serum." should be stated in the Distribution section of the labeling instead.

9. The statement "17-deacetylnorgestimate, the primary active metabolite of norgestimate, does not bind to SHBG but to other serum proteins such as albumin." in the Distribution section of the labeling should be removed. The statement "17-deacetylnorgestimate, the primary active metabolite of norgestimate, does not bind to SHBG but to other serum proteins." should be stated in the Distribution section of the labeling instead.
10. The statement "The half-life ($t_{1/2}$) of 17-deacetylnorgestimate in postmenopausal women receiving ORTHO-PREFEST™ is approximately 37 hours." in the Excretion section of the labeling needs to be substantiated.
11. The statements "Women with body weight higher than 80 kg, however, had approximately % lower peak serum levels of 17-deacetylnorgestimate. This difference, however, is not considered clinically significant." should be removed from the Effects of Race, Age, and Body Weight section of the labeling. The statements "However, women with body weight higher than 80 kg had approximately % lower peak serum concentrations of 17-deacetylnorgestimate, % lower $AUC_{0\text{-last}}$ values for 17-deacetylnorgestimate, and % lower peak serum concentrations of norgestrel as compared to the women with 60 - 80 kg body weight group. The clinical relevance of these observations is unknown." should be stated in the Effects of Race, Age, and Body Weight section of the labeling instead.
12. The table for the "Pharmacokinetic Parameters of E_2, E_1, E_1S, and 17d-NGM Following Single and Multiple Dosing of ORTHO-PREFEST™" should report baseline uncorrected data for E_2, E_1, and E_1S instead. See other suggested changes to this table in the Suggested Labeling Statements for Clinical Pharmacology section below.
13. The statements "Estradiol, norgestimate, and their metabolites inhibit a variety of P450 enzymes in human liver microsomes. However, the clinical and toxicological consequences of such interaction are likely to be insignificant because, under the recommended dosing regimen, the in vivo concentrations of these steroids, even at the peak serum levels, are relatively low compared to the inhibitory constant (Ki)." in the Drug-Drug Interactions section of the labeling should be removed. The statements "Estradiol, norgestimate, and their metabolites can inhibit a variety of cytochrome P450 isoenzymes via in vitro human liver microsome systems. However, the inhibitory constants (K_i) are in the order of 10^3 and 10^4 times higher than the peak serum concentrations of these steroids. Thus, the potential for estradiol, norgestimate, and their metabolites to interact with each other via inhibition of cytochrome P450 isoenzymes is minimal." should be stated in the Drug-Drug Interactions section of the labeling instead.
14. The statement "A clinical study conducted in 36 healthy menopausal women demonstrated that norgestimate and its metabolites did not affect the pharmacokinetics of estradiol and its metabolites." in the Drug-Drug Interactions section of the labeling should be removed. The statement "Per parallel-treatment-group (12 healthy postmenopausal women per group) comparisons within a study, steady state serum estradiol C_{max} and $AUC_{0\text{-}24h}$ may be % lower on average upon continuous oral administration of the treatment 1 mg estradiol alone daily for 3 days and then 1 mg estradiol plus 90 µg norgestimate daily for 3 days than those upon continuous oral administration of the treatment 1 mg estradiol alone daily for 3 days and then 1 mg estradiol plus 30 µg norgestimate daily for 3 days." should be stated in the Drug-Drug Interactions section of the labeling instead.
15. Comments 5-14 above on labeling statements were appropriately communicated to and agreed by the sponsor.

Comments NOT to be conveyed to the Sponsor

- Sponsor provided synopsis of detailed information on all Clinical Pharmacology and Biopharmaceutics studies, which are in Attachment 18.

Recommendations:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed NDA 21-040 dated December 23, 1998. OCPB/DPEII finds that the submitted data support the "Human Pharmacokinetics and Bioavailability" section of NDA 21-040. Comments 1 to 3 should be conveyed to the clinical division HFD-580.

Suggested Labeling Statements:
CLINICAL PHARMACOLOGY

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Some statements in the Clinical Pharmacology section of the final accepted label dated October 22, 1999 differ from some statements in this Suggested Labeling Statements of Clinical Pharmacology section above. However, the Office of Clinical Pharmacology and Biopharmaceutics agrees to the statements in the final label dated October 22, 1999.

October 22, 1999

S.W. Johnny Lau, R.Ph., Ph.D.
OCPB/DPEII

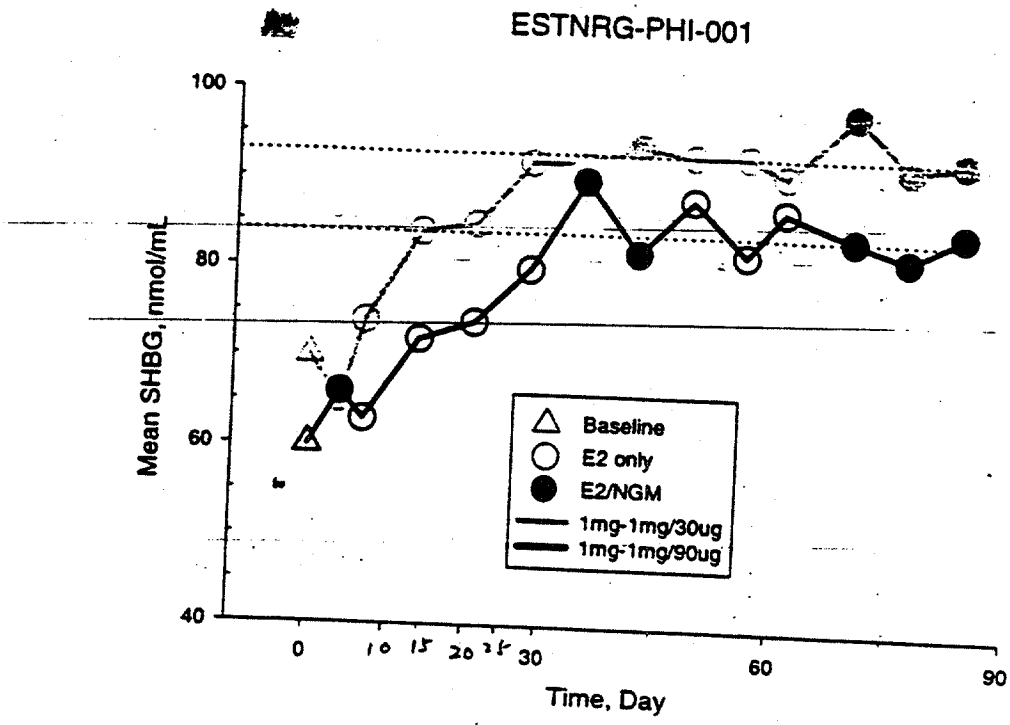
FT signed by Ameeta Parekh, Ph.D., Team Leader /S/ 10/22/99

cc: NDA 21-040, HFD-870 (M. Chen, A. Parekh, J. Lau), HFD-580 (T. van der Vlugt, D. Moore), CDR (B. Murphy for Drugs)

Attachment 1

NDA 21-040 April 30, 1999 Amendment Page 6

Figure 1: Mean SHBG Concentrations During Treatment with 1 mg E2/0.030 mg NGM or 1 mg E2/0.090 mg NGM
(Study ESTNRG-PHI-001)



The results from Study ESTNRG-PHI-001, measuring SHBG levels repeatedly over a period of 90 days in samples obtained both during the E2-only and E2/NGM combined phase of the pulsed regimen show only small differences over the threefold range of adjunctive NGM. In the absence of an estrogen-only arm, direct comparisons of the effect of adjunctive NGM are not possible.

3.1.3. ETHINYL ESTRADIOL/OTHER PROGESTINS

The (inhibitory) effects of progestins, other than NGM, on SHBG generally correlate with their androgenicity, as tested in competitive binding studies[13,14] and in bioassays. LNG, 3-keto desogestrel (i.e., the active metabolite of desogestrel), gestodene, and norethindrone all influence SHBG levels and bind to SHBG.[17-19] The relative binding affinity for SHBG and the attenuation of estrogen induction of SHBG in most, but not all studies, are in decreasing order: LNG>gestodene>norethindrone> 3-keto desogestrel.

