Attachment 16

Proposed Product Dissolution Method and Specification

Applicant:	The R.W. Johnson Pharmaceutical Research Institute
Drug:	E_2/NGM CYCLIC/BASIC HRT
NDA No.:	21-040
E_2 Tablet	
Dosage Form	Compressed tablets
Strength(s)	
Apparatus Type	
Media	
Volume	
Speed of Rotation	
Sampling Time(s)	
Brief Description of Dissolution Analytical Method	
Recommended Dissolution Specification	
E_2/NGM Tablet	
Dosage Form	Compressed tablets
Strength(s)	
Apparatus Type	
Media	
Volume	
Speed of Rotation	
Sampling Time(s)	
Brief Description of Dissolution Analytical Method	
Recommended Dissolution Specification	

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Attachment 18

ABBREVIATED HUMAN PHARMACOKINETICS REPORT SUMMARY

Title of Trial A Randomized, Parallel Group, Multiple-Dose Pharmacokinetic Study of Three Dosage Regimens of Cyclophasic Hormone Replacement in Postmenopausal Women (Protocol ESTNRG-PHI-001)
Investigator(s)/Center(s):
Trial Period: Clinical Conduct: June 1996 to September 1996 Bioanalytical Sample Analysis: June 1996 to November 1996 Data Analysis and Report Preparation: July 1996 to May 1997
Objectives: To determine the pharmacokinetics of 17β-estradiol (E_2) and its metabolites estrone (E_1) and estrone sulfate (E_1S), and of norgestimate (NGM) and its metabolites 17-deacetyl norgestimate (17d-NGM), norgestrel (NG), and norgestrel acetate (NGAc) during three months of multiple-dose administration of three different cyclophasic hormone replacement treatment (HRT) regimens.
Design: The study was a randomized, parallel-group design in 36 postmenopausal females. The majority of the subjects were between 51 and 60 years of age, and weighed 50 to 91 kg (mean 71.1 ± 11.21 kg). Subjects were equally divided into one of three dose groups in which they received a single daily dose of E_2 for three days followed by single daily doses of E_2/NGM for three days, with this cycle repeated for 90 days. The three dosing regimens were E_2 1 mg/E_2 1 mg + NGM 30 µg, E_2 1 mg/E_2 1 mg + NGM 90 µg, and E_2 2 mg/ E_2 2 mg + NGM 180 µg. Pharmacokinetic profile blood sampling was conducted for 24 hours after E_2 on Day 1, after E_2/NGM on Day 4, after E_2 on Day 87, and for 168 hours after E_2/NGM on Day 90. Sex hormone binding globulin (SHBG) determinations were done prior to the first dose, and approximately weekly throughout the study.
Subjects: -36 Healthy, adult, female volunteers Number of subjects: - enrolled = 36 - completed = 34 - evaluated = 36
Criteria for inclusion (trial population): Healthy postmenopausal women aged 42 to 65 years of age were enrolled. Serum estradiol concentrations ≤20 pg/mL and serum FSH concentrations ≥40 mIU/mL were required for subjects who had been postmenopausal for ≥12 months and who had previously received hormone replacement therapy. FSH concentrations ≥30 mIU/mL were required for subjects who had been postmenopausal for ≥12 months and had not received hormone replacement therapy. Subjects must not have experienced menses without exogenous hormone replacement therapy for at least 12 months prior to the start of the study, have discontinued injectable sex hormone use 180 days prior to dosing, have no history of implantable steroid use, have discontinued all hormone replacement therapy at least 30 days prior to dosing, have no contraindications to steroid hormone use, and have not used tobacco within six months of dosing.
Test product, dose and mode of administration, batch and formulation Nos.: 17β-estradiol, 1 mg tablet, Batch R6135, FD#01551-000-F-21; 17β-estradiol, 2 mg tablet, Batch R6138, FD#01551-000-K-21; 17β-estradiol 1 mg with norgestimate 30 µg tablet, Batch R6262, FD#01551-000-C-21; 17β-estradiol 1 mg with norgestimate 90 µg tablet, Batch R6133, FD#01551-000-D-21; 17β-estradiol 2 mg with norgestimate 180 µg tablet, Batch R6137, FD#01551-000-J-21.
Reference therapy, dose and mode of administration, batch and formulation Nos.: None
Duration of treatment: Once daily doses of E_2 only for 3 days, followed by once daily doses of E_2/NGM for 3 days with this cycle repeated for 90 days.
Analytical method(s)/Analytical Center(s)

NGM

Statistical methods:

1. Pharmacokinetics

Descriptive statistics for pharmacokinetic parameters from single and multiple dose administration were calculated. C_{max} and AUC from dose-normalized data were compared to evaluate proportionality across dosage regimens. The accumulation of E_2 and its metabolites from baseline corrected and noncorrected data were evaluated by constructing 95% confidence intervals for the ratio of the means of C_{max} and C_{min} from Day 87 to Day 1. Accumulation of 17d-NGM and NG was evaluated separately for each dose group by constructing 95% confidence intervals for the ratio of the means of partial AUCs from Day 90 to Day 4. The effect of NGM on the pharmacokinetics of E_2, E_1, and E_1S was evaluated by comparing C_{max} and AUC during E_2 only administration (Day 87) with those parameters from E_2/NGM combination administration (Day 90). For these analyses, a repeated measures model was fit to the dose-normalized parameters of interest with dose, day, and dose by day interaction as factors.

2. Safety

Summary statistics were calculated for demographic data and adverse events.

Results:

Pharmacokinetics:

The pharmacokinetics and accumulation of E_2 and its metabolites and of the metabolites of NGM, and the effect of NGM on the pharmacokinetics of E_2 and its metabolites were successfully determined from this cyclophasic hormone replacement study of 90 days of consecutive once-daily dosing in three dose regimen groups. Because of the very low doses of NGM, concentrations of NGM and NGAc were below the lower limits of analytical quantitation, even at steady-state conditions following multiple dosing. Thus, no data were obtained for these analytes. The analytes E_2, E_1, E_1S, 17d-NGM, and NG were quantifiable and their pharmacokinetics are described and compared from the first dose and again during the steady-state condition following multiple dosing.

Mean (SD) pharmacokinetic parameters for E_2, E_1, E_1S (baseline uncorrected and corrected), and for 17d-NGM and NG are presented in Tables 1 to 8.

Table 1: 17β-Estradiol Serum Pharmacokinetic Parameters - (Baseline Uncorrected)
(Protocol ESTNRG-PHI-001)

Parameter	Day 1	Day 4	Day 87	Day 90
1 mg E_2/30 µg NGM Group				
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 (0-24 h) (pg•h/mL)	438 (149)	723 (298)	937 (467)	803 (449)
1 mg E_2/90 µg NGM Group				
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 (0-24 h) (pg•h/mL)	424 (105)	681 (285)	864 (443)	779 (381)
2 mg E_2/180 µg NGM Group				
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 (0-24 h) (pg•h/mL)	693 (273)	1391 (877)	1513 (573)	1492 (687)

Table 2: 17β-Estradiol Serum Pharmacokinetic Parameters - (Baseline Corrected)
(Protocol ESTNRG-PHI-001)

Parameter	Day 1	Day 4	Day 87	Day 90
1 mg E_2/30 µg NGM Group				
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 (0-24 h) (pg•h/mL)	378 (135)	662 (273)	871 (437)	737 (425)
AUC (0-∞) (pg•h/mL)	-	-	-	1258 (918)
$t_{½}$ (h)	-	-	-	15.0 (2.3)
k_e (h^{-1})	-	-	-	0.0472 (0.0072)
CL/F (mL/min)				34968 (29634)
1 mg E_2/90 µg NGM Group				
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 (0-24 h) (pg•h/mL)	347 (97)	604 (309)	787 (468)	702 (395)
AUC (0-∞) (pg•h/mL)	-	-	-	1179 (866)
$t_{½}$ (h)	-	-	-	15.8 (5.5)
k_e (h^{-1})	-	-	-	0.0510 (0.0243)
CL/F (mL/min)	-	-	-	30329 (14675)
2 mg E_2/180 µg NGM Group				
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 (0-24h) (pg•h/mL)	615 (246)	1314 (856)	1442 (573)	1421 (667)
AUC (0-∞) (pg•h/mL)	-	-	-	2365 (1213)
$t_{½}$ (h)	-	-	-	14.2 (3.0)
k_e (h^{-1})	-	-	-	0.0512 (0.0127)
CL/F (mL/min)	-	-	-	29514 (16707)

Table 3: Estrone Serum Pharmacokinetic Parameters - (Baseline Uncorrected)
(Protocol ESTNRG-PHI-001)

Parameter	Day 1	Day 4	Day 87	Day 90
1 mg E_2/30 µg NGM Group				
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 (0-24 h) (pg•h/mL)	2853 (1029)	4279 (1855)	5125 (2453)	4675 (2570)
1 mg E_2/90 µg NGM Group				
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 (0-24 h) (pg•h/mL)	2774 (885)	4153 (1991)	5429 (3079)	4957 (2645)
2 mg E_2/180 µg NGM Group				
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 (0-24 h) (pg•h/mL)	4342 (1615)	8063 (4424)	8762 (3624)	8566 (3266)

ABBREVIATED HUMAN PHARMACOKINETICS REPORT SUMMARY

Table 4: Estrone Serum Pharmacokinetic Parameters - (Baseline Corrected)
(Protocol ESTNRG-PHI-001)

Parameter	Day 1	Day 4	Day 87	Day 90
1 mg E_2/30 µg NGM Group				
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 (0-24 h) (pg•h/mL)	2439 (978)	3865 (1772)	4694 (2382)	4244 (2501)
AUC (0-∞) (pg•h/mL)	-	-	-	6788 (4900)
$t_{½}$ (h)	-	-	-	13.0 (3.5)
k_e (h^{-1})	-	-	-	0.0580 (0.0204)
1 mg E_2/90 µg NGM Group				
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 (0-24 h) (pg•h/mL)	2443 (931)	3821 (2036)	5098 (3130)	4625 (2676)
AUC (0-∞) (pg•h/mL)	-	-	-	7292 (5417)
$t_{½}$ (h)	-	-	-	15.1 (5.1)
k_e (h^{-1})	-	-	-	0.0524 (0.0227)
2 mg E_2/180 µg NGM Group				
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 (0-24 h) (pg•h/mL)	3921 (1514)	7643 (4346)	8367 (3642)	8170 (3269)
AUC (0-∞) (pg•h/mL)	-	-	-	12654 (6127)
$t_{½}$ (h)	-	-	-	13.5 (3.8)
k_e (h^{-1})	-	-	-	0.0558 (0.0184)

Table 5: Estrone Sulfate Serum Pharmacokinetic Parameters - (Baseline Uncorrected)
(Protocol ESTNRG-PHI-001)

Parameter	Day 1	Day 4	Day 87	Day 90
1 mg E_2/30 µg NGM Group				
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 (0-24 h) (ng•h/mL)	128 (78.0)	193 (165)	161 (128)	164 (137)
1 mg E_2/90 µg NGM Group				
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 (0-24 h) (ng•h/mL)	135 (82.4)	180 (131)	198 (159)	198 (141)
2 mg E_2/180 µg NGM Group				
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 (0-24 h) (ng•h/mL)	168 (122)	278 (295)	190 (90.4)	186 (81.6)

Table 6: Estrone Sulfate Serum Pharmacokinetic Parameters - (Baseline Corrected) (Protocol ESTNRG-PHI-001)

Parameter	Day 1	Day 4	Day 87	Day 90
1 mg E_2/30 µg NGM Group				
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 (0-24 h) (ng•h/mL)	115 (75.4)	181 (162)	148 (125)	151 (134)
1 mg E_2/90 µg NGM Group				
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 (0-24 h) (ng•h/mL)	125 (82)	170 (131)	188 (159)	188 (141)
2 mg E_2/180 µg NGM Group				
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 (0-24 h) (ng•h/mL)	157 (117)	266 (290)	180 (91.6)	176 (82.5)

Table 7: 17d-Norgestimate Serum Pharmacokinetic Parameters (Protocol ESTNRG-PHI-001)