Attachment 2

NDA 21040, ESTNRG-PHI-001, 1 mg E2, 1mg E2+90ug NGM

Subj #	D87	D90	D87	D90
	E2 conc		E2 baseline cor. Conc	
101	18.7		18.7	
105	10.6	6.63	6.67	2.7
109	66.6	49.3	66.6	49.3
112	16	11.8	12.3	8.1
113	21.9	22.2	21.9	22.2
116	17.8	13.1	17.8	13.1
121	14.7	13.4	11.46	10.16
122	23.2	30.2	19.92	26.92
126	20.1	30.5	3.87	14.27
127	45	50.2	40.02	45.22
133	20.2	20.2	17.22	17.22
134	13	6.8	13	6.8
Mean	23.98333	23.1209	20.78833	19.6355
SD	15.97736	15.4724	17.06103	15.3165
Min				
Max				

Extracted from sponsor's electronic database:
ESTNRG_PHI_001/E2__001c.txt
and
ESTNRG_PHI_001/E2bc001c.txt

Attachment 3

NDA 21-040 Item 6 Volume 9/Page 53

Table 4: Demographic and Baseline Characteristics
(All Subjects Enrolled in Protocol ESTNRG-PHI-001)

	E_2 1 mg/E_2 1 mg + NGM 30 µg (N=12)	E_2 1 mg/E_2 1 mg + NGM 90 µg (N=12)	E_2 2 mg/E_2 2 mg + NGM 180 µg (N=12)	Total (N=36)
Age (Years)				
40-45	1 (8%)	1 (8%)	0 (0%)	2 (6%)
46-50	0 (0%)	1 (8%)	4 (33%)	5 (14%)
51-55	3 (25%)	3 (25%)	3 (25%)	9 (25%)
56-60	5 (42%)	4 (33%)	5 (42%)	14 (39%)
61-65	3 (25%)	3 (25%)	0 (0%)	6 (17%)
Race				
White	12 (100%)	11 (92%)	12 (100%)	35 (97%)
Other	0 (0%)	1 (8%)	0 (0%)	1 (3%)
Height (cm)				
Mean ± SD	165.8 ± 6.99	163.6 ± 8.43	168.1 ± 5.78	165.8 ± 7.19
Median	166.5	164.0	165.0	165.0
Range	(155.0, 175.0)	(152.0, 180.0)	(163.0, 178.0)	(152.0, 180.0)
Weight (kg)				
Mean ± SD	72.1 ± 9.57	67.6 ± 13.03	73.5 ± 10.84	71.1 ± 11.21
Median	72.0	63.0	72.0	71.5
Range	(53.0, 85.0)	(50.0, 90.0)	(58.0, 91.0)	(50.0, 91.0)

Cross-reference: Appendix 3.1.1

B. STUDY COMPLETION/WITHDRAWAL INFORMATION

Subjects were considered to have completed the study if they received 90 days of study medication and completed all study procedures on Day 97. As seen in Table 5, 34 subjects completed the study. One subject (Subject 129) in the E_2 1 mg/E_2 1 mg + NGM 30 µg group elected to discontinue the study on Day 82. One additional subject (Subject 136) in the E_2 2 mg/E_2 2 mg + NGM 180 µg group prematurely discontinued the study on Day 60 due to an adverse event (depression). In accord with the protocol, these subjects were not replaced. Study completion information for each subject is contained in Appendix 3.2.

Attachment 4

Table 1: Bioequivalence Evaluation Results Between the RWJPRI 0.5-mg E_2 Tablet and the ESTRACE® 0.5-mg E_2 Tablet (RWJPRI Study ESTNRG-PHI-006)

Parameter	ESTRACE® Geo[a] Mean	RWJPRI Geo Mean	Ratio of Means[b] (%)	90% Confidence Intervals Lower Bound[c]	90% Confidence Intervals Upper Bound[c]
(A) E_2					
Baseline Uncorrected					
$AUC_{0-\infty}$	2113.32	2027.45	95.94		
AUC_{0-last}	1648.04	1619.90	98.29		
C_{max}	50.90	46.84	92.03		
Baseline Corrected					
$AUC_{0-\infty}$	1647.76	1532.00	92.97		
AUC_{0-last}	1407.91	1339.34	95.13		
C_{max}	47.16	42.78	90.70		
(B) E_1					
Baseline Uncorrected					
$AUC_{0-\infty}$	10584.76	10704.89	101.13		
AUC_{0-last}	8910.32	8997.75	100.98		
C_{max}	372.80	383.06	102.75		
Baseline Corrected					
$AUC_{0-\infty}$	8069.86	8205.39	101.68		
AUC_{0-last}	7511.03	7563.64	100.70		
C_{max}	353.37	363.41	102.84		
(C) E_1S					
Baseline Uncorrected					
$AUC_{0-\infty}$	295.72	309.00	104.49		
AUC_{0-last}	255.99	261.24	102.05		
C_{max}	15.61	16.54	105.95		
Baseline Corrected					
$AUC_{0-\infty}$	234.83	235.89	100.45		
AUC_{0-last}	222.16	223.30	100.51		
C_{max}	15.13	15.98	105.56		

[a] Geometric mean.
[b] (RWJPRI tablet/ESTRACE® tablet) × 100.
[c] % reference.

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Table 2: Bioequivalence Evaluation Results Between the RWJPRI 2-mg E_2 Tablet and the ESTRACE® 2-mg E_2 Tablet (RWJPRI Study ESTNRG-PHI-007)

Parameter	ESTRACE® Geo[a] Mean	RWJPRI Geo Mean	Ratio of Means[b] (%)	90% Confidence Intervals Lower Bound[c]	90% Confidence Intervals Upper Bound[c]
(A) E_2					
Baseline Uncorrected					
$AUC_{0-\infty}$	1521.5	1611.4	106.65		
AUC_{0-last}	1290.03	1333.71	103.39		
C_{max}	47.86	43.86	91.65		
Baseline Corrected					
$AUC_{0-\infty}$	1192.7	1260.4	106.26		
AUC_{0-last}	1099.40	1125.32	102.36		
C_{max}	44.99	40.59	90.22		
(B) E_1					
Baseline Uncorrected					
$AUC_{0-\infty}$	8747.60	8942.22	102.23		
AUC_{0-last}	7775.67	7784.91	100.12		
C_{max}	364.31	337.99	92.78		
Baseline Corrected					
$AUC_{0-\infty}$	6877.36	6965.03	101.27		
AUC_{0-last}	6597.42	6594.57	99.96		
C_{max}	347.80	321.48	92.43		
(C) E_1S					
Baseline Uncorrected					
$AUC_{0-\infty}$	222.91	222.01	99.60		
AUC_{0-last}	206.77	207.61	100.41		
C_{max}	14.6	14.9	94.06		
Baseline Corrected					
$AUC_{0-\infty}$	215.76	217.43	100.78		
AUC_{0-last}	204.62	204.93	100.15		
C_{max}	14.75	13.86	93.99		

[a] Geometric mean.
[b] (RWJPRI tablet/ESTRACE® tablet) × 100.
[c] % reference.

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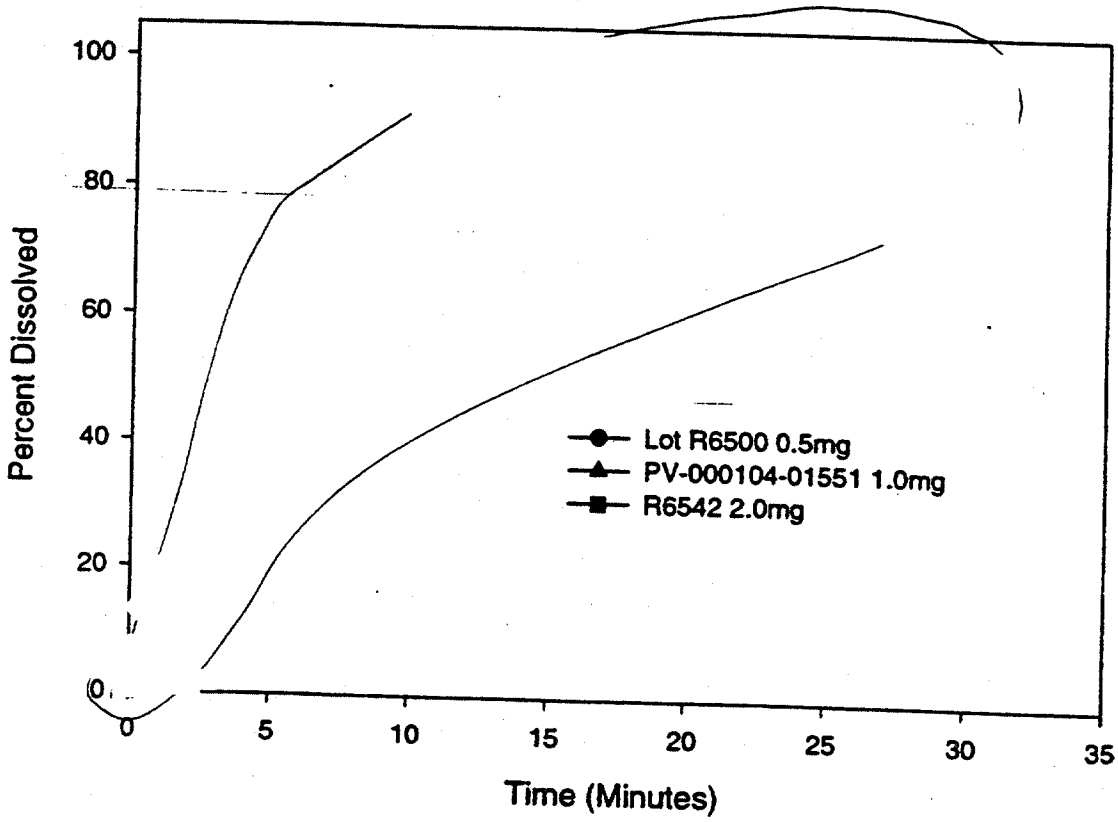
Dissolution Profiles of 0.5, 1.0 and 2.0mg Estradiol ORTHO-PREFEST Tablets