Parameter	Day 4	Day 90
1 mg E_2/30 µg NGM Group		
C_{max} (pg/mL)	190 (129)	274 (53)
t_{max} (h)	1.4 (1.0)	1.3 (0.6)
AUC (0-24 h) (pg•h/mL)	482 (388)	1718 (967)
AUC (0-6 h) (pg•h/mL)	-	855 (328)
1 mg E_2/90 µg NGM Group		
C_{max} (pg/mL)	515 (184)	643 (184)
t_{max} (h)	1.8 (0.6)	1.9 (0.8)
AUC (0-24 h) (pg•h/mL)	2146 (1319)	5322 (1286)
AUC (0-4 h) (pg•h/mL)	1320 (482)	1820 (444)
AUC (0-6 h) (pg•h/mL)	-	2420 (549)
2 mg E_2/180 µg NGM Group		
C_{max} (pg/mL)	884 (248)	1095 (298)
t_{max} (h)	1.8 (0.4)	1.8 (0.9)
AUC (0-24 h) (pg•h/mL)	4632 (2366)	9945 (2114)
AUC (0-6 h) (pg•h/mL)	2869 (874)	4251 (1053)

Table 8: Norgestrel Serum Pharmacokinetic Parameters (Protocol ESTNRG-PHI-001)

Parameter	Day 4	Day 90
1 mg E_2/30 µg NGM Group		
C_{max} (pg/mL)	56 (121)[a]	194 (54)[a]
t_{max} (h)	11.3 (11.4)[a]	16.4 (31.5)[a]
AUC (0-24 h) (pg•h/mL)	227 (573)[a]	1665 (1179)[a]
1 mg E_2/90 µg NGM Group		
C_{max} (pg/mL)	142 (93)	380 (206)
t_{max} (h)	2.3 (0.95)	2.7 (1.9)
AUC (0-24 h) (pg•h/mL)	893 (1171)	5415 (3363)
AUC (0-3 h) (pg•h/mL)	205 (211)	903 (529)
2 mg E_2/180 µg NGM Group		
C_{max} (pg/Ml)	225 (95)	717 (209)
t_{max} (h)	2.0 (0.63)	2.5 (2.1)
AUC (0-24 h) (pg•h/mL)	1708 (1402)	10398 (3089)
AUC (0-4 h) (pg•h/mL)	558 (278)	2261 (679)

[a] Sparse data, AUC calculated with missing values

Serum concentrations of E_2 were observed to accumulate from once-daily dosing with all three dosing regimens. The degrees of accumulation, expressed as the ratios of means of C_{max} as well as C_{min} from data obtained at steady state to those from the first dose, ranged from 1.95 to 2.17. These ratios were somewhat higher than would be predicted from the estimated mean terminal phase serum half-lives (accumulation based on a 15-hour half-life would be approximately 1.5). The greater degree of accumulation may be related to the increase in SHBG concentrations resulting from administration of E_2. The SHBG concentrations rose from the start of E_2 dosing, reaching apparent plateaus by approximately the 35th consecutive day of once-daily E_2 or E_2/NGM administration. Accumulation was also observed for E_1, E_1S, 17d-NGM, and NG by factors ranging from 1.80 to 2.22, 1.21 to 1.72, 1.38 to 1.50, and 2.61 to 3.89, respectively for these analytes. The higher degree of accumulation for NG may also be related to its binding to SHBG. Data showing the accumulation of E_2, E_1, E_1S, 17d-NGM, and NG can be seen in Tables 9 to 13.

Table 9: 95% Confidence Intervals for Ratio of the Means of E_2 From Day 87 to Day 1 - Evaluation of Accumulation, Single Dose vs. Multiple Dose (Protocol ESTNRG-PHI-001)

Analyte	Baseline Correction	Parameter	Geometric Mean Day 1	Geometric Mean Day 87	Std. Error	df	Ratio of the Geometric Mean (%)	Lower Limit (%)	Upper Limit (%)
E_2	No	C_{max}	23.10	45.87	2.952	96	198.56	173.19	223.93
		C_{min}	11.87	23.18	1.448	96	195.35	171.14	219.56
	Yes	C_{max}	20.87	43.64	2.952	96	209.08	181.00	237.15
		C_{min}	9.64	20.96	1.448	96	217.38	187.57	247.19

Table 10: 95% Confidence Intervals for Ratio of the Means of E_1 From Day 87 to Day 1 - Evaluation of Accumulation Single Dose vs. Multiple Dose (Protocol ESTNRG-PHI-001)

Analyte	Baseline Correction	Parameter	Geometric Mean Day 1	Geometric Mean Day 87	Std. Error	df	Ratio of the Geometric Mean (%)	Lower Limit (%)	Upper Limit (%)
E_1	No	C_{max}	170.63	306.46	15.540	96	179.61	161.53	197.69
		C_{min}	58.58	115.27	8.187	96	196.76	169.02	224.50
	Yes	C_{max}	158.61	294.44	15.540	96	185.64	166.19	205.09
		C_{min}	46.57	103.26	8.187	96	221.72	186.83	256.62

Table 11: 95% Confidence Intervals for Ratio of the Means of E_1S From Day 87 to Day 1 - Evaluation of Accumulation Single Dose vs. Multiple Dose (Protocol ESTNRG-PHI-001)

Analyte	Baseline Correction	Parameter	Geometric Mean Day 1	Geometric Mean Day 87	Std. Error	df	Ratio of the Geometric Mean (%)	Lower Limit (%)	Upper Limit (%)
E_1S	No	C_{max}	8.55	10.30	0.747	96	120.52	103.17	137.87
		C_{min}	1.80	2.84	0.300	96	158.05	124.87	191.23
	Yes	C_{max}	8.21	9.96	0.747	96	121.37	103.30	139.44
		C_{min}	1.46	2.50	0.300	96	171.59	130.68	212.51

Table 12: 95% Confidence Intervals for Ratio of the Means of 17d-NGM 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 (%)
17d-NGM	AUC (0-4 h)	1320.17	1820.00	112.572	11	137.86	119.09	156.63
	AUC (0-6 h)	2840.64	4251.45	275.247	10	149.67	128.08	171.26
	C_{max}	477.31	595.40	31.460	21	124.74	111.03	138.45

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

Dose proportionality for C_{max} and AUC was shown at steady state for all analytes (across the twofold range of E_2 doses, and across the sixfold range of NGM doses) except for E_1S and for NG from the 30 µg NGM dose, due to low serum concentrations. Stastical comparisons for dose proportionality are presented in Tables 17 to 21

Table 17: Results of Statistical Comparisons for Dose Proportionality of E_2 1 mg Dose vs. 2 mg Dose on Day 87 (Protocol ESTNRG-PHI-001)

Analyte	Baseline Corrected	Dose-Normalized Parameter	F-value[a]	df[b]	p-value
E_2	No	AUC (0-24h)	1.51	1,96	0.222
		C_{max}	2.81	1,96	0.097
	Yes	AUC (0-24h)	0.86	1,96	0.356
		C_{max}	2.20	1,96	0.142

[a] F-value denotes the value of the test statistics.
[b] df denotes the degrees of freedom.

Table 18: Results of Statistical Comparisons for Dose Proportionality of E_1 1 mg Dose vs. 2 mg Dose on Day 87 (Protocol ESTNRG-PHI-001)

Analyte	Baseline Corrected	Dose-Normalized Parameter	F-value[a]	df[b]	p-value
E_1	No	AUC (0-24 h)	1.57	1,96	0.214
		C_{max}	1.62	1,96	0.206
	Yes	AUC (0-24 h)	1.01	1,96	0.318
		C_{max}	1.19	1,96	0.278

[a] F-value denotes the value of the test statistics.
[b] df denotes the degrees of freedom.

Table 19: Results of Statistical Comparisons for Dose Proportionality of E_1S 1 mg Dose vs. 2 mg Dose on Day 87 (Protocol ESTNRG-PHI-001)

Analyte	Baseline Corrected	Dose-Normalized Parameter	F-value[a]	df[b]	p-value
E_1S	No	AUC (0-24 h)	4.54	1,96	0.036*
		C_{max}	6.24	1,96	0.014*
	Yes	AUC (0-24 h)	3.96	1,96	0.049*
		C_{max}	5.82	1,96	0.018*

[a] F-value denotes the value of the test statistics.
[b] df denotes the degrees of freedom.
* Statistically significantly different, $p < 0.05$.

Table 20: Results of Statistical Comparisons for Dose Proportionality of 17d-NGM at Steady State - Day 90 (Protocol ESTNRG-PHI-001)

Analyte	Dose-Normalized Parameter	F-value[a]	df[b]	p-value
17d-NGM	AUC (0-6 h)[c]	1.09	2,31	0.348
	AUC (0-24h)[d]	0.50	1,21	0.487
	C_{max}[d]	1.93	1,21	0.179

[a] F-value denotes the value of the test statistics.
[b] df denotes the degrees of freedom.
[c] 30 µg vs. 90 µg vs. 180 µg from Day 90.
[d] 90 µg vs. 180 µg from Day 90.

Table 21: Results of Statistical Comparisons for Dose Proportionality of NG at Steady State - Day 90 (Protocol ESTNRG-PHI-001)

Analyte	Dose-Normalized Parameter	F-value[a]	df[b]	p-value
NG	AUC (0-24h)[c]	0.04	1,21	0.848
	C_{max}[c]	0.33	1,18	0.573

[a] F-value denotes the value of the test statistics.

[b] df denotes the degrees of freedom.

[c] 90 µg vs. 180 µg from Day 90.

Adverse experiences and safety monitoring

Treatment with 17β-estradiol/norgestimate, administered as one of three treatment regimens: E_2 1 mg/E_2 1 mg + NGM 30 µg tablets, E_2 1 mg/E_2 1 mg + NGM 90 µg tablets, and E_2 2 mg/E_2 2 mg + NGM 180 µg tablets, was well tolerated by female postmenopausal subjects. Thirty-four (94%) of the 36 subjects enrolled in this study reported at least one treatment-emergent adverse event. Adverse events were evenly distributed among the three treatment groups (Table I).

The most common adverse events following treatment in all three groups were headache, insomnia, fatigue, vaginal hemorrhage, and breast pain. The majority of adverse events were mild or moderate in severity with most considered by the investigator to be unrelated to treatment. No subject died or had a serious adverse event during this three-month study and only one subject in the E_2 2 mg/E_2 2 mg + NGM 180 µg group discontinued prematurely for an adverse event (depression).

There were no clinically meaningful prestudy to poststudy changes in physical and gynecological examination findings or vital sign measurements. Clinical laboratory abnormalities were unremarkable

Table 22: Number and Percentage of Most Frequently Reported Adverse Events

Adverse Event	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)
Headache	5 (42%)	4 (33%)	6 (50%)	15 (42%)
Insomnia	3 (25%)	5 (42%)	3 (25%)	11 (31%)
Fatigue	2 (17%)	3 (25%)	4 (33%)	9 (25%)
Vaginal Hemorrhage	2 (17%)	4 (33%)	3 (25%)	9 (25%)
Breast Pain Female	1 (8%)	2 (17%)	5 (42%)	8 (22%)
Number of Subjects with at Least One AE	12 (100%)	10 (83%)	12 (100%)	34 (94%)

Conclusions: . At steady-state conditions during multiple dose administration of the cyclophasic hormone replacement therapy regimen, dose proportionality for C_{max} and AUC was shown for E_2 and its metabolite E_1 across the twofold dose range of 1 to 2 mg of E_2. For E_1S, dose proportionality was not shown. Similarly, dose proportionality for C_{max} and AUC was shown across the sixfold dose range of NGM from 30 to 180 µg for the metabolites 17d-NGM and across the twofold dose range from 90 to 180 µg for NG. There were no statistically significant effects of NGM or its metabolites on the pharmacokinetics of E_2 or any of its metabolites during steady-state conditions of the cyclophasic regimens. Thus, the concentrations of E_2 and its metabolites will remain equivalent during the cycling on and off of NGM in the regimens. Accumulation of various analytes during multiple dose therapy ranged from approximately 1.21 to 3.89. Accumulation to a slightly greater degree than predicted by the serum half-lives for some analytes may be due to the observed increases in SHBG, which occurred as a result of E_2 therapy.

The results of this study indicate that treatment with any of the of three cyclophasic HRT regimens was safe and well tolerated by healthy, postmenopausal women.

ABBREVIATED HUMAN PHARMACOKINETICS REPORT SUMMARY

Title of Trial: Food Effect Study of RWJPRI 17β-Estradiol/Norgestimate 2 mg/180 µg Tablet Formulation in Healthy Postmenopausal Female Subjects (Protocol ESTNEG-PHI-004)

Investigator(s)/Center(s):

Trial Period:. Clinical Conduct Dates: June 1996 to August 1996

Analytical Conduct Dates: August 1996 to January 1997

Data Analysis and Report Preparation: October 1997 to December 1997

Objectives:. To determine the effect of a high-fat meal on the pharmacokinetics of 17β-estradiol (E_2) and its metabolites, estrone (E_1) and estrone sulfate (E_1S), and of norgestimate (NGM) and its metabolites, 17-deacetyl norgestimate (17d-NGM) and norgestrel (NG), following single oral dose administration of the formulation tablet in the fed and fasted states.

Design:. This was an open-label, randomized, complete, two period crossover design study in 24 postmenopausal female subjects for a total period of approximately 25 days. Equal numbers of subjects were randomly assigned to two treatment sequences indicating the order of fed and fasting treatments. Blood samples were drawn at -48, -24, and 0 hours prior to dose administration and at 14 time points after dosing for determination of E_2. E_1, E_1S, 17-NGM and NG.

Subjects:
- 24 Healthy, postmenopausal, adult, female volunteers

Number of subjects:
- enrolled = 24
- completed = 24
- evaluated = 24

Criteria for inclusion (trial population):. Healthy postmenopausal women aged 40-65 who had not experienced menses without exogenous hormone replacement therapy for at least 12 months prior to the start of the study were enrolled. Subjects must have had serum estradiol concentrations ≤20pg/mL and serum follicle stimulating hormone (FSH) concentrations ≥40 mIU/mL for subjects who had been postmenopausal for ≥12 months and who had previously received hormone replacement therapy, or serum FSH concentrations ≥30 mIU/mL for subjects who had been postmenopausal for ≥12 months and had not received hormone replacement therapy previously, must have discontinued injectable sex hormone use 6 months (180 days) prior to dosing, and have had no exposure to implantable sex steroids, must have discontinued all hormone replacement therapy at least 30 days prior to dosing, and must have had no contraindications to steroid hormone use and not used tobacco in any form within 6 months of dosing.

Test product, dose and mode of administration, batch and formulation Nos.: RWJPRI process tablet, one 2 mg 17β-estradiol/180 µg norgestimate, oral, Batch R6137, FD# 01551-000-J-21.

Reference therapy, dose and mode of administration, batch and formulation Nos.: The reference is to the fasted treatment.

Duration of treatment: Single dose in the fed and fasted states over 25 days.

Analytical method(s)/Analytical Center(s):

Statistical methods:

1. Pharmacokinetics

The pharmacokinetic parameters peak concentration (C_{max}), time to peak concentration (t_{max}) and area under the concentration vs. time curve to the time of last concentration above assay quantification limit AUC (0-*) and to infinity AUC (0-∞) for E_2, E_1, E_1S, 17d-NGM and NG were estimated from serum data and were tabulated to evaluate the food effect on the pharmacokinetics of estradiol and metabolites and on norgestimate and metabolites. Oral clearance, elimination rate constant, and serum elimination half-life were estimated where appropriate and summarized; safety was based on adverse events, vital sign measurements, physical and gynecological examinations, and laboratory (hematology, chemistry, urinalysis) results. Pharmacokinetic data analysis was performed at RWJPRI. The effect of a high-fat meal on the absorption and/or pharmacokinetics of E_2, E_1, E_1S, 17d-NGM, and NG were determined from this two-way complete crossover study in 24 postmenopausal female subjects. The effect of food on NGM was not evaluated as planned in the protocol because it had been determined after the completion of the study that NGM concentrations from a single 180 µg NGM dose were not detectable.

Analysis of variance models were fit to the data with one of the bioavailability parameters of interest (log-transformed) as the dependent variable and the effects due to treatment sequence group, subjects nested within the sequence groups, treatment and period as predictors. The test for the treatment sequence group effect was carried out at the 10% level by using the mean square due to the subjects nested within sequence groups as the error term. The period effect was tested at the 5% level using the residual error term. The estimated least square means and intra-subject variability from the above model were used to construct 90% confidence intervals for the ratio of the mean bioavailability parameters from the high-fat fed condition to those from the fasted condition.

2. Safety

Safety was based on adverse events, vital sign measurements, physical and gynecological examinations, and laboratory (hematology, chemistry, urinalysis) results.

Results:

Pharmacokinetics:

The high-fat meal did not affect the rate or extent of absorption of the pharmacologically active estrogen species, E_2, as indicated by C_{max} and AUC data. The 90% confidence interval limits for the ratios of mean C_{max} and AUC (0-*) and AUC (0-∞) for the fed to fasted treatments were within 80 to 125% for both baseline uncorrected and baseline corrected data. For both E_1 and E_1S, which are pharmacologically less active metabolites of E_2, there were effects of food resulting in higher values for C_{max} (mean increased by 13.7 and 13.9% for E_1 baseline corrected and baseline uncorrected data, and mean increased by 23.5 and 22.6% for E_1S corrected and uncorrected data), and decreases in t_{max}. The upper limits for the 90% confidence intervals for the ratios of the means of C_{max} were above 125%. These results show that the rates of formation of the metabolites were increased in the fed condition as compared to the fasted condition. Because these metabolites are less pharmacologically active, there is no clinical significance to the transient elevations of C_{max}. The 90% confidence intervals for the ratios of means of AUC (0-*) and AUC (0-∞) fell within 80 and 125%, indicating that the high-fat meal did not affect the extent of metabolite formation.

For 17d-NGM, treatment with food slowed the formation of the metabolite as shown by reduced mean C_{max} values (decreased by 15.7% compared to the fasted treatment), and by increased mean t_{max} (increased by 39% compared to the fasted treatment). These differences in 17d-NGM concentrations were only observed for a short time period around t_{max} otherwise the mean serum concentration curves for the two treatments are superimposable. This small effect of food on C_{max} is considered not to be clinically significant. The extent of formation of 17d-NGM, as measured by AUC (0-*) and AUC (0-∞) was not affected by the high-fat meal. The 90% confidence interval for the ratio of the mean AUC's fell within 80 and 125%.

For NG the high-fat meal did not affect the rate or extent of formation as shown by C_{max} and AUC data and the 90% confidence intervals for the ratios of means for both parameters fell within 80 to 125%. The terminal phase of serum NG concentrations could not be accurately extrapolated in order to obtain AUC (0-∞)..

There were statistically significant treatment sequence effects observed for C_{max} for E_2 and E_1, for AUC (0-*) for NG, and there were statistically significant treatment group effects observed for C_{max} for 17d-NGM and NG. The reason for these effects is unknown. Clinical conduct was the same on both periods including the fasting period, the diet, the meals, and the times of medication administration. There was nothing observed during study conduct which was different between the periods. There were no analytical issues and there was no carryover in serum concentrations between treatment periods.

Mean pharmacokinetic parameters for E2, E1, and E1S (baseline uncorrected and corrected) and for 17d-NMG and NG are presented in Tables 1 to 8. The ninety percent confidence intervals are shown for the fed vs. fasted condition in Table 9.

Results:

Table 1: 17β-Estradiol - Mean (SD) Pharmacokinetic Data Summary For 24 Postmenopausal Female Subjects Receiving a Single Dose of 2 mg Estradiol/180 µg Norgestimate in the Fasted and Fed States (Baseline Uncorrected Data) (Protocol ESTNRG-PHI-004)

Parameter	TRT A Fasted Mean (±SD)	TRT B Fed Mean (±SD)	% Difference[b]	90% Confidence Interval Test Results
C_{max} (pg/mL)	46.74 (16.8)	49.86 (11.9)	6.68	EQ
C_{max} Ratio [a]	NA	1.12 (0.3)	NA	----
t_{max} (h)	8.54 (3.11)	8.87 (3.25)	3.86	----
AUC (0-*) pg.h/mL	1635.9 (591.4)	1763.7 (561.9)	7.81	EQ
AUC Ratio [a]	NA	1.11 (0.23)	NA	----
AUC (0-∞) pg.h/mL	1986.2 (820.8)	2115.9 (809.2)	6.93	EQ
AUC Ratio [a]	NA	1.10 (0.22)	NA	----
$t_{1/2}$ (h)	24.9 (7.1)	24.2 (8.3)	-2.81	----
k_e	0.03 (0.008)	0.03 (0.014)	<1.0	----
CL/F (mL/min)	20410.4 (10515.9)	18632.7 (9600.0)	-8.71	----

[a] With reference to fasted.
[b] With reference to Treatment A, [B-A]/A x 100%.
* AUC from time zero to the last measured time point.

Table 2: 17β-Estradiol - Mean (SD) Pharmacokinetic Data Summary For 24 Postmenopausal Female Subjects Receiving a Single Dose of 2 mg Estradiol/180 µg Norgestimate in the Fasted and Fed States(Baseline Corrected Data) (Protocol ESTNRG-PHI-004)

Parameter	TRT A Fasted Mean (±SD)	TRT B Fed Mean (±SD)	% Difference[b]	90% Confidence Interval Test Results
C_{max} (pg/mL)	43.66 (16.36)	46.96 (12.06)	7.56	EQ
C_{max} Ratio [a]	NA	1.13 (0.26)	NA	----
t_{max} (h)	8.54 (3.11)	8.87 (3.25)	3.86	----
AUC (0-*) pg.h/mL	1413.7 (504.6)	1554.9 (487.4)	9.99	EQ
AUC Ratio [a]	NA	1.13 (0.24)	NA	----
AUC (0-∞) pg.h/mL	1590.9 (608.4)	1737.9 (615.0)	9.24	EQ
AUC Ratio [a]	NA	1.12 (0.24)	NA	----
$t_{1/2}$ (h)	19.1 (5.89)	18.6 (5.44)	-2.31	----
k_e	0.04 (0.014)	0.04 (0.013)	<1.0	----
CL/F (mL/min)	24544.9 (10615.3)	22280.1 (10345.0)	-9.2	----

[a] With reference to fasted.
[b] With reference to Treatment A, [B-A]/A x 100%.
* AUC from time zero to the last measured time point.

Table 3: Estrone - Mean (SD) Pharmacokinetic Data Summary For 24 Postmenopausal Female Subjects Receiving a Single Dose of 2 mg Estradiol/180 µg Norgestimate in the Fasted and Fed States (Baseline Uncorrected Data) (Protocol ESTNRG-PHI-004)

Parameter	TRT A Fasted Mean (±SD)	TRT B Fed Mean (±SD)	% Difference[b]	90% Confidence Interval Test Results
C_{max} (pg/mL)	340.0 (103.2)	387.4 (89.0)	13.9	NEQ
C_{max} Ratio [a]	NA	1.20 (0.31)	NA	----
t_{max} (h)	8.15 (2.18)	5.50 (2.28)	-32.9	----
AUC (0-*) pg.h/mL	9456.9 (3372.4)	10238.3 (3077.0)	8.26	EQ
AUC Ratio [a]	NA	1.10 (0.14)	NA	----
AUC (0-∞) pg.h/mL	11000.4 (4082.3)	11924.7 (3937.0)	8.40	EQ
AUC Ratio [a]	NA	1.10 (0.12)	NA	----
$t_{1/2}$ (h)	26.4 (7.82)	26.8 (10.3)	1.59	----

[a] With reference to fasted.
[b] With reference to Treatment A, [B-A]/A x 100%.
* AUC from time zero to the last measured time point.