The tables below contain the f_2 dissolution similarity factor values for the requested products. All products were tested using the same dissolution media and conditions. The test conditions consisted of 500mL of aqueous media with % sodium lauryl sulfate. The testing was conducted using USP Apparatus 2 with 50 RPM paddle speed. The f2 values of are in the acceptable range to support profile similarity.

Table 1. Average Percent Dissolved (standard deviation) Across Time points and Strengths

Estradiol Tablet Strength	Lot Number	Time		
		10 minutes	20 minutes	30 minutes
0.5mg	R6500			
1.0mg	PV-000104-01551			
2.0mg	R6542			

*Tablets 5 and 6 have missing values

Table 2. f_2 Statistics

Comparison	f_2
1.0mg versus 0.5mg	
1.0mg versus 2.0mg	

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Attachment 6

DISKPRIHRT:[E2ORLMGM.CHRT-104.OUTPUT]SHF2_ADGS.LIS
program: DISKPRIHRT:[E2ORLMGM.CHRT-104.DEVELOP]SHF2_ADGS.SAS August 5, 1999 17:15 PAGE 1

PROTOCOL CHRT-104

CHANGES IN THE MEAN DAILY NUMBER OF MODERATE/SEVERE HOT FLUSHES DURING THERAPY
ALL SUBJECTS WITH MEAN PRESTUDY MODERATE/SEVERE HOT FLUSHES >= 7 AT BASELINE
(SECOND RANDOMIZATION: STUDY ESTHRO-CHRT-104)

WEEK		PLACEBO	CONT. 0.5 MG E2	CONT. 1 MG E2	ESTIMATED DIFFERENCE FROM PLACEBO AND p-VALUE* PLACEBO VS 0.5 ESTIMATE	PLACEBO VS 0.5 P-VALUE	PLACEBO VS 1 MG ESTIMATE	PLACEBO VS 1 MG P-VALUE
BASELINE**	N	47	48	48				
	MEAN	13.16	13.02	14.56				
WEEK 4	N	44	45	45				
	BASELINE MEAN	12.64	13.14	14.83				
	WEEK 4 MEAN	6.13	5.68	3.34				
	MEAN CHANGE	-6.51	-7.46	-11.49	0.832	0.321	3.876	<.001
WEEK 8	N	41	41	43				
	BASELINE MEAN	12.41	12.27	15.03				
	WEEK 4 MEAN	5.59	3.42	2.33				
	MEAN CHANGE	-6.83	-8.85	-12.70	2.296	0.806	4.008	<.001
WEEK 12	N	39	38	42				
	BASELINE MEAN	12.50	12.36	15.20				
	WEEK 4 MEAN	5.99	3.46	1.55				
	MEAN CHANGE	-6.60	-8.90	-13.65	2.408	0.806	4.836	<.001

* BASED ON LEAST SQUARES ESTIMATES OF THE MEAN CHANGE FROM THE ANALYSIS OF COVARIANCE.
** INCLUDES ALL SUBJECTS AT BASELINE WITH AN AVERAGE OF AT LEAST 7 MODERATE-TO SEVERE HOT FLUSHES.

Sponsor's August 9, 1999 response

output: DISKPRIHRT:[E2ORLNGM.C102-103.OUTPUT]TBL_29_0803A.LIS
program: DISKPRIHRT:[E2ORLNGM.C102-103.DEVELOP]HF_ANOV_0803A.SAS

August 5, 1999 14:48 PAGE 1

CHANGES IN THE MEAN DAILY NUMBER OF MODERATE/SEVERE HOT FLUSHES DURING THERAPY
ALL SUBJECTS IN THE 1MG E2 GROUPS WITH MEAN MODERATE/SEVERE HOT FLUSHES >= 7 AT BASELINE
(STUDIES ESTNRG-CHRT-102/103)

WEEK		E2 1MG	E2 1MG/30	E2 1MG/90	E2 1MG/180	ESTIMATED DIFFERENCE FROM E2 1 MG AND p-Va				
						E2 vs E2/30		E2 vs E2/90		E2 VS E:
						ESTIMATE	p-Value	ESTIMATE	p-Value	ESTIMATE
BASELINE**	N	29	27	26	37					
	MEAN	10.99	10.13	10.86	11.48					
WEEK 4	N	29	26	26	35					
	BASELINE MEAN	10.99	10.14	10.86	10.78					
	WEEK 4 MEAN	3.33	2.68	2.60	1.38					
	MEAN CHANGE	-7.66	-7.46	-8.26	-9.40					
WEEK 8	N	29	26	23	34	0.356	0.681	-0.806	0.995	1.220
	BASELINE MEAN	10.99	10.14	11.03	10.79					
	WEEK 8 MEAN	1.10	1.71	0.88	0.28					
	MEAN CHANGE	-9.88	-8.43	-10.16	-10.51					
WEEK 12	N	29	26	23	33	-0.704	0.300	0.089	0.898	0.570
	BASELINE MEAN	10.99	10.14	10.88	10.86					
	WEEK 12 MEAN	1.13	1.13	0.71	0.12					
	MEAN CHANGE	-9.85	-9.01	-10.17	-10.74	0.178	0.752	0.736	0.201	1.173

* Based on least squares estimates of the mean change from the analysis of covariance.
** Includes all subjects at baseline with an average of at least 7 moderate to severe hot flushes.

Sponsor's August 9, 1999 response

Attachment 7

The dissolution profiles of the clinical and the commercial tablets were compared using the dissolution similarity factor, f_2 (Federal Register Vol. 60, No. 230, 11/95, p 61642). Commercial tablets from stability Batch RR-D-98-0070- were compared to clinical tablets from the same batch, and the resulting f_2 statistics were 93.4 and 82.5 for NGM and E_2, respectively. The same commercial tablets from Batch RR-D-98-0070-A were compared to clinical tablets from clinical Batch -6133, and the resulting f_2 statistics were 83.6 and 88.2 for NGM and E_2, respectively. Tables 3 and 4 list the mean (standard deviation [±SD]) dissolution data and the calculated f_2 statistics test results comparing the dissolution profiles between the clinical and the commercial tablets.

Table 3: The Mean (±SD) Dissolution Data: Clinical vs. Commercial Tablets

Batch	Tablet	10 min	20 min	30 min	45 min
		17β-Estradiol			
RR-D-98-0070-A	Clinical	73.8±4.7	89.5±3.4	93.6±2.5	95.7±2.5
RR-D-98-0070-A	Commercial	77.8±6.2	89.8±2.0	93.9±1.9	95.1±1.7
R-6133	Clinical	77.8±4.9	91.0±3.3	96.0±2.6	Not Done
		Norgestimate			
RR-D-98-0070-A	Clinical	89.8±5.2	97.4±2.8	99.9±2.6	100.8±2.5
RR-D-98-0070-A	Commercial	91.2±3.4	98.1±1.9	100.9±1.6	100.7±1.5
R-6133	Clinical	90.6±5.4	100.5±2.8	103.0±2.7	Not Done

Table 4: Comparison of the Dissolution Profiles Between the Clinical and the Commercial Tablets: Calculated f_2 Statistics

Comparison	17β-Estradiol	Norgestimate
RR-D-98-0070-A Clinical Tablet vs. Commercial Tablet	82.5	93.4
Commercial Tablet RR-D-98-0070-A vs. Clinical Tablet R-6133	88.2	83.6

Since all calculated f_2 values were greater than 50, the similarity of dissolution profiles between the clinical and the commercial tablets, for both NGM and E_2, is supported.

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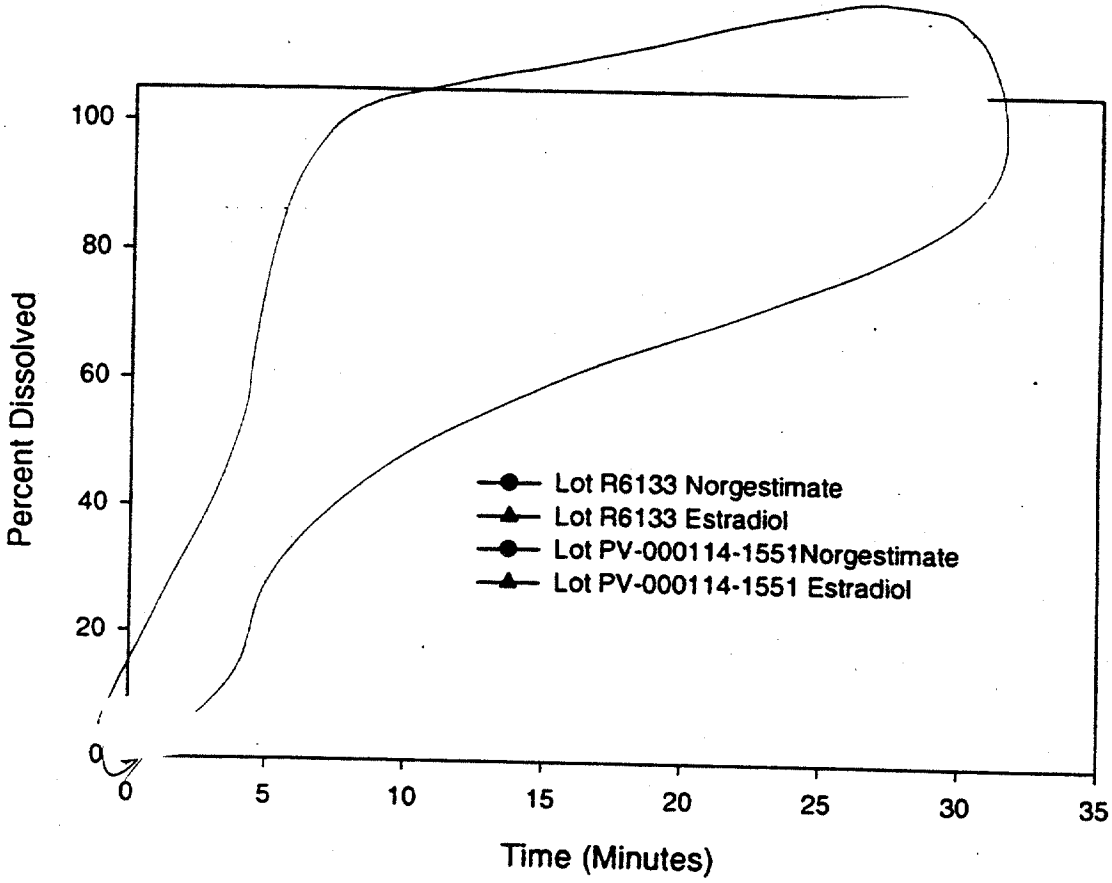
Dissolution Profiles of Estradiol/Norgestimate
Clinical and To-Be-Marketed ORTHO-PREFEST Tablets



1. Please provide f_2 dissolution similarity factor values for the to-be marketed 1mg Estradiol/90mcg Norgestimate ORTHO-PREFEST tablets to the clinically tested 1mgEstradiol/90 mcg Norgestimate ORTHO-PREFEST tablets.

The tables below contain the f_2 dissolution similarity factor values for the requested products. All products were tested using the same dissolution media and conditions. The test conditions consisted of 500mL of aqueous media with % sodium lauryl sulfate. The testing was conducted using USP Apparatus 2 with 50 RPM paddle speed. The f_2 values of are in the acceptable range to support profile similarity.

Table 1. Average Percent Dissolve (standard deviation) Across Time Points and Active Components

Lot and Type of Material	Active Component	Time		
		10 minutes	20 minutes	30 minutes
To-Be-Marketed PV-000114-1551	Norgestimate			
	Estradiol			
Clinically Tested R6133	Norgestimate			
	Estradiol			

Table 2. f_2 Statistics Across Active Components

Active Component	f_2
Norgestimate	
Estradiol	

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Table 3: Mean (±SD) (A) E_2, (B) E_1, (C) E_1S, (D) 17d-NGM, and (E) NG Pharmacokinetic Parameters in 36 Healthy Postmenopausal Women Receiving a Single 2 mg/180 µg Oral Dose of E_2/NGM as Two

Parameter	Solution	
(A) E_2		
Baseline Uncorrected		
C_{max} (pg/mL)	524.3	(190.0)
T_{max} (h)	0.5	(0.0)
$AUC_{0\text{-last}}$ (pg·h/mL)	2152.4	(827.5)
$AUC_{0\text{-}\infty}$ (pg·h/mL)	2416.2	(1070.2)
$t_{½}$ (h)	22.51	(10.13)
Baseline Corrected		
C_{max} (pg/mL)	522.3	(189.2)
T_{max} (h)	0.5	(0.0)
$AUC_{0\text{-last}}$ (pg·h/mL)	2015.4	(713.4)
$AUC_{0\text{-}\infty}$ (pg·h/mL)	2185.2	(828.0)
$t_{½}$ (h)	19.51	(9.87)
(B) E_1		
Baseline Uncorrected		
C_{max} (pg/mL)	415.1	(149.6)
T_{max} (h)	3.6	(2.0)
$AUC_{0\text{-last}}$ (pg·h/mL)	9278.8	(3958.9)
$AUC_{0\text{-}\infty}$ (pg·h/mL)	10491.1	(4625.6)
$t_{½}$ (h)	23.97	(7.21)
Baseline Corrected		
C_{max} (pg/mL)	398.5	(147.6)
T_{max} (h)	3.6	(2.0)
$AUC_{0\text{-last}}$ (pg·h/mL)	8074.4	(3793.7)
$AUC_{0\text{-}\infty}$ (pg·h/mL)	8539.9	(4258.9)
$t_{½}$ (h)	16.03	(5.09)
(C) E_1S		
Baseline Uncorrected		
C_{max} (ng/mL)	19.9	(11.5)
T_{max} (h)	2.2	(1.1)
$AUC_{0\text{-}\infty}$ (ng·h/mL)	335.7	(286.1)
Baseline Corrected		
C_{max} (ng/mL)	19.4	(11.3)
T_{max} (h)	2.2	(1.1)
$AUC_{0\text{-last}}$ (ng·h/mL)	294.9	(269.0)
$AUC_{0\text{-}\infty}$ (ng·h/mL)	321.8	(307.4)
$t_{½}$ (h)	22.21	(10.99)
(D) 17d-NGM		
C_{max} (pg/mL)	1396.8	(338.8)
T_{max} (h)	1.1	(0.2)
$AUC_{0\text{-last}}$ (pg·h/mL)	10913.7	(2821.7)
$AUC_{0\text{-}\infty}$ (pg·h/mL)	14181.9	(4448.9)
$t_{½}$ (h)	37.01	(16.54)
(E) NG		
C_{max} (pg/mL)	304.4	(123.8)
T_{max} (h)	1.2	(0.4)
$AUC_{0\text{-last}}$ (pg·h/mL)	6577.3	(3040.9)

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Table 13: Mean (±SD) (A) E_2, (B) E_1, (C) E_1S, (D) 17d-NGM, and (E) NG Pharmacokinetic Parameters in Healthy Postmenopausal Women Receiving the Three-Day Cyclophasic Regimen of E_2-E_2/NGM for 90 Days (Protocol ESTNRG-PHI-001)