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Results:

Table 4: Estrone- Mean (SD) Pharmacokinetic Data Summary For 24 Postmenopausal Female Subjects Receiving a Single Dose of 2 mg Estradiol/180 µg Norgestimate in the Fasted and Fed States (Baseline Corrected Data) (Protocol ESTNRG-PHI-004)

Parameter	TRT A Fasted Mean (±SD)	TRT B Fed Mean (±SD)	% Difference[b]	90% Confidence Interval Test Results
C_{max} (pg/mL)	325.46 (98.85)	370.08 (90.51)	13.7	NEQ
C_{max} Ratio [a]	NA	1.19 (0.31)	NA	----
t_{max} (h)	8.31 (2.17)	5.50 (2.28)	-33.8	----
AUC (0-*) pg.h/mL	8359.5 (3022.7)	8993.2 (2878.5)	7.58	EQ
AUC Ratio [a]	NA	1.11 (0.23)	NA	----
AUC (0-∞) pg.h/mL	8977.2 (3397.2)	9782.0 (3475.4)	8.96	EQ
AUC Ratio [a]	NA	1.12 (0.26)	NA	----
$t_{1/2}$ (h)	16.6 (5.04)	18.6 (8.25)	12.1	----

[a] With reference to fasted.
[b] With reference to Treatment A, [B-A]/A x 100%.
* AUC from time zero to the last measured time point.

Table 5: Estrone Sulfate - Mean (SD) Pharmacokinetic Data Summary For 24 Postmenopausal Female Subjects Receiving a Single Dose of 2 mg Estradiol/180 µg Norgestimate in the Fasted and Fed States(Baseline Uncorrected Data) (Protocol ESTNRG-PHI-004)

Parameter	TRT A Fasted Mean (±SD)	TRT B Fed Mean (±SD)	% Difference[b]	90% Confidence Interval Test Results
C_{max} (ng/mL)	18.0 (8.44)	22.1 (9.01)	22.6	NEQ
C_{max} Ratio [a]	NA	1.31 (0.43)	NA	----
t_{max} (h)	5.60 (2.41)	4.23 (1.68)	-24.5	----
AUC (0-*) ng.h/mL	393.9 (209.3)	412.7 (212.6)	4.77	EQ
AUC Ratio [a]	NA	1.07 (0.14)	NA	----
AUC (0-∞) ng.h/mL	466.5 (271.8)	488.3 (265.8)	4.67	EQ
AUC Ratio [a]	NA	1.07 (0.14)	NA	----
$t_{1/2}$ (h)	31.4 (15.7)	31.2 (11.7)	-0.70	----

[a] With reference to fasted.
[b] With reference to Treatment A, [B-A]/A x 100%.
* AUC from time zero to the last measured time point.

Table 6: Estrone Sulfate - Mean (SD) Pharmacokinetic Data Summary For 24 Postmenopausal Female Subjects Receiving a Single Dose of 2 mg Estradiol/180 µg Norgestimate in the Fasted and Fed States (Baseline Corrected Data) (Protocol ESTNRG-PHI-004)

Parameter	TRT A Fasted Mean (±SD)	TRT B Fed Mean (±SD)	% Difference[b]	90% Confidence Interval Test Results
C_{max} (ng/mL)	17.41 (8.26)	21.51 (8.88)	23.5	NEQ
C_{max} Ratio [a]	NA	1.32 (0.44)	NA	----
t_{max} (h)	5.60 (2.41)	4.23 (1.68)	-24.5	----
AUC (0-*) ng.h/mL	350.8 (195.2)	371.2 (199.8)	5.82	EQ
AUC Ratio [a]	NA	1.09 (0.16)	NA	----
AUC (0-∞) ng.h/mL	383.8 (230.9)	410.1 (235.2)	6.85	EQ
AUC Ratio [a]	NA	1.10 (0.16)	NA	----
$t_{1/2}$ (h)	21.8 (8.80)	22.3 (8.31)	2.43	----

[a] With reference to fasted.
[b] With reference to Treatment A, [B-A]/A x 100%.
* AUC from time zero to the last measured time point.

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Table 7: 17d-Norgestimate Mean (SD) Pharmacokinetic Data Summary For 24 Postmenopausal Female Subjects Receiving a Single Dose of 2 mg Estradiol/180 µg Norgestimate in the Fasted and Fed States(Protocol ESTNRG-PHI-004)

Parameter	TRT A Fasted Mean (±SD)	TRT B Fed Mean (±SD)	% Difference[b]	90% Confidence Interval Test Results
C_{max} (pg/mL)	779.2 (237.2)	656.7 (143.7)	-15.7	NEQ
C_{max} Ratio [a]	NA	0.90 (0.28)	NA	---
t_{max} (h)	1.77 (0.55)	2.46 (0.94)	39.0	---
AUC (0-*) pg.h/mL	6782.7 (2192.1)	6733.8 (2071.3)	-0.72	EQ
AUC Ratio [a]	NA	1.02 (0.20)	NA	---
AUC (0-∞) pg.h/mL	9522.7 (3202.5)	9716.0 (3313.3)	2.03	EQ
AUC Ratio [a]	NA	1.07 (0.29)	NA	---
$t_{1/2}$ (h)	30.4 (12.6)	32.1 (12.4)	5.59	---

[a] With reference to fasted.
[b] With reference to Treatment A, [B-A]/A x 100%.
* AUC from time zero to the last measured time point.

Table 8: Norgestrel - Mean (SD) Pharmacokinetic Data Summary For 24 Postmenopausal Female Subjects Receiving a Single Dose of 2 mg Estradiol/180 µg Norgestimate in the Fasted and Fed States(Protocol ESTNRG-PHI-004)

Parameter	TRT A Fasted Mean (±SD)	TRT B Fed Mean (±SD)	% Difference[b]	90% Confidence Interval Test Results
C_{max} (pg/mL)	257.7 (125.3)	236.5 (80.4)	-8.20	EQ
C_{max} Ratio [a]	NA	1.02 (0.31)	NA	---
t_{max} (h)	2.31 (0.89)	2.63 (0.86)	13.9	---
AUC (0-*) pg.h/mL	5091.5 (3327.5)	4657.6 (2755.8)	-8.52	EQ
AUC Ratio [a]	NA	1.13 (0.65)	NA	---

[a] With reference to fasted.
[b] With reference to Treatment A, [B-A]/A x 100%.
* AUC from time zero to the last measured time point.

Table 9: 90% Confidence Intervals for the Ratio of Mean Parameters from High-Fat Fed Conditions to the Fasted Condition (Protocol ESTNRG-PHI-004)

Analyte	Baseline Correction	Parameter	Geometric Mean Fasted	Geometric Mean Fed	Ratio of the Geometric Means (%)	90% Conf. Limits Lower (%)	90% Conf. Limits Upper (%)
Estradiol	No	AUC (0-∞)	1814.14	1961.06	108.10	101.47	115.16
		AUC (0-*)	1519.94	1664.35	109.50	102.57	116.90
		C_{max}	44.38	48.56	109.40	101.53	117.89
	Yes	AUC (0-∞)	1474.69	1623.45	110.09	103.00	117.67
		AUC (0-*)	1321.23	1469.17	111.20	103.99	118.91
		C_{max}	41.39	45.55	110.05	101.95	118.80
Estrone	No	AUC (0-∞)	10216.74	11179.70	109.43	105.18	113.84
		AUC (0-*)	8818.98	9654.67	109.48	104.36	114.85
		C_{max}	324.53	378.68	116.68	108.25	125.77
	Yes	AUC (0-∞)	8312.66	9026.81	108.59	98.80	119.36
		AUC (0-*)	7786.04	8396.71	107.84	98.42	118.17
		C_{max}	310.71	360.73	116.10	107.33	125.59
Estrone Sulfate	No	AUC (0-∞)	432.96	459.74	106.18	101.33	111.28
		AUC (0-*)	344.88	365.83	106.07	101.49	110.86
		C_{max}	16.37	20.58	125.76	113.55	139.28
	Yes	AUC (0-∞)	348.13	378.28	108.66	103.26	114.34
		AUC (0-*)	303.83	326.43	107.44	102.22	112.93
		C_{max}	15.80	20.01	126.68	114.20	140.53
17-d NGM		AUC (0-∞)	9211.17	9580.67	104.01	95.23	113.60
		AUC (0-*)	6371.75	6420.79	100.77	94.55	107.40
		C_{max}	742.65	640.97	86.31	78.52	94.87
Norgestrel		AUC (0-*)	3739.26	3800.74	101.64	87.88	117.57
		C_{max}	231.37	224.42	97.00	88.94	105.78

ABBREVIATED HUMAN PHARMACOKINETICS REPORT SUMMARY

Adverse experiences and safety monitoring:
Treatment with the dry process tablet containing 17β-estradiol/norgestimate (2 mg/180 µg) was well-tolerated by the female subjects when administered under fed and fasting conditions. Seven adverse events were reported by five subjects during this study. Three occurred following administration of a dry process tablet with a high-fat meal and three occurred during fasting conditions (see Table 10). All but one of the adverse events (hot flushes of moderate severity) were rated by the investigator as mild in severity and only three (taste perversion, hot flushes, headache) were considered related to treatment. None of the adverse events were serious or necessitated the discontinuation of treatment.

There were no clinically significant prestudy to poststudy changes in physical or gynecological examination findings or in the vital sign measurements. Eight subjects with normal baseline chlorides had modest elevations to above the normal range following treatment. Five subjects had modest elevations in inorganic phosphorus following treatment. Three subjects had triglyceride levels that increased above the normal range posttreatment. Consistent with the known effects of hormone replacement, neutrophils were reduced in 15 of the 24 women (63%), only two of whom had low values prior to treatment. Lymphocytes were elevated in seven women following treatment, all of whom had normal baseline values. Bands were elevated in 12 subjects following treatment. Prior to treatment, bands were elevated in four of the 12. Four other subjects had band levels that were elevated at baseline, but returned to normal range posttreatment. Clinical laboratory abnormalities were unremarkable.

Table 10: Number and Percentage of Subjects Reporting Adverse Events (Protocol ESTNRG-PHI-004)

Adverse Event	Dry Tablet Fed (N=24)	Dry Tablet Fasted (N=24)
Nausea	1 (4%)	0 (0%)
Tooth disorder (toothache)	0 (0%)	1 (4%)
Hot Flushes	1 (4%)	1 (4%)
Headache	1 (4%)	0 (0%)
Taste perversion (medicine taste)	0 (0%)	1 (4%)
Urinary tract infection	1 (4%)	0 (0%)
Number of Subjects with at Least One AE	**3 (13%)**	**3 (13%)**

Conclusions: The effects of a high-fat meal on the absorption and/or pharmacokinetics of E_2, E_1, E_1S, 17d-NGM, and NG were either non existent or were minimal and are not considered to be of clinical relevance. The hormone replacement therapy oral tablet combination product E_2/NGM can be given without regard to the timing of meals in relation to dosing.

The results of this study indicate that administration of a dry formulation tablet containing 17β-estradiol/norgestimate (2 mg/180 µg) under fed and fasting conditions was safe and well-tolerated by healthy women.

ABBREVIATED HUMAN PHARMACOKINETICS REPORT SUMMARY

Title of Trial Bioequivalence Study of RWJPRI 17β-Estradiol 0.5 mg Process Tablets vs. ESTRACE® 17β-Estradiol 0.5 mg Tablets in Healthy Postmenopausal Female Subjects (Protocol ESTNRG-PHI-006)

Investigator(s)/Center(s):

Trial Period: Clinical Phase: October 1996 to November 1996

Bioanalytical: January 1997 to March 1997

Data Analysis and Report Preparation: September 1997 to February 1998

Objectives: To evaluate the bioequivalence of 0.5 mg RWJPRI process tablets of micronized 17β-estradiol as compared to the marketed ESTRACE® 0.5 mg 17β-estradiol tablets, when administered as four tablets in the fasted condition

Design:. The study was an open-label, randomized, complete, two-way crossover design in 36 postmenopausal female subjects for a total period of approximately 18 days. Equal numbers of subjects were randomly assigned to receive four RWJPRI 0.5 mg 17β-estradiol dry process tablets in one treatment period and four 0.5 mg ESTRACE® brand 17β-estradiol tablets in the other treatment period. Treatment periods were separated by a washout period of 14 days. Blood samples were drawn at -48, -24, and 0 hours prior to dose administration and at 18 time points after dosing for determination of E_2, E_1, and E_1S.