Parameter	Day 1	Day 4	Day 87	Day 90
(A) E_2				
Baseline Uncorrected Data				
1 mg E_2/30 µg NGM Group, N = 11				
C_{max} (pg/mL)	28.6 (14.2)	44.5 (21.1)	52.9 (21.7)	48.2 (21.9)
T_{max} (h)	7.0 (3.4)	5.2 (2.6)	5.4 (3.1)	5.6 (3.0)
$AUC_{0\text{-}24h}$ (pg·h/mL)	438 (149)	723 (298)	937 (467)	803 (449)
1 mg E_2/90 µg NGM Group, N = 12				
C_{max} (pg/mL)	27.4 (9.0)	39.3 (12.8)	49.7 (23.2)	46.2 (20.4)
T_{max} (h)	7.4 (2.3)	7.4 (3.6)	7.3 (3.6)	6.8 (2.5)
$AUC_{0\text{-}24h}$ (pg·h/mL)	424 (105)	681 (285)	864 (443)	779 (381)
2 mg E_2/180 µg NGM Group, N = 11				
C_{max} (pg/mL)	39.2 (15.7)	73.5 (39.2)	81.0 (27.3)	85.9 (47.7)
T_{max} (h)	9.0 (2.9)	7.4 (3.7)	6.2 (2.3)	5.5 (1.4)
$AUC_{0\text{-}24h}$ (pg·h/mL)	693 (273)	1391 (877)	1513 (573)	1492 (687)
Baseline Corrected Data				
1 mg E_2/30 µg NGM Group, N = 11				
C_{max} (pg/mL)	26.1 (14.0)	42.0 (20.5)	50.1 (20.4)	45.4 (20.8)
T_{max} (h)	7.0 (3.4)	5.2 (2.6)	5.4 (3.1)	5.6 (3.0)
$AUC_{0\text{-}24h}$ (pg·h/mL)	378 (135)	662 (273)	871 (437)	737 (425)
$AUC_{0\text{-}\infty}$ (pg·h/mL)	-	-	-	1258 (918)
$t_{½}$ (h)	-	-	-	15.0 (2.3)
1 mg E_2/90 µg NGM Group, N = 12				
C_{max} (pg/mL)	24.2 (8.3)	36.1 (13.8)	46.5 (22.1)	43.0 (19.9)
T_{max} (h)	7.4 (2.3)	7.4 (3.6)	7.3 (3.6)	6.8 (2.5)
$AUC_{0\text{-}24h}$ (pg·h/mL)	347 (97)	604 (309)	787 (468)	702 (395)
$AUC_{0\text{-}\infty}$ (pg·h/mL)	-	-	-	1179 (866)
$t_{½}$ (h)	-	-	-	15.8 (5.5)
2 mg E_2/180 µg NGM Group, N = 11				
C_{max} (pg/mL)	36.0 (14.8)	70.3 (38.4)	78.1 (27.4)	82.9 (46.8)
T_{max} (h)	9.0 (2.9)	7.4 (3.7)	6.2 (2.3)	5.5 (1.4)
$AUC_{0\text{-}24h}$ (pg·h/mL)	615 (246)	1314 (856)	1442 (573)	1421 (667)
$AUC_{0\text{-}\infty}$ (pg·h/mL)	-	-	-	2365 (1213)
$t_{½}$ (h)	-	-	-	14.2 (3.0)
(B) E_1				
Baseline Uncorrected Data				
1 mg E_2/30 µg NGM Group, N = 11				
C_{max} (pg/mL)	204 (74.2)	287 (110)	324 (128)	293 (129)
T_{max} (h)	6.4 (2.5)	5.8 (1.8)	5.3 (1.6)	5.2 (1.7)
$AUC_{0\text{-}24h}$ (pg·h/mL)	2853 (1029)	4279 (1855)	5125 (2453)	4675 (2570)
1 mg E_2/90 µg NGM Group, N = 12				
C_{max} (pg/mL)	210 (88.0)	285 (145)	341 (144)	325 (158)
T_{max} (h)	6.4 (2.7)	6.4 (1.9)	6.7 (1.3)	6.3 (2.2)
$AUC_{0\text{-}24h}$ (pg·h/mL)	2774 (885)	4153 (1991)	5429 (3079)	4957 (2645)
2 mg E_2/180 µg NGM Group, N = 11				
C_{max} (pg/mL)	289 (104)	509 (234)	560 (201)	554 (194)
T_{max} (h)	7.2 (2.0)	6.2 (1.3)	7.3 (1.8)	6.4 (1.2)
$AUC_{0\text{-}24h}$ (pg·h/mL)	4342 (1615)	8063 (4424)	8762 (3624)	8566 (3266)

(Continued)

Table 13: Mean (±SD) (A) E_2, (B) E_1, (C) E_1S, (D) 17d-NGM, and (E) NG Pharmacokinetic Parameters in Healthy Postmenopausal Women Receiving the Three-Day Cyclophasic Regimen of E_2-E_2/NGM for 90 Days (Protocol ESTNRG-PHI-001) (Continued)

Parameter	Day 1	Day 4	Day 87	Day 90
(B) E_1 (continued)				
Baseline Corrected Data				
1 mg E_2/30 µg NGM Group, N = 11				
C_{max} (pg/mL)	187 (73.0)	269 (107)	306 (125)	275 (127)
T_{max} (h)	6.4 (2.5)	5.8 (1.8)	5.3 (1.6)	5.2 (1.7)
AUC_{0-24h} (pg·h/mL)	2439 (978)	3865 (1772)	4694 (2382)	4244 (2501)
$AUC_{0-\infty}$ (pg·h/mL)	-	-	-	6788 (4900)
$t_{½}$ (h)	-	-	-	13.0 (3.5)
1 mg E_2/90 µg NGM Group, N = 12				
C_{max} (pg/mL)	196 (89.9)	271 (147)	327 (146)	311 (160)
T_{max} (h)	6.4 (2.7)	6.4 (1.9)	6.7 (1.3)	6.3 (2.2)
AUC_{0-24h} (pg·h/mL)	2443 (931)	3821 (2036)	5098 (3130)	4625 (2676)
$AUC_{0-\infty}$ (pg·h/mL)	-	-	-	7292 (5417)
$t_{½}$ (h)	-	-	-	15.1 (5.1)
2 mg E_2/180 µg NGM Group, N = 11				
C_{max} (pg/mL)	272 (99.9)	491 (230)	544 (201)	538 (194)
T_{max} (h)	7.2 (2.0)	6.2 (1.3)	7.3 (1.8)	6.4 (1.2)
AUC_{0-24h} (pg·h/mL)	3921 (1514)	7643 (4346)	8367 (3642)	8170 (3269)
$AUC_{0-\infty}$ (pg·h/mL)	-	-	-	12654 (6127)
$t_{½}$ (h)	-	-	-	13.5 (3.8)
(C) E_1S				
Baseline Uncorrected Data				
1 mg E_2/30 µg NGM Group, N = 11				
C_{max} (ng/mL)	10.7 (5.06)	14.3 (11.6)	12.5 (9.19)	13.0 (8.64)
T_{max} (h)	4.5 (2.4)	5.3 (3.8)	3.5 (0.9)	3.9 (1.9)
AUC_{0-24h} (ng·h/mL)	128 (78.0)	193 (165)	161 (128)	164 (137)
1 mg E_2/90 µg NGM Group, N = 12				
C_{max} (ng/mL)	11.1 (6.66)	13.9 (9.20)	14.9 (11.1)	14.5 (8.7)
T_{max} (h)	5.3 (2.7)	4.3 (1.7)	5.9 (4.0)	5.3 (2.3)
AUC_{0-24h} (ng·h/mL)	135 (82.4)	180 (131)	198 (159)	198 (141)
2 mg E_2/180 µg NGM Group, N = 11				
C_{max} (ng/mL)	14.8 (10.3)	19.7 (17.0)	13.7 (5.2)	13.8 (5.93)
T_{max} (h)	5.9 (2.6)	5.2 (2.3)	6.8 (3.8)	4.9 (2.6)
AUC_{0-24h} (ng·h/mL)	168 (122)	278 (295)	190 (90.4)	186 (81.6)
Baseline Corrected Data				
1 mg E_2/30 µg NGM Group, N = 11				
C_{max} (ng/mL)	10.2 (4.97)	13.8 (11.5)	11.9 (9.12)	12.5 (8.55)
T_{max} (h)	4.5 (2.4)	5.3 (3.8)	3.5 (0.9)	3.9 (1.9)
AUC_{0-24h} (ng·h/mL)	115 (75.4)	181 (162)	148 (125)	151 (134)
1 mg E_2/90 µg NGM Group, N = 12				
C_{max} (ng/mL)	10.7 (6.62)	13.5 (9.18)	14.5 (11.1)	14.1 (8.68)
T_{max} (h)	5.3 (2.7)	4.3 (1.7)	5.9 (4.0)	5.3 (2.3)
AUC_{0-24h} (ng·h/mL)	125 (82)	170 (131)	188 (159)	188 (141)
2 mg E_2/180 µg NGM Group, N = 11				
C_{max} (ng/mL)	14.3 (10.1)	19.2 (16.8)	13.3 (5.27)	13.4 (6.00)
T_{max} (h)	5.9 (2.6)	5.2 (2.3)	6.8 (3.8)	4.9 (2.6)
AUC_{0-24h} (ng·h/mL)	157 (117)	266 (290)	180 (91.6)	176 (82.5)

(Continued)

Table 13: Mean (±SD) (A) E_2, (B) E_1, (C) E_1S, (D) 17d-NGM, and (E) NG Pharmacokinetic Parameters in Healthy Postmenopausal Women Receiving the Three-Day Cyclophasic Regimen of E_2-E[redacted]NGM for 90 Days (Protocol ESTNRG-PHI-001) (Continued)

Parameter	Day 4	Day 90
(D) 17d-NGM		
1 mg E_2/30 µg NGM Group, N = 11		
C_{max} (pg/mL)	190 (129)	274 (53)
T_{max} (h)	1.4 (1.0)	1.3 (0.6)
AUC_{0-24h} (pg·h/mL)	482 (388)	1718 (967)
AUC_{0-6h} (pg·h/mL)	-	855 (328)
1 mg E_2/90 µg NGM Group, N = 12		
C_{max} (pg/mL)	515 (184)	643 (184)
T_{max} (h)	1.8 (0.6)	1.9 (0.8)
AUC_{0-24h} (pg·h/mL)	2146 (1319)	5322 (1286)
AUC_{0-4h} (pg·h/mL)	1320 (482)	1820 (444)
AUC_{0-6h} (pg·h/mL)	-	2420 (549)
2 mg E_2/180 µg NGM Group, N = 11		
C_{max} (pg/mL)	884 (248)	1095 (298)
T_{max} (h)	1.8 (0.4)	1.8 (0.9)
AUC_{0-24h} (pg·h/mL)	4632 (2366)	9945 (2114)
AUC_{0-6h} (pg·h/mL)	2869 (874)	4251 (1053)
(E) NG		
1 mg E_2/30 µg NGM Group, N = 11		
C_{max} (pg/mL)	56 (121)[a]	194 (54)[a]
T_{max} (h)	11.3 (11.4)[a]	16.4 (31.5)
AUC_{0-24h} (pg·h/mL)	227 (573)[a]	1665 (1179)[a]
1 mg E_2/90 µg NGM Group, N = 12		
C_{max} (pg/mL)	142 (93)	380 (206)
T_{max} (h)	2.3 (0.95)	2.7 (1.9)
AUC_{0-24h} (pg·h/mL)	893 (1171)	5415 (3363)
AUC_{0-3h} (pg·h/mL)	205 (211)	903 (529)
2 mg E_2/180 µg NGM Group, N = 11		
C_{max} (pg/mL)	225 (95)	717 (209)
T_{max} (h)	2.0 (0.63)	2.5 (2.1)
AUC_{0-24h} (pg·h/mL)	1708 (1402)	10398 (3089)
AUC_{0-4h} (pg·h/mL)	558 (278)	2261 (679)

[a] Sparse data, AUC calculated with missing values.

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Table 4: Accumulation of E_2 and its Metabolites in Postmenopausal Women Receiving Once-Daily Multiple Doses of E_2-E_2/NGM (Protocol ESTNRG-PHI-001)

Analyte	Baseline Correction	Parameter	Mean Day 1[a]	Mean Day 87[b]	Ratio[c] (%)
E_2	No	C_{max}	23.10	45.87	198.56
		C_{min}	11.87	23.18	195.35
	Yes	C_{max}	20.87	43.64	209.08
		C_{min}	9.64	20.96	217.38
E_1	No	C_{max}	170.63	306.46	179.61
		C_{min}	58.58	115.27	196.76
	Yes	C_{max}	158.61	294.44	185.64
		C_{min}	46.57	103.26	221.72
E_1S	No	C_{max}	8.55	10.30	120.52
		C_{min}	1.80	2.84	158.05
	Yes	C_{max}	8.21	9.96	121.37
		C_{min}	1.46	2.50	171.59

[a] Dose normalized mean. Single-dose, subjects received the first of the three daily E_2 tablet doses on Day 1.
[b] Dose normalized mean. Multiple-dose, subjects received the last of three daily E_2 tablet dose on Day 87.
[c] Day 87/Day 1

Table 5: Accumulation of NGM and its Metabolites in Postmenopausal Women Receiving Once-Daily Multiple Doses of E_2-E_2/NGM (Protocol ESTNRG-PHI-001)

Analyte	Parameter	Mean Day 4[a]	Mean Day 90[b]	Ratio[c] (%)
NGM	NGM was below assay detection limit			
17d-NGM	AUC_{0-4h}	1320.17	1820.00	137.86
	AUC_{0-6h}	2840.64	4251.45	149.67
	C_{max}	477.31	595.40	124.74
NG	AUC_{0-3h}	246.20	958.10	389.16
	AUC_{0-4h}	605.90	2330.00	384.55
	C_{max}	147.58	385.10	260.95

[a] Dose normalized mean. Single-dose, subjects received the first of the three daily E_2/NGM tablet dose on Day 4.
[b] Dose normalized mean. Multiple-dose, subjects received the last of three daily E_2/NGM tablet doses on Day 90.
[c] Day 90/Day 4

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Table 13: 95% Confidence Intervals for Ratio of the Means of NG From Day 90 to Day 4 - Evaluation of Accumulation Single Dose vs. Multiple Dose (Protocol ESTNRG-PHI-001)

Analyte	Parameter	Geometric Mean Day 4	Geometric Mean Day 90	Std. Error	df	Ratio of the Geometric Mean(%)	Lower Limit (%)	Upper Limit (%)
NG	AUC (0-3 h)	246.20	958.10	143.762	9	389.16	257.06	521.25
	AUC (0-4 h)	605.90	2330.00	214.951	9	384.55	304.30	464.81
	C_{max}	147.58	385.10	29.394	18	260.95	219.11	302.80

There were no statistically significant effects of NGM or any of its metabolites on the pharmacokinetics of E_2 or any of its metabolites during the respective cyclophasic dosing regimens (E_2 alone as compared to the E_2/NGM combination) at steady-state conditions during once-daily dosing. These results also provide evidence that there are no clinically significant differences in serum concentrations of E_2 or any of its metabolites as a result of the on and off cycling of norgestimate dosing regimens during administration of the once-daily cyclophasic hormone replacement therapy regimens.

The above comments related to the results of E_2, E_1, and E_1S apply to both baseline corrected data as well as data which was not baseline corrected. The conclusions are equally applicable to both baseline corrected and uncorrected results for E_2 and its metabolites and can be seen in Tables 14 to 16.

Table 14: 95% Confidence Intervals for Ratio of the Means of E_2 From Day 90 to Day 87 - Evaluation of the Effect of NGM on E_2 Pharmacokinetics at Steady State (Protocol ESTNRG-PHI-001)

Analyte	Baseline Correction	Parameter	Geometric Mean Day 87	Geometric Mean Day 90	Std. Error	df	Ratio of the Geometric Mean(%)	Lower Limit (%)	Upper Limit (%)
E_2	No	AUC (0-24 h)	827.57	768.18	46.698	96	92.82	81.62	104.02
		C_{max}	45.87	45.02	2.952	96	98.16	85.38	110.93
	Yes	AUC (0-24 h)	774.10	714.71	46.705	96	92.33	80.35	104.30
		C_{max}	43.64	42.80	2.952	96	98.06	84.64	111.49

Table 15: 95% Confidence Intervals for Ratio of the Means of E_1 From Day 90 to Day 87 - Evaluation of the Effect of NGM on E_1 Pharmacokinetics at Steady State (Protocol ESTNRG-PHI-001)

Analyte	Baseline Correction	Parameter	Geometric Mean Day 87	Geometric Mean Day 90	Std. Error	df	Ratio of the Geometric Mean (%)	Lower Limit (%)	Upper Limit (%)
E_1	No	AUC (0-24 h)	4832.39	4552.33	269.219	96	94.20	83.15	105.26
		C_{max}	306.46	293.20	15.540	96	95.67	85.61	105.74
	Yes	AUC (0-24 h)	4544.06	4264.00	269.226	96	93.84	82.08	105.60
		C_{max}	294.44	281.18	15.540	96	95.50	85.02	105.97