Subjects:
-36 Healthy, adult, female volunteers
Number of subjects:
- enrolled = 36
- completed = 35
- evaluated = 36 for safety and 35 for pharmacokinetics

Criteria for inclusion (trial population): Healthy postmenopausal women aged 43-65 who had not experienced menses without exogenous hormone replacement therapy for at least 12 months prior to the start of the study were enrolled. Subjects must have had serum estradiol concentrations ≤20pg/mL and serum follicle stimulating hormone (FSH) concentrations ≥40 mIU/mL for subjects who had been postmenopausal for ≥12 months and who had previously received hormone replacement therapy, or serum FSH concentrations ≥30 mIU/mL for subjects who had been postmenopausal for ≥12 months and had not received hormone replacement therapy previously, must have discontinued injectable sex hormone use 6 months (180 days) prior to dosing, and have had no exposure to implantable sex steroids, must have discontinued all hormone replacement therapy at least 30 days prior to dosing, and must have no contraindications to steroid hormone use and have not used tobacco in any form within 6 months of dosing.

Test product, dose and mode of administration, batch and formulation Nos.: RWJPRI process tablet, four 0.5 mg (2 mg total dose) micronized 17β-estradiol, oral, Batch R6500, FD#01551-000-AL-21.

Reference therapy, dose and mode of administration, batch and formulation Nos.: Reference Therapy: currently marketed tablet, four 0.5 mg (2 mg total dose) ESTRACE®, oral, Batch R6507, FD#01551-000-AT-21

Duration of treatment: Single dose each of test product and reference therapy over 18 days.

Analytical method(s)/Analytical Center(s):

Statistical methods:
1. Pharmacokinetics
Pharmacokinetic data analysis was performed at RWJPRI.

The pharmacokinetic parameters peak concentration (C_{max}) and area under the concentration vs. time curve to the time of last concentration above assay quantification limit AUC (0-*) and to infinity AUC (0-∞) for E_2, E_1, and E_1S were estimated from serum concentration data (both corrected to baseline and not corrected to baseline) and compared statistically; t_{max}, $t_{½}$, k_e, and CL/F (for E_2 only) were also estimated and tabulated. Descriptive statistics for pharmacokinetic parameters (C_{max}, t_{max}, AUC (0-last), AUC (0-∞), $t_{½}$, k_e, and CL/F) were calculated and tabulated. C_{max}, AUC (0-last), and AUC (0-∞) were compared by analysis of log-transformed parameters. For C_{max}, AUC (0-last), and AUC (0-∞), analysis of variance models were fit to the data with the log-transformed parameter as the dependent variable and the effects due to treatment sequence group, subjects nested within the sequence groups, treatment, and period as predictors. The estimated least squares and intra-subject variability for the model were used to construct 90% confidence intervals for the ratio of the mean bioavailability parameters (C_{max}, AUC (0-*), and AUC (0-∞) for the RWJPRI dry tablet treatment to the ESTRACE® tablet treatment using the classic confidence interval approach (Schuirmann's two one-sided test procedure).

2. Safety

Safety was based on adverse events, vital sign measurements, physical and gynecological examinations, and laboratory (hematology, chemistry, urinalysis) results.

Results:

Pharmacokinetics:

The results show that the mean bioavailability parameters for the two treatments (for both baseline corrected and baseline uncorrected data) differed at most by less than 8% for AUC, and by less than 13% for C_{max}. The 90% confidence interval for the ratio of the mean AUC and C_{max} values from the RWJPRI dry process tablet to those from the ESTRACE® tablets fell within the region of bioequivalence (80-125%) for all three analytes. The mean (SD) pharmacokinetic parameters for uncorrected and baseline corrected E_2, E_1, and E_1S data are presented in Tables 1, 4, and 7 respectively. Confidence intervals are in Tables 2, 5, and 8.

At the 10% level of significance, the ANOVA model showed no significant difference in the treatment sequence group effect for any of the parameters for uncorrected and baseline corrected E_2, E_1 or E_1S data. At the 5% level of significance, the ANOVA model showed no significant difference in the period effect for any of the parameters for both uncorrected and baseline corrected E_2 and E_1S data. The period effect was significant for the C_{max} of uncorrected and baseline corrected E_1 data. ANOVA results for E_2, E_1, and E_1S are presented in Tables 3, 6, and 9, respectively.

Table 1: Mean (±SD) E_2 Serum Pharmacokinetic Parameters (Protocol ESTNRG-PHI-006)

Parameter	ESTRACE® Tablet		RWJPRI Tablet		% Difference[a]
Baseline Uncorrected					
C_{max} (pg/mL)	55.4	(26.5)	49.3	(16.1)	-11.01
C_{max} Ratio	NA		0.95	(0.23)	-
t_{max} (h)	9.2	(5.7)	9.1	(3.8)	-1.09
AUC (0-*) (pg·h/mL)	1832	(918)	1766	(779)	-3.60
AUC (0-*) Ratio	NA		1.0	(0.2)	-
AUC (0-∞) (pg·h/mL)	2438	(1407)	2274	(1156)	-6.73
AUC (0-∞) Ratio	NA		1.0	(0.1)	-
$t_{½}$ (h)	31.5	(11.0)	29.9	(10.8)	-5.08
k_e (h-1)	0.025	(0.009)	0.026	(0.008)	4.00
CL/F (mL/min)	17935	(9148)	18307	(8637)	2.07
Baseline Corrected					
C_{max} (pg/mL)	51.7	(25.6)	45.4	(15.9)	-12.19
C_{max} Ratio	NA		0.94	(0.23)	-
t_{max} (h)	9.2	(5.7)	9.1	(3.8)	-1.09
AUC (0-*) (pg·h/mL)	1565	(788)	1481	(722)	-5.37
AUC (0-*) Ratio	NA		1.0	(0.2)	-
AUC (0-∞) (pg·h/mL)	1883	(1085)	1746	(999)	-7.28
AUC (0-∞) Ratio	NA		0.9	(0.2)	-
$t_{½}$ (h)	23.8	(7.58)	21.9	(6.77)	-7.98
k_e (h-1)	0.032	(0.011)	0.035	(0.013)	9.38
CL/F (mL/min)	22624	(10645)	24281	(11017)	7.32

[a] Difference of means, (RWJPRI Tablet - ESTRACE®)/ESTRACE®) × 100

* AUC from time zero until the last measured time point

ABBREVIATED HUMAN PHARMACOKINETICS REPORT SUMMARY

Table 2: Summary of Statistical Comparisons of Log-Transformed E_2 Pharmacokinetic Parameters for Treatment Effects (Protocol ESTNRG-PHI-006)

Parameter	ESTRACE® Geometric Mean	RWJPRI Geometric Mean	Ratio of the Geometric Means[a] (%)	Confidence Intervals Lower Bound (% Reference)	Confidence Intervals Upper Bound (% Reference)
Baseline Uncorrected					
AUC (0-∞)	2113.32	2027.45	95.94	91.78	100.28
AUC (0-*)	1648.04	1619.90	98.29	93.95	102.84
C_{max}	50.90	46.84	92.03	85.27	99.33
Baseline Corrected					
AUC (0-∞)	1647.76	1532.00	92.97	87.39	98.92
AUC (0-*)	1407.91	1339.34	95.13	90.20	100.32
C_{max}	47.16	42.78	90.70	83.85	98.12

[a] (RWJPRI Dry Tablet/ ESTRACE® Tablet) x 100
* AUC from time zero until the last measured time point

Table 3: Summary of ANOVA[a] Comparisons of E_2 Pharmacokinetic Parameters for Effects of Treatment, Treatment Sequence, and Period Effects (Protocol ESTNRG-PHI-006)

Parameter	Treatment Sequence Effect F	df	p-value	Period Effect F	df	p-value
Baseline Uncorrected						
AUC (0-∞)	0.213	(1, 33)	0.647	0.510	(1, 33)	0.480
AUC (0-*)	0.087	(1, 33)	0.770	0.981	(1, 33)	0.329
C_{max}	1.307	(1, 33)	0.261	3.414	(1, 33)	0.074
Baseline Corrected						
AUC (0-∞)	0.642	(1, 33)	0.429	1.692	(1, 33)	0.202
AUC (0-*)	0.275	(1, 33)	0.603	1.911	(1, 33)	0.176
C_{max}	1.440	(1, 33)	0.239	3.840	(1, 33)	0.059

* AUC from time zero until the last measured time point.

Table 4: Mean (±SD) E_1 Serum Pharmacokinetic Parameters (Protocol ESTNRG-PHI-006)

Parameter	ESTRACE® Tablet		RWJPRI Tablet		% Difference[a]
Baseline Uncorrected					
C_{max} (pg/mL)	393.6	(129.2)	409.1	(148.3)	3.94
C_{max} Ratio	NA		1.04	(0.15)	-
t_{max} (h)	6.6	(2.3)	6.3	(2.1)	-4.55
AUC (0-*) (pg·h/mL)	9723	(4283)	9790	(4304)	0.69
AUC (0-*) Ratio	NA		1.0	(0.2)	-
AUC (0-∞) (pg·h/mL)	11591	(5355)	11781	(5659)	1.64
AUC (0-∞) Ratio	NA		1.0	(0.1)	-
$t_{½}$ (h)	29.3	(8.62)	29.0	(11.0)	-1.02
k_e (h-1)	0.025	(0.007)	0.026	(0.007)	4.00
Baseline Corrected					
C_{max} (pg/mL)	374.6	(126.6)	390.5	(148.0)	4.24
C_{max} Ratio	NA		1.04	(0.16)	-
t_{max} (h)	6.6	(2.3)	6.3	(2.1)	-4.55
AUC (0-*) (pg·h/mL)	8358	(4036)	8445	(4251)	1.04
AUC (0-*) Ratio	NA		1.0	(0.2)	-
AUC (0-∞) (pg·h/mL)	9124	(4901)	9326	(5189)	2.21
AUC (0-∞) Ratio	NA		1.0	(0.2)	-
$t_{½}$ (h)	18.4	(5.19)	19.4	(6.10)	5.43
k_e (h-1)	0.041	(0.011)	0.039	(0.013)	-4.88

[a] Difference of means, (RWJPRI Tablet - ESTRACE®)/ESTRACE®) x 100
* AUC from time zero until the last measured time point

ABBREVIATED HUMAN PHARMACOKINETICS REPORT SUMMARY

Table 5: Summary of Statistical Comparisons of Log-Transformed E_1 Pharmacokinetic Parameters for Treatment Effects (Protocol ESTNRG-PHI-006)

Parameter	ESTRACE® Geometric Mean	RWJPRI Geometric Mean	Ratio of the Geometric Means[a] (%)	Confidence Intervals	
				Lower Bound (% Reference)	Upper Bound (% Reference)
Baseline Uncorrected					
AUC (0-∞)	10584.76	10704.89	101.13	97.31	105.11
AUC (0-*)	8910.32	8997.75	100.98	96.51	105.66
C_{max}	372.80	383.06	102.75	98.74	106.94
Baseline Corrected					
AUC (0-∞)	8069.86	8205.39	101.68	96.85	106.75
AUC (0-*	7511.03	7563.64	100.70	95.68	105.99
C_{max}	353.37	363.41	102.84	98.71	107.14

[a] (RWJPRI Tablet/ ESTRACE® Tablet) x 100
* AUC from time zero until the last measured time point.

Table 6: Summary of ANOVA Comparisons of E_1 Pharmacokinetic Parameters for Effects of Treatment Sequence and Period Effects (Protocol ESTNRG-PHI-006)

Parameter	Treatment Sequence Effect			Period Effect		
	F	df	p-value	F	df	p-value
Baseline Uncorrected						
AUC (0-∞)	0.329	(1, 33)	0.570	0.135	(1, 33)	0.716
AUC (0-*)	0.099	(1, 33)	0.756	2.107	(1, 33)	0.156
C_{max}	0.012	(1, 33)	0.913	4.875	(1, 33)	0.034
Baseline Corrected						
AUC (0-∞)	0.171	(1, 33)	0.682	0.629	(1, 33)	0.434
AUC (0-*)	0.081	(1, 33)	0.778	1.643	(1, 33)	0.209
C_{max}	0.011	(1, 33)	0.919	4.861	(1, 33)	0.035

* AUC from time zero until the last measured time point.

Table 7: Mean (±SD) E_1S Serum Pharmacokinetic Parameters (Protocol ESTNRG-PHI-006)

Parameter	ESTRACE® Tablet		RWJPRI Tablet		% Difference[a]
Baseline Uncorrected					
C_{max} (ng/mL)	17.5	(10.1)	18.9	(12.2)	8.00
C_{max} Ratio	NA	NA	1.16	(0.72)	-
t_{max} (h)	4.6	(1.9)	4.7	(1.0)	2.17
AUC (0-*) (ng·h/mL)	309	(221)	308	(214)	-0.32
AUC (0-*) Ratio	NA	NA	1.0	(0.2)	-
AUC (0-∞) (ng·h/mL)	360	(270)	376	(301)	4.44
AUC (0-∞) Ratio	NA	NA	1.0	(0.2)	-
$t_{½}$ (h)	30.8	(16.6)	35.9	(29.4)	16.6
k_e (h-1)	0.028	(0.014)	0.028	(0.017)	0.0
Baseline Corrected					
C_{max} (ng/mL)	17.1	(10.0)	18.4	(12.2)	7.60
C_{max} Ratio	NA	NA	1.16	(0.72)	-
t_{max} (h)	4.6	(1.9)	4.7	(1.0)	2.17
AUC (0-*) (ng·h/mL)	274	(208)	274	(211)	0.0
AUC (0-*) Ratio	NA	NA	1.0	(0.3)	-
AUC (0-∞) (ng·h/mL)	294	(238)	304	(284)	3.40
AUC (0-∞) Ratio	NA	NA	1.0	(0.3)	-
$t_{½}$ (h)	19.1	(7.56)	18.9	(10.6)	-1.05
k_e (h-1)	0.042	(0.018)	0.049	(0.030)	16.7

[a] Difference of means, (RWJPRI Tablet - ESTRACE®)/ESTRACE®) x 100
* AUC from time zero until the last measured time point.

ABBREVIATED HUMAN PHARMACOKINETICS REPORT SUMMARY

Table 8: Summary of Statistical Comparisons of Log-Transformed E_1S Pharmacokinetic Parameters for Treatment Effects (Protocol ESTNRG-PHI-006)

Parameter	ESTRACE® Geometric Mean	RWJPRI Geometric Mean	Ratio of the Geometric Means[a] (%)	Confidence Intervals Lower Bound (% Reference)	Confidence Intervals Upper Bound (% Reference)
Baseline Uncorrected					
AUC (0-∞)	295.72	309.00	104.49	96.89	112.68
AUC (0-*)	255.99	261.24	102.05	95.11	109.50
C_{max}	15.61	16.54	105.95	95.16	117.96
Baseline Corrected					
AUC (0-∞)	234.83	235.89	100.45	92.73	108.82
AUC (0-*)	222.16	223.30	100.51	93.48	108.07
C_{max}	15.13	15.98	105.56	94.79	117.54

[a] (RWJPRI Tablet/ ESTRACE® Tablet) x 100

* AUC from time zero until the last measured time point.

Table 9: Summary of ANOVA Comparisons of E_1S Pharmacokinetic Parameters for Effects of Treatment Sequence and Period Effects (Protocol ESTNRG-PHI-006)

Parameter	Treatment Sequence Effect F	Treatment Sequence Effect df	Treatment Sequence Effect p-value	Period Effect F	Period Effect df	Period Effect p-value
Baseline Uncorrected						
AUC (0-∞)	0.225	(1, 31)	0.638	0.287	(1, 31)	0.596
AUC (0-*)	0.253	(1, 33)	0.618	0.859	(1, 33)	0.361
C_{max}	0.356	(1, 33)	0.555	0.359	(1, 33)	0.553
Baseline Corrected						
AUC (0-∞)	0.246	(1, 31)	0.624	0.139	(1, 31)	0.712
AUC (0-*)	0.198	(1, 33)	0.660	0.545	(1, 33)	0.465
C_{max}	0.303	(1, 33)	0.585	0.404	(1, 33)	0.529

* AUC from time zero until the last measured time point

Adverse experiences and safety monitoring

Treatment with both the dry process tablet and ESTRACE®, each containing 2 mg 17β-estradiol, was well-tolerated by the subjects. Two (6%) of the 36 subjects enrolled in this study reported one treatment-emergent adverse event, one in each treatment group (Table 12). One subject reported abdominal pain and one reported back pain. Both adverse events were mild; the abdominal pain was reported as possibly related to treatment, while the back pain was considered unlikely related to treatment (see Table 10). None of the adverse events were serious or necessitated the discontinuation of treatment.

There were no clinically significant prestudy to poststudy changes in physical or gynecologic examination findings or in the vital sign measurements. Clinical laboratory abnormalities were unremarkable, other than approximately 10 to 15% of subjects with prestudy glucose levels near the upper limit of normal had values that increased above the normal range posttreatment.

Table 10: Number and Percentage of most Frequent Adverse Events (Protocol ESTNRG-PHI-006)

Adverse Event	ESTRACE (N=36)		Dry Tablet (N=36)		Total (N=36)	
Gastrointestinal Systems Disorders	0	(0%)	1	(3%)	1	(3%)
Abdominal Pain	0	(0%)	1	(3%)	1	(3%)
Body as a Whole - General Disorders	1	(3%)	0	(0%)	1	(3%)
Back Pain	1	(3%)	0	(0%)	1	(3%)
Number of Subjects with at Least One AE	1	(3%)	1	(3%)	2	(6%)

Conclusions: The pharmacokinetic results from this study show that a 2.0 mg dose of the RWJPRI process micronized 17β-estradiol formulation administered as four (4) 0.5 mg tablets is bioequivalent to a 2.0 mg dose of the ESTRACE® micronized 17β-estradiol formulation when administered as four (4) 0.5 mg tablets.

The safety results of this study indicate that administration of 17β-estradiol (2.0 mg) given as four 0.5 mg RWJPRI process tablets (micronized) and as four 0.5 mg marketed ESTRACE® tablets was safe and well tolerated by healthy, postmenopausal women.

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ABBREVIATED HUMAN PHARMACOKINETICS REPORT SUMMARY

Title of Trial Bioequivalence Study of RWJPRI 17β-Estradiol 2 mg Process Tablets vs. ESTRACE® 17β-Estradiol 2 mg Tablets in Healthy Postmenopausal Female Subjects (Protocol ESTNRG-PHI-007)
Investigator(s)/Center(s): [
Trial Period: Clinical Conduct: January 1997 to July 1997 Analytical Conduct: April 1997 to August 1997 Data Analysis and Report Preparation: October 1997 to February 1998
Objectives: To demonstrate bioequivalence of the RWJPRI process 2 mg tablet of micronized 17β-estradiol vs. the currently marketed ESTRACE® 2 mg 17β-estradiol tablet.
Design:. The study was an open-label, randomized, complete, two period crossover design in 36 postmenopausal female subjects for a total period of approximately 18 days. Equal numbers of subjects were randomly assigned to receive one RWJPRI 2 mg 17β-estradiol dry process tablet in one treatment period and one 2 mg ESTRACE® brand 17β-estradiol tablet in the other treatment period. Treatment periods were separated by a washout period of 14 days. Subjects ranged from 42 to 66 years old (mean age, 56.2 years), with the majority between the ages of 51 and 65 years. Thirty-three subjects were Caucasian, two were Hispanic and one was Philipino. Weight ranged from 49.5 to 93.2 kg (mean 68.4). Blood samples at each treatment period were drawn at -48, -24, and 0 hours prior to dose administration and at 18 time points after dosing for determination of 17β-estradiol (E_2), estrone (E_1), and estrone sulfate (E_1S).
Subjects: -36 Healthy, adult, female volunteers Number of subjects: - enrolled = 36 - completed = 36 - evaluated = 36
Criteria for inclusion (trial population): Healthy postmenopausal women aged 42-66 who had not experienced menses without exogenous hormone replacement therapy for at least 12 months prior to the start of the study were enrolled. Subjects must have had serum estradiol concentrations ≤20pg/mL and serum follicle-stimulating hormone (FSH) concentrations ≥40 mIU/mL if they had been postmenopausal for ≥12 months and who had previously received hormone replacement therapy, or serum FSH concentrations ≥30 mIU/mL were acceptable for subjects who had been postmenopausal for ≥12 months and had not received hormone replacement therapy previously. Subjects must have discontinued injectable sex hormone use 6 months (180 days) prior to dosing, and have had no exposure to implantable sex steroids, must have discontinued all hormone replacement therapy at least 30 days prior to dosing, and must have no known contraindications to steroid hormone use and have not used tobacco in any form within 6 months of dosing.
Test product, dose and mode of administration, batch and formulation Nos.: RWJPRI process tablet, one 2 mg micronized 17β-estradiol, oral, Batch R6542, FD#01551-000-AN-21.
Reference therapy, dose and mode of administration, batch and formulation Nos.: ESTRACE® one 2 mg 17β-estradiol tablet, oral, Batch R6505, FD#01551-000-AA-21.
Duration of treatment: Single dose each of test product and reference therapy over 18 days.
Analytical method(s)/Analytical Center(s): [

ABBREVIATED HUMAN PHARMACOKINETICS REPORT SUMMARY

Statistical methods:

1. Pharmacokinetics -

Pharmacokinetic data analysis was performed at RWJPRI.

The pharmacokinetic parameters peak concentration (C_{max}), time to peak concentration (t_{max}) and area under the concentration vs. time curve to the time of last concentration above assay quantification limit AUC (0-last) and to infinity AUC (0-∞) for E_2, E_1, and E_1S were estimated from serum data and compared statistically; t_{max}, $t_{½}$, k_e, and CL/F (for E_2 only) were also estimated and tabulated. Descriptive statistics for pharmacokinetic parameters (C_{max}, t_{max}, AUC (0-last), AUC (0-∞), $t_{½}$, k_e, and CL/F) were calculated and tabulated. C_{max}, AUC (0-last), and AUC (0-∞) were compared by analysis of log-transformed parameters. For C_{max}, AUC (0-last), and AUC (0-∞), analysis of variance models were fit to the data with the log-transformed parameter as the dependent variable and the effects due to treatment sequence group, subjects nested within the sequence groups, treatment, and period as predictors. The estimated least squares and intra-subject variability for the model were used to construct 90% confidence intervals for the ratio of the mean bioavailability parameters (C_{max}, AUC (0-*), and AUC (0-∞) for the RWJPRI dry tablet treatment to the ESTRACE® tablet treatment using the classic confidence interval approach (Schuirmann's two one-sided test procedure).

2. Safety

Summary statistics were calculated for demographic data and adverse events.

Results:

Pharmacokinetics:

The percent difference between the mean values of the E2, E1, and E1S pharmacokinetic parameters for the two treatments were all less than 12%. The 90% confidence interval for the ratio of the mean AUC and Cmax values from the RWJPRI dry process tablet to those from the ESTRACE® tablets fell within the region of bioequivalence (80-125%) for all three analytes. The mean (SD) pharmacokinetic parameters for uncorrected and baseline corrected E2, E1, and E1S data are presented in Tables 1, 4, and 7 respectively. Confidence intervals are in Tables 2, 5, and 8.

At the 10% level of significance, the ANOVA model showed no significant difference in the treatment sequence group effect for any of the parameters except for Cmax for uncorrected and baseline corrected E2 data. There were no significant differences in the treatment sequence group effect for any of the parameters for both uncorrected and baseline corrected E1 or E1S data. At the 5% level of significance, the ANOVA model showed no significant difference in the period effect for any of the parameters for both uncorrected and baseline corrected E2data, and was not significant for Cmax of uncorrected and baseline corrected E1 parameters. The period effect was significant for the AUC's of uncorrected and baseline corrected E1 data. The period effect was significant for the all three parameters of E1S (uncorrected and baseline corrected). ANOVA results for E2, E1, and E1S are presented in Tables 3, 6, and 9, respectively.

Table 1: Mean (±SD) 17β-Estradiol Serum Pharmacokinetic Parameters (Protocol ESTNRG-PHI-007)

Parameter	ESTRACE® Tablet	RWJPRI Tablet	% Difference[a]
Baseline Uncorrected			
C_{max} (pg/mL)	50.2 (18.5)	45.3 (11.1)	-9.76
C_{max} Ratio		0.948 (0.219)	
t_{max} (h)	8.0 (4.3)	8.0 (3.7)	0.0
AUC (0-*) (pg·h/mL)	1380.5 (474.1)	1441.6 (529.6)	4.43
AUC (0-*) Ratio		1.08 (0.39)	
AUC (0-∞) (pg·h/mL)	1720.1 (1077.2)	1852.0 (1108.6)	7.67
AUC (0-∞) Ratio		1.21 (1.01)	
$t_{½}$ (h)	22.31 (6.28)	23.50 (8.00)	5.33
k_e (h-1)	0.035 (0.015)	0.032 (0.014)	-8.57
CL/F (mL/min)	24547.80 (13347.00)	23770.50 (14119.95)	-3.17

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Table 1: Mean (±SD) 17β-Estradiol Serum Pharmacokinetic Parameters (Protocol ESTNRG-PHI-007) (Continued)

Baseline Corrected			
C_{max} (pg/mL)	47.3 (17.7)	42.0 (10.8)	-11.21
C_{max} Ratio		0.935 (0.220)	
t_{max} (h)	8.0 (4.3)	8.0 (3.7)	0.0
AUC (0-*) (pg·h/mL)	1170.6 (384.7)	1207.8 (430.1)	3.18
AUC (0-*) Ratio		1.05 (0.27)	
AUC (0-∞) (pg·h/mL)	1276.5 (450.4)	1376.0 (561.4)	7.79
AUC (0-∞) Ratio		1.12 (0.49)	
$t_{½}$ (h)	18.61 (6.27)	20.18 (6.17)	8.44
k_e (h-1)	0.043 (0.009)	0.041 (0.012)	-4.65
CL/F (mL/min)	30222.54 (13190.02)	29285.28 (14948.70)	-3.10

[a] Difference of means, (RWJPRI Tablet - ESTRACE®/ESTRACE®) × 100

* AUC from time zero until the last measured time point.

Table 2: Summary of Statistical Comparisons of Log-Transformed 17β-Estradiol Pharmacokinetic Parameters for Treatment Effects (Protocol ESTNRG-PHI-007)

Parameter	ESTRACE® Geometric Mean	RWJPRI Geometric Mean	Ratio of the Geometric Means[a] (%)	Confidence Intervals	
				Lower Bound (% Reference)	Upper Bound (% Reference)
Baseline Uncorrected					
AUC (0-∞)	1559.41	1663.18	106.65	94.36	120.55
AUC (0-*)	1290.03	1333.71	103.39	96.07	111.25
C_{max}	47.86	43.86	91.65	84.47	99.43
Baseline Corrected					
AUC (0-∞)	1213.71	1289.72	106.26	97.42	115.91
AUC (0-*)	1099.40	1125.32	102.36	96.22	108.89
C_{max}	44.99	40.59	90.22	82.85	98.25

[a] (RWJPRI Tablet/ ESTRACE® Tablet) × 100

* AUC from time zero until the last measured time point.

Table 3: Summary of ANOVA[a] Comparisons of 17β-Estradiol Pharmacokinetic Parameters for Effects of Treatment Sequence, and Period Effects (Protocol ESTNRG-PHI-007)

Parameter	Treatment Sequence Effect			Period Effect		
	F	df	p-value	F	df	p-value
Baseline Uncorrected						
AUC (0-∞)	0.445	(1, 33)	0.509	0.853	(1, 33)	0.363
AUC (0-*)	0.051	(1, 34)	0.823	0.009	(1, 34)	0.926
C_{max}	5.024	(1, 34)	0.032	0.221	(1, 34)	0.641
Baseline Corrected						
AUC (0-∞)	0.091	(1, 33)	0.765	0.110	(1, 33)	0.742
AUC (0-*)	0.003	(1, 34)	0.957	0.370	(1, 34)	0.547
C_{max}	7.042	(1, 34)	0.012	0.053	(1, 34)	0.819

* AUC from time zero until the last measured time point.

Table 4: Mean (±SD) Estrone Serum Pharmacokinetic Parameters (Protocol ESTNRG-PHI-007)

Parameter	ESTRACE® Tablet	RWJPRI Tablet	% Difference[a]
Baseline Uncorrected			
C_{max} (pg/mL)	378.7 (114.7)	349.5 (90.2)	-7.71
C_{max} Ratio		0.941 (0.159)	
t_{max} (h)	6.8 (2.8)	6.3 (2.0)	-7.35
AUC (0-*) (pg·h/mL)	8207.2 (2490.8)	8197.1 (2524.6)	-0.12
AUC (0-*) Ratio		1.02 (0.19)	
AUC (0-∞) (pg·h/mL)	9233.1 (2863.1)	9411.7 (2959.9)	1.93
AUC (0-∞) Ratio		1.04 (0.19)	
$t_{½}$ (h)	23.72 (8.31)	25.33 (8.87)	6.79
k_e (h-1)	0.032 (0.008)	0.030 (0.008)	-6.25
Baseline Corrected			
C_{max} (pg/mL)	362.9 (116.4)	333.7 (91.7)	-8.05
C_{max} Ratio		0.938 (0.164)	
t_{max} (h)	6.8 (2.8)	6.3 (2.0)	-7.35
AUC (0-*) (pg·h/mL)	7071.9 (2401.2)	7062.7 (2517.4)	-0.13
AUC (0-*) Ratio		1.02 (0.21)	
AUC (0-∞) (pg·h/mL)	7419.4 (2661.4)	7523.5 (2920.4)	1.40
AUC (0-∞) Ratio		1.03 (0.21)	
$t_{½}$ (h)	14.79 (3.59)	16.38 (4.33)	10.8
k_e (h-1)	0.049 (0.012)	0.045 (0.010)	-8.16

[a] Difference of means, (RWJPRI Tablet - ESTRACE®)/ESTRACE®) x 100

* AUC from time zero until the last measured time point.

Table 5: Summary of Statistical Comparisons of Log-Transformed Estrone Pharmacokinetic Parameters for Treatment Effects (Protocol ESTNRG-PHI-007)

Parameter	ESTRACE® Geometric Mean	RWJPRI Dry Geometric Mean	Ratio of the Geometric Means[a] (%)	Confidence Intervals	
				Lower Bound (% Reference)	Upper Bound (% Reference)
Baseline Uncorrected					
AUC (0-∞)	8747.60	8942.22	102.23	99.72	106.94
AUC (0-*)	7775.67	7784.91	100.12	95.76	104.68
C_{max}	364.31	337.99	92.78	88.54	97.22
Baseline Corrected					
AUC (0-∞)	6877.36	6965.03	101.27	96.22	106.59
AUC (0-*)	6597.42	6594.57	99.96	95.14	105.02
C_{max}	347.80	321.48	92.43	88.04	97.04

[a] (RWJPRI Tablet/ ESTRACE® Tablet) x 100

* AUC from time zero until the last measured time point.

Table 6: Summary of ANOVA Comparisons of Estrone Pharmacokinetic Parameters for Effects of Treatment Sequence and Period Effects (Protocol ESTNRG-PHI-007)

	Treatment Sequence Effect			Period Effect		
Parameter	F	df	p-value	F	df	p-value
Baseline Uncorrected						
AUC (0-∞)	0.101	(1, 34)	0.753	11.056	(1, 34)	0.002
AUC (0-*)	0.173	(1, 34)	0.680	13.534	(1, 34)	0.001
C_{max}	1.578	(1, 34)	0.218	3.621	(1, 34)	0.066
Baseline Corrected						
AUC (0-∞)	0.313	(1, 34)	0.580	9.035	(1, 34)	0.005
AUC (0-*)	0.349	(1, 34)	0.559	11.923	(1, 34)	0.002
C_{max}	1.769	(1, 34)	0.192	3.289	(1, 34)	0.079

* AUC from time zero until the last measured time point.

Table 7: Mean (±SD) Estrone Sulfate Serum Pharmacokinetic Parameters (Protocol ESTNRG-PHI-007)

Parameter	ESTRACE® Tablet	RWJPRI Tablet	% Difference[a]
Baseline Uncorrected			
C_{max} (ng/mL)	17.1 (10.0)	16.2 (9.0)	-5.26
C_{max} Ratio		0.958 (0.813)	
t_{max} (h)	5.0 (2.0)	5.0 (1.8)	0.0
AUC (0-*) (ng·h/mL)	254.5 (165.3)	255.1 (158.2)	0.24
AUC (0-*) Ratio		1.02 (0.20)	
AUC (0-∞) (ng·h/mL)	271.1 (173.8)	270.8 (168.1)	-0.11
AUC (0-∞) Ratio		1.02 (0.20)	
$t_{½}$ (h)	17.37 (4.49)	17.15 (4.55)	-1.27
k_e (h-1)	0.049 (0.026)	0.048 (0.025)	-2.04
Baseline Corrected			
C_{max} (ng/mL)	17.0 (10.0)	16.1 (9.0)	-5.29
C_{max} Ratio		0.957 (0.183)	
t_{max} (h)	5.0 (2.0)	5.0 (1.8)	0.0
AUC (0-*) (ng·h/mL)	250.5 (159.8)	250.1 (152.3)	-0.16
AUC (0-*) Ratio		1.02 (0.20)	
AUC (0-∞) (ng·h/mL)	263.6 (167.2)	263.1 (158.8)	-0.19
AUC (0-∞) Ratio		1.02 (0.19)	
$t_{½}$ (h)	16.61 (4.71)	16.32 (4.89)	-1.75
k_e (h-1)	0.058 (0.031)	0.052 (0.028)	-10.35

[a] Difference of means, (RWJPRI Tablet - ESTRACE®)/ESTRACE®) x 100

* AUC from time zero until the last measured time point.

Table 8: Summary of Statistical Comparisons of Log-Transformed Estrone Sulfate Pharmacokinetic Parameters for Treatment Effects (Protocol ESTNRG-PHI-007)

				Confidence Intervals	
Parameter	ESTRACE® Geometric Mean	RWJPRI Geometric Mean	Ratio of the Geometric Means[a] (%)	Lower Bound (% Reference)	Upper Bound (% Reference)
Baseline Uncorrected					
AUC (0-∞)	222.91	222.01	99.60	94.35	105.14
AUC (0-*)	206.77	207.61	100.41	95.59	105.48
C_{max}	14.79	13.91	94.06	89.60	98.75

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Table 8: Summary of Statistical Comparisons of Log-Transformed Estrone Sulfate Pharmacokinetic Parameters for Treatment Effects (Protocol ESTNRG-PHI-007) (Continued)

Parameter	ESTRACE® Geometric Mean	RWJPRI Geometric Mean	Ratio of the Geometric Means[a] (%)	Confidence Intervals Lower Bound (% Reference)	Confidence Intervals Upper Bound (% Reference)
Baseline Corrected					
AUC (0-∞)	215.76	217.43	100.78	96.05	105.74
AUC (0-*)	204.62	204.93	100.15	95.34	105.20
C_{max}	14.75	13.86	93.99	89.51	98.69

[a] (RWJPRI Tablet/ ESTRACE® Tablet) x 100

* AUC from time zero until the last measured time point.

Table 9: Summary of ANOVA Comparisons of Estrone Sulfate Pharmacokinetic Parameters for Effects of Treatment Sequence and Period Effects (Protocol ESTNRG-PHI-007)

Parameter	Treatment Sequence Effect F	df	p-value	Period Effect F	df	p-value
Baseline Uncorrected						
AUC (0-∞)	0.613	(1, 34)	0.439	5.020	(1, 34)	0.032
AUC (0-*)	0.552	(1, 34)	0.463	11.569	(1, 34)	0.002
C_{max}	1.153	(1, 34)	0.290	10.258	(1, 34)	0.003
Baseline Corrected						
AUC (0-∞)	0.586	(1, 34)	0.449	8.449	(1, 34)	0.006
AUC (0-*)	0.599	(1, 34)	0.444	11.215	(1, 34)	0.002
C_{max}	1.169	(1, 34)	0.287	10.107	(1, 34)	0.003

* AUC from time zero until the last measured time point.

Adverse experiences and safety monitoring

Treatment with both the dry process tablet and ESTRACE®, each containing 2 mg 17β-estradiol, was well-tolerated by the subjects. Twelve subjects reported adverse events during this study. Eleven subjects reported adverse events following administration of a dry process tablet and six reported adverse events following administration of ESTRACE. Headache, dizziness, and nausea were the most common adverse events (see Table 10). All of the adverse events except one were rated by the investigator as mild in severity. One adverse event (neuralgia) was considered by the investigator to be of marked severity, but, unlikely to be related to treatment. Most of the adverse events were considered unlikely to be related to treatment according to the investigator. None of the adverse events were serious or necessitated the discontinuation of treatment.

There were no clinically significant prestudy to poststudy changes in physical or gynecologic examination findings or in the vital sign measurements. Clinical laboratory abnormalities were unremarkable, other than urinalysis for several subjects suggestive of possible urinary tract infection or poor sample collection.

Table 10: Number and Percentage of Most Frequent Adverse Events (Protocol ESTNRG-PHI-007)

Adverse Event	ESTRACE (N=36)		Tablet (N=36)		Total (N=36)	
Headache	3	(8%)	4	(11%)	6	(17%)
Dizziness	2	(6%)	3	(8%)	3	(8%)
Nausea	1	(3%)	3	(8%)	3	(8%)
Leg cramps	0	(0%)	2	(6%)	2	(6%)
Number of Subjects with at Least One AE	**6**	**(17%)**	**11**	**(31%)**	**12**	**(33%)**

Conclusions: . The pharmacokinetic results show that the RWJPRI 17-β Estradiol 2.0 mg dry process tablet is bioequivalent to the ESTRACE® 2.0 mg tablet formulation.

The results of this study indicate that administration of both ESTRACE and a formulation tablet, each containing 2 mg 17β-estradiol, was safe and well-tolerated by healthy women.

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Title of Trial: A Randomized, Single-Dose, Open-Label, Complete Three-Way Crossover Study to Determine the Bioequivalence of RWJPRI Process 17β-Estradiol/Norgestimate (1 mg/90 µg) Tablets vs. Process Tablets, and the Relative Bioavailabilities of the Process Tablets with Respect to an Oral Solution Dosage Form (Protocol ESTNRG-PHI-008)

Investigator(s)/Center(s):

Trial Period: Clinical Conduct: October 1996 to December 1996
Bioanalytical Sample Analysis: November 1996 to February 1997
Data Analysis and Report Preparation: March 1997 to April 1998

Objectives: To determine the bioequivalence of 17β-estradiol (E_2) and its metabolites estrone (E_1), and estrone sulfate (E_1S), and of the norgestimate (NGM) metabolites 17-deacetylnorgestimate (17d-NGM) and norgestrel (NG) from the RWJPRI process E_2/NGM (1 mg/90 µg) tablet vs. the RWJPRI process tablet of the same strength, and to determine the relative bioavailabilities of the tablet formulations vs. an equal dose of a liquid formulation of E_2/NGM.

Design:. This was an open-label, randomized, complete three-way crossover study in 36 postmenopausal female subjects for a total period of approximately 32 days. Equal numbers of subjects were randomly assigned to receive each of the three treatments (one treatment per period) according to one of six possible treatment sequence groups. Subjects ranged from 44 to 65 years old (mean age, 55.6 years), with the majority between the ages of 51 and 65 years. Thirty-five subjects were Caucasian and one was Black. The mean weight for four of six treatment sequences was in the narrow range from 65.3 kg-67.9 kg, while for one sequence the mean weight was 61.5 kg and for the other 73.2 kg. Blood samples were drawn at -48, -24 and 0 h (predose) and up to 72 hours post dose for determination of serum concentrations of E_2, E_1, E_1S, 17d-NGM and NG.

Subjects:
-36 Healthy, adult, female volunteers
Number of subjects:
- enrolled = 36
- completed = 36
- evaluated = 36

Criteria for inclusion (trial population): Healthy females aged 40 - 65 years who were postmenopausal for ≥ 12 months prior to the start of the study and who have not experienced menses without exogenous hormone replacement therapy were enrolled. The subjects must not have had injectable sex hormones within 6 months (180 days) prior to the first dose, must have no history of implantable sex hormone use, must have discontinued all hormone replacement therapy at least 30 days prior to the first dose, must have no contraindication to use of 17β-Estradiol, norgestimate or other hormones and must have not used tobacco in any form within 6 months of dosing. Subjects who tested positive for hepatitis B, HIV or drugs of abuse were excluded..

Test product, dose and mode of administration, batch and formulation Nos.: RWJPRI process tablet, 1 mg/90 µg E_2/NGM, oral, (Batch R6133, FD#01551-000-D-21); RWJPRI process tablet, 1 mg/90 µg E_2/NGM, oral, (Batch R6292, FD#01551-097-K-21). The dose for each treatment was 2mg/180µg E_2/NGM given as two 1mg/90 µg E_2/NGM tablets..

Reference therapy, dose and mode of administration, batch and formulation Nos.: Solution containing 2 mg/180 µg E_2/NGM per 5 mL, oral, (Batch R6515, FD#01551-000-AG-41).

Duration of treatment: Three single doses, over 32 days.

Analytical method(s)/Analytical Center(s):

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Statistical methods:

1. Pharmacokinetics

Pharmacokinetic data analysis was performed at RWJPRI. The parameters of interest for the analysis were AUC to infinity (AUC (0-∞)), AUC to last measurable concentration (AUC (0-*)) and the maximum observed concentration (C_{max}). E_2, E_1, E_1S pharmacokinetic parameters were analyzed with and without correction for baseline. Statistical analysis was carried out on log-transformed bioavailability parameters. Analysis of variance models were fit to the data with one of the bioavailability parameters of interest (log-transformed) as the dependent variable and the effects due to treatment sequence group, subjects nested within the sequence groups, treatment and period as predictors. Testing for the treatment sequence group effect was carried out at the 10% level by using the mean square due to the subjects nested within sequence groups as the error term. The period effect was tested at the 5% level using the residual error term. The estimated least square means and intra-subject variability from the above model were used to construct 90% confidence intervals for the ratio of the mean bioavailability parameters for the following three combinations: 1. dry process tablets (test) vs. wet process tablets (reference) 2. wet process tablets (test) vs. solution (reference) and 3. dry process tablets (test) vs. solution (reference).

2. Safety

Summary statistics were calculated for demographic data and adverse events.

Results:

Pharmacokinetics:

The data from this study show that there were marked increases in the rate and less so the extent of absorption of E_2 from the alcoholic solution dosage form as compared to the wet or dry process tablets. The extent of absorption of E_2 from the tablets relative to the solution averaged from 66 to 73%. In addition, the rate but not the extent of absorption for E_2 was increased from the wet process tablets as compared to the dry process tablets, resulting in higher C_{max} but no increase in AUC.

Similar results were obtained for 17d-NGM although the difference between the solution and the tablet dosage forms were not as large. Less marked differences were observed for E_1 and E_1S, and essentially no differences between dosage forms were noted for NG.

Mean pharmacokinetic parameters for E_1, E_2, and E_1S (baseline uncorrected and corrected) and for 17d-NGM and NG are presented in Tables 1 to 8. Ninety percent confidence intervals are shown for the dry vs. wet formulations in Table 9, for the wet vs. solution in Table 10, and for the dry vs. solution in Table 11.

Table 1: 17β-Estradiol Mean (SD) Pharmacokinetic Data Summary for Thirty-Six Healthy Postmenopausal Women Following a Single Oral Dose of Two 1.0 mg 17β-Estradiol/ 90.0 µg Norgestimate RWJPR' , Process Tablets, Process Tablets and the Oral Solution (Baseline Uncorrected) (Protocol ESTNRG-PHI-008)

Parameter		Solution
C_{max} (pg/mL)	524.3	(190.0)
C_{max} Ratio [a]	NA	
C_{max} Ratio [b]	NA	
t_{max} (h)	0.5	(0.0)
AUC 0-* (pg·h/mL)	2152.4	(827.5)
AUC 0-* Ratio [a]	NA	
AUC 0-* Ratio [b]	NA	
AUC 0-∞ (pg·h/mL)	2416.2	(1070.2)
AUC 0-∞ Ratio [a]	NA	
AUC 0-∞ Ratio [b]	NA	
CL/F (mL/min)	16002.45	(6190.72)
k_e (h^{-1})	0.036	(0.015)
$t_{½}$ (h)	22.51	(10.13)

[a] Using Solution as reference.

[b] Using ablet as reference.

* AUC from time zero until the last measured time point.

Table 2: 17β-Estradiol Mean (SD) Pharmacokinetic Data Summary For Thirty-Six Healthy Postmenopausal Women Following a Single Oral Dose of Two 1.0 mg 17β-Estradiol/ 90.0 µg Norgestimate RWJPRI Process Tablets. Process Tablets and the Oral Solution (Baseline Corrected) (Protocol ESTNRG-PHI-008)

Parameter	Solution	
C_{max} (pg/mL)	522.3	(189.2)
C_{max} Ratio [a]	NA	
C_{max} Ratio [b]	NA	
t_{max} (h)	0.5	(0.0)
AUC 0-* (pg· h/mL)	2015.4	(713.4)
AUC 0-* Ratio [a]	NA	
AUC 0-* Ratio [b]	NA	
AUC 0-∞ (pg· h/mL)	2185.2	(828.0)
AUC 0-∞ Ratio [a]	NA	
AUC 0-∞ Ratio [b]	NA	
CL/F (mL/min)	17248.05	(6219.68)
k_e (h^{-1})	0.041	(0.016)
$t_{½}$ (h)	19.51	(9.87)

[a] Using Solution as reference.
[b] Using tablet as reference.
* AUC from time zero until the last measured time point.

Table 3: Estrone Mean (SD) Pharmacokinetic Data Summary For Thirty-Six Healthy Postmenopausal Women Following a Single Oral Dose of two 1.0 mg 17β-Estradiol/ 90.0 µg Norgestimate RWJPRI rocess Tablets, Process Tablets and the Oral Solution (Baseline Uncorrected) (Protocol ESTNRG-PHI-008)

Parameter	Solution	
C_{max} (pg/mL)	415.1	(149.6)
C_{max} Ratio [a]	NA	
C_{max} Ratio [b]	NA	
t_{max} (h)	3.6	(2.0)
AUC 0-* (pg· h/mL)	9278.8	(3958.9)
AUC 0-* Ratio [a]	NA	
AUC 0-* Ratio [b]	NA	
AUC 0-∞ (pg· h/mL)	10491.1	(4625.6)
AUC 0-∞ Ratio [a]	NA	
AUC 0-∞ Ratio [b]	NA	
k_e (h^{-1})	0.032	(0.009)
$t_{½}$ (h)	23.97	(7.21)

[a] Using Solution as reference.
[b] Using tablet as reference.
* AUC from time zero until the last measured time point.

Table 4: Estrone Mean (SD) Pharmacokinetic Data Summary For Thirty-Six Healthy Postmenopausal Women Following a Single Oral Dose of two 1.0 mg 17β-Estradiol/ 90.0 µg Norgestimate RWJPRI Process Tablets and the Oral Solution (Baseline Corrected) (Protocol ESTNRG-PHI-008)

Parameter	Solution	
C_{max} (pg/mL)	398.5	(147.6)
C_{max} Ratio [a]	NA	
C_{max} Ratio [b]	NA	
t_{max} (h)	3.6	(2.0)
AUC 0-* (pg· h/mL)	8074.4	(3793.7)
AUC 0-* Ratio [a]	NA	
AUC 0-* Ratio [b]	NA	
AUC 0-∞ (pg· h/mL)	8539.9	(4258.9)
AUC 0-∞ Ratio [a]	NA	
AUC 0-∞ Ratio [b]	NA	
k_e (h^{-1})	0.048	(0.015)
$t_{½}$ (h)	16.03	(5.09)

[a] Using Solution as reference.
[b] Using tablet as reference.
* AUC from time zero until the last measured time point.

Table 5: Estrone Sulfate Mean (SD) Pharmacokinetic Data Summary For Thirty-Six Healthy Postmenopausal Women Following a Single Oral Dose of two 1.0 mg 17β-Estradiol/ 90.0 µg Norgestimate RWJPRI Process Tablets, Process Tablets and the Oral Solution (Baseline Uncorrected) (Protocol ESTNRG-PHI-008)

Parameter	Solution	
C_{max} (ng/mL)	19.9	(11.5)
C_{max} Ratio [a]	NA	
C_{max} Ratio [b]	NA	
t_{max} (h)	2.2	(1.1)
AUC 0-* (ng· h/mL)	335.7	(286.1)
AUC 0-* Ratio [a]	NA	
AUC 0-* Ratio [b]	NA	

[a] Using Solution as reference