Table 16: 95% Confidence Intervals for Ratio of the Means of E_1S From Day 90 to Day 87 - Evaluation of the Effect of NGM on E_1S Pharmacokinetics at Steady State (Protocol ESTNRG-PHI-001)

Analyte	Baseline Correction	Parameter	Geometric Mean Day 87	Geometric Mean Day 90	Std. Error	df	Ratio of the Geometric Mean(%)	Lower Limit (%)	Upper Limit (%)
E_1S	No	AUC (0-24 h)	137.72	137.41	10.449	96	99.78	84.72	114.84
		C_{max}	10.30	10.34	0.747	96	100.42	86.02	114.81
	Yes	AUC (0-24 h)	129.57	129.26	10.448	96	99.77	83.76	115.77
		C_{max}	9.96	10.00	0.747	96	100.43	85.55	115.32

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P450 activity. Ki values are useful indicators in estimating significant impairment in drug metabolism, specifically for inhibitors of major cytochrome P450 isoenzymes in human liver microsomes. C_{max} values for the contraceptive steroids and metabolites and Ki values estimated for each respective cytochrome P450 enzyme are summarized in the following table:

Summary of C_{max} and Inhibition Constants (Ki) for the Inhibition of Human P450 Enzymes by Ethinyl Estradiol, Norgestimate, D(-)-Norgestrel, Norgestrel Acetate, and 17-Deacetylnorgestimate

Cytochrome P450 Enzyme	Ethinyl Estradiol		Norgestimate		D(-)-Norgestrel	
	C_{max} (μM)	Ki (μM)	C_{max} (μM)	Ki (μM)	C_{max} (μM)	Ki (μM)
CYP1A2	0.001	17.7	0.00027	>90	0.00352	>90
CYP2A6	0.001	15.8	0.00027	>90	0.00352	40.3
CYP2C9	0.001	5 - 15[a]	0.00027	60.9	0.00352	40.6
CYP2C19	0.001	14.8	0.00027	14.3	0.00352	42.8
CYP2D6	0.001	11.9	0.00027	3.52	0.00352	>90
CYP2E1	0.001	>90	0.00027	>90	0.00352	>90
CYP3A4/5	0.001	5.78	0.00027	20.2	0.00352	51.2
CYP4A9/11	0.001	>90	0.00027	>90	0.00352	>90

Cytochrome P450 Enzyme	Norgestrel Acetate		17-Deacetylnorgestimate	
	C_{max} (μM)	Ki (μM)	C_{max} (μM)	Ki (μM)
CYP1A2	0.00056	>90	0.00892	34.1
CYP2A6	0.00056	>90	0.00892	>90
CYP2C9	0.00056	5 - 15[a]	0.00892	11.1
CYP2C19	0.00056	>90	0.00892	5.90
CYP2D6	0.00056	82.9	0.00892	10.4
CYP2E1	0.00056	>90	0.00892	>90
CYP3A4/5	0.00056	16.1[b]	0.00892	11.3
CYP4A9/11	0.00056	>90	0.00892	>90

[a] Mixed inhibition
[b] Non-competitive inhibition

NOTEBOOK REFERENCE(S)

RWJPRI Project Notebook DM95334

Attachment 14

Table 6: Pharmacokinetic Parameter Estimates and Statistical Evaluation Results of (A) E_2, (B) E_1, (C) E_1S, (D) 17d-NGM, and (E) NG in 24 Postmenopausal Women Receiving a Single 2 mg/180 µg E_2/NGM Tablet: Fasted vs. Fed (RWJPRI Study ESTNRG-PHI-004)

Parameter	Fasted Mean (±SD)	Fed Mean (±SD)	Difference[a] (%)	90% CI Test Results[b]
(A) E_2				
Baseline Uncorrected				
C_{max} (pg/mL)	46.74 (16.8)	49.86 (11.9)	6.68	EQ
T_{max} (h)	8.54 (3.11)	8.87 (3.25)	3.86	—
$AUC_{0\text{-last}}$ pg·h/mL	1635.9 (591.4)	1763.7 (561.9)	7.81	EQ
$AUC_{0\text{-}\infty}$ pg·h/mL	1986.2 (820.8)	2115.9 (809.2)	6.93	EQ
$t_{½}$ (h)	24.9 (7.1)	24.2 (8.3)	-2.81	—
CL/F (mL/min)	20410.4 (10515.9)	18632.7 (9600.0)	-8.71	—
Baseline Corrected				
C_{max} (pg/mL)	43.66 (16.36)	46.96 (12.06)	7.56	EQ
T_{max} (h)	8.54 (3.11)	8.87 (3.25)	3.86	—
$AUC_{0\text{-last}}$ pg·h/mL	1413.7 (504.6)	1554.9 (487.4)	9.99	EQ
$AUC_{0\text{-}\infty}$ pg·h/mL	1590.9 (608.4)	1737.9 (615.0)	9.24	EQ
$t_{½}$ (h)	19.1 (5.89)	18.6 (5.44)	-2.31	—
CL/F (mL/min)	24544.9 (10615.3)	22280.1 (10345.0)	-9.2	—
(B) E_1				
Baseline Uncorrected				
C_{max} (pg/mL)	340.0 (103.2)	387.4 (89.0)	13.9	NEQ (108-126)
T_{max} (h)	8.15 (2.18)	5.50 (2.28)	-32.9	—
$AUC_{0\text{-last}}$ pg·h/mL	9456.9 (3372.4)	10238.3 (3077.0)	8.26	EQ
$AUC_{0\text{-}\infty}$ pg·h/mL	11000.4 (4082.3)	11924.7 (3937.0)	8.40	EQ
$t_{½}$ (h)	26.4 (7.82)	26.8 (10.3)	1.59	—
Baseline Corrected				
C_{max} (pg/mL)	325.46 (98.85)	370.08 (90.51)	13.7	NEQ (107-126)
T_{max} (h)	8.31 (2.17)	5.50 (2.28)	-33.8	—
$AUC_{0\text{-last}}$ pg·h/mL	8359.5 (3022.7)	8993.2 (2878.5)	7.58	EQ
$AUC_{0\text{-}\infty}$ pg·h/mL	8977.2 (3397.2)	9782.0 (3475.4)	8.96	EQ
$t_{½}$ (h)	16.6 (5.04)	18.6 (8.25)	12.1	—
(C) E_1S				
Baseline Uncorrected				
C_{max} (ng/mL)	18.0 (8.44)	22.1 (9.01)	22.6	NEQ (114-139)
T_{max} (h)	5.60 (2.41)	4.23 (1.68)	-24.5	—
$AUC_{0\text{-last}}$ ng·h/mL	393.9 (209.3)	412.7 (212.6)	4.77	EQ
$AUC_{0\text{-}\infty}$ ng·h/mL	466.5 (271.8)	488.3 (265.8)	4.67	EQ
$t_{½}$ (h)	31.4 (15.7)	31.2 (11.7)	-0.70	—
Baseline Corrected				
C_{max} (ng/mL)	17.41 (8.26)	21.51 (8.88)	23.5	NEQ (114-141)
T_{max} (h)	5.60 (2.41)	4.23 (1.68)	-24.5	—
$AUC_{0\text{-last}}$ ng·h/mL	350.8 (195.2)	371.2 (199.8)	5.82	EQ
$AUC_{0\text{-}\infty}$ ng·h/mL	383.8 (230.9)	410.1 (235.2)	6.85	EQ
$t_{½}$ (h)	21.8 (8.80)	22.3 (8.31)	2.43	—
(D) 17d-NGM				
C_{max} (pg/mL)	779.2 (237.2)	656.7 (143.7)	-15.7	NEQ (79-95)
T_{max} (h)	1.77 (0.55)	2.46 (0.94)	39.0	—
$AUC_{0\text{-last}}$ pg·h/mL	6782.7 (2192.1)	6733.8 (2071.3)	-0.72	EQ
$AUC_{0\text{-}\infty}$ pg·h/mL	9522.7 (3202.5)	9716.0 (3313.3)	2.03	EQ
$t_{½}$ (h)	30.4 (12.6)	32.1 (12.4)	5.59	—
(E) NG				
C_{max} (pg/mL)	257.7 (125.3)	236.5 (80.4)	-8.20	EQ
T_{max} (h)	2.31 (0.89)	2.63 (0.86)	13.9	—
$AUC_{0\text{-last}}$ pg·h/mL	5091.5 (3327.5)	4657.6 (2755.8)	-8.52	EQ

[a] [Fed-fasted]/fasted × 100%.

[b] EQ = equivalent; absence of a food effect; 90% CI for the ratio of means (based on log-transformed data) of fed and fasted treatments fall within 80-125%.
NEQ = not equivalent; food effect was observed; 90% CI for the ratio of means (based on log-transformed data) of fed and fasted treatments fall outside 80-125%.

Attachment 15

Table 7: Statistical Evaluation Results from Testing the Effects of Race, Body Weight, and Age on the Pharmacokinetics of E_2, NGM, and their Metabolites: the p Value

Analyte	Parameter	Studies	Race	Weight Group	Age Group
E_2[a]	$AUC_{0\text{-last}}$	All[b]	0.172	0.685	0.082
	C_{max}	All	0.420	0.179	0.755
E_1[a]	$AUC_{0\text{-last}}$	All	0.326	0.477	0.061
	C_{max}	All	0.901	0.054	0.581
E_1S[a]	$AUC_{0\text{-last}}$	All	0.267	0.620	0.248
	C_{max}	All	0.574	0.127	0.541
17d-NGM	$AUC_{0\text{-last}}$	004, 008	NT[c]	0.045[d]	0.488
	C_{max}	002, 004, 008	0.219	<0.001[d]	0.177
NG	$AUC_{0\text{-last}}$	004, 008	NT	0.167	0.600
	C_{max}	004, 008	NT	<0.001[d]	0.171

[a] Baseline corrected.
[b] All five studies (ESTNRG-PHI-002, ESTNRG-PHI-004, ESTNRG-PHI-006, ESTNRG-PHI-007, and ESTNRG-PHI-008)
[c] Not included in the model.
[d] Significant at the 5% level.

Table 8: Statistical Evaluation Results from Testing the Effects of Race, Body Weight, and Age on the Pharmacokinetics of E_2, NGM, and their Metabolites: the Ratios of the Means from Various Comparisons

Analyte[a]	Parameter	Characteristic	Reference	Comparison[b]	Geometric Mean of Reference	Geometric Mean of Test	Ratio[c] (%)
E_2[d]	$AUC_{0\text{-last}}$	Race	White	Hispanic vs. White	1131.15	1261.74	112
		Weight group	60-80 kg	<60 kg vs. 60-80 kg	1237.11	1139.54	92
				>80 kg vs. 60-80 kg	1237.11	1209.48	98
		Age group	51-55 yr	40-50 yr vs. 51-55 yr	1208.79	995.22	82
				56-60 yr vs. 51-55 yr	1208.79	1370.85	113
				61-70 yr vs. 51-55 yr	1208.79	1235.16	102
	C_{max}	Race	White	Hispanic vs. White	39.64	41.60	105
		Weight group	60-80 kg	<60 kg vs. 60-80 kg	41.58	43.80	105
				>80 kg vs. 60-80 kg	41.58	36.76	88
		Age group	51-55 yr	40-50 kg vs. 51-55 yr	39.75	38.91	98
				56-60 yr vs. 51-55 yr	39.75	41.39	104
				61-70 yr vs. 51-55 yr	39.75	42.47	107
E_1[d]	$AUC_{0\text{-last}}$	Race	White	Hispanic vs. White	6509.80	7073.88	109
		Weight group	60-80 kg	<60 kg vs. 60-80 kg	7052.96	7170.22	102
				>80 kg vs. 60-80 kg	7052.96	6179.22	88

[a] E_2=17β-estradiol, E_1 = estrone, E_1S = estrone sulfate, 17d-NGM = 17-deacetylnorgestimate, NG = norgestrel
[b] Test vs. reference
[c] Test/reference

[d] Baseline corrected

Table 20: Statistical Evaluation Results from Testing the Effects of Race, Body Weight and Age on the Pharmacokinetics of E_2, NGM, and their Metabolites: The Ratios of the Means from Various Comparisons (Continued)

(Continued)

Analyte[a]	Parameter	Characteristic	Reference	Comparison[b]	Geometric Mean of Reference	Geometric Mean of Test	Ratio[c] (%)
E_1[d] (continued)		Age group	51-55 yr	40-50 yr vs. 51-55 yr	6923.90	5518.24	80
				56-60 yr vs. 51-55 yr	6923.90	7884.78	114
				61-70 yr vs. 51-55 yr	6923.90	7038.98	102
	C_{max}	Race	White	Hispanic vs. White	309.62	312.53	101
		Weight group	60-80 kg	<60 kg vs. 60-80 kg	314.70	357.69	114
				>80 kg vs. 60-80 kg	314.70	267.41	85
		Age group	51-55 yr	40-50 yr vs. 51-55 yr	305.87	292.52	96
				56-60 yr vs. 51-55 yr	305.87	338.73	111
				61-70 yr vs. 51-55 yr	305.87	308.94	101
E_1S	AUC_{0-last}	Race	White	Hispanic vs. White	220.46	249.07	113
		Weight group	60-80 kg	<60 kg vs. 60-80 kg	245.91	245.69	100
				>80 kg vs. 60-80 kg	245.91	212.97	87
		Age group	51-55 yr	40-50 yr vs. 51-55 yr	240.67	205.79	86
				56-60 yr vs. 51-55 yr	240.67	279.36	116
				61-70 yr vs. 51-55 yr	240.67	217.92	91
	C_{max}	Race	White	Hispanic vs. White	13.95	14.69	105
		Weight group	60-80 kg	<60 kg vs. 60-80 kg	14.54	16.48	113
				>80 kg vs. 60-80 kg	14.54	12.24	84
		Age group	51-55 yr	40-50 yr vs. 51-55 yr	14.59	13.26	91
				56-60 yr vs. 51-55 yr	14.59	15.89	109
				61-70 yr vs. 51-55 yr	14.59	13.66	94
17d-NGM	AUC_{0-last}	Weight group	60-80 kg	<60 kg vs. 60-80 kg	8231.99	8093.77	98
				>80 kg vs. 60-80 kg	8231.99	5800.63	70
		Age group	51-55 yr	40-50 yr vs. 51-55 yr	7330.43	6194.33	85
				56-60 yr vs. 51-55 yr	7330.43	8071.64	110
				61-70 yr vs. 51-55 yr	7330.43	7681.07	105

[a] E_2=17β-estradiol, E_1 = estrone, E_1S = estrone sulfate, 17d-NGM = 17-deacetylnorgestimate, NG = norgestrel

[b] Test vs. reference

[c] Test/reference

[d] Baseline corrected

(Continued)

Table 20: Statistical Evaluation Results from Testing the Effects of Race, Body Weight and Age on the Pharmacokinetics of E_2, NGM, and their Metabolites: The Ratios of the Means from Various Comparisons (Continued)

Analyte[a]	Parameter	Characteristic	Reference	Comparison[b]	Geometric Mean of Reference	Geometric Mean of Test	Ratio[c] (%)
17d-NGM (continued)	C_{max}	Race	White	Hispanic vs. White	820.57	902.90	110
		Weight group	60-80 kg	<60 kg vs. 60-80 kg	964.61	1118.30	116
				>80 kg vs. 60-80 kg	964.61	591.19	61
		Age group	51-55 yr	40-50 yr vs. 51-55 yr	897.11	745.89	83
				56-60 yr vs. 51-55 yr	897.11	853.60	95
				61-70 yr vs. 51-55 yr	897.11	961.04	107
NG	$AUC_{0\text{-last}}$	Weight group	60-80 kg	<60 kg vs. 60-80 kg	4465.63	7056.94	158
				>80 kg vs. 60-80 kg	4465.63	4533.85	102
		Age group	51-55 yr	40-50 yr vs. 51-55 yr	5400.33	5071.86	94
				56-60 yr vs. 51-55 yr	5400.33	4366.99	81
				61-70 yr vs. 51-55 yr	5400.33	6244.80	116
	C_{max}	Weight group	60-80 kg	<60 kg vs. 60-80 kg	252.68	388.48	154
				>80 kg vs. 60-80 kg	252.68	175.68	70
		Age group	51-55 yr	40-50 yr vs. 51-55 yr	257.53	282.77	110
				56-60 yr vs. 51-55 yr	257.53	215.64	84
				61-70 yr vs. 51-55 yr	257.53	283.71	110

[a] E_2=17β-estradiol, E_1 = estrone, E_1S = estrone sulfate, 17d-NGM = 17-deacetylnorgestimate, NG = norgestrel

[b] Test vs. reference

[c] Test/reference

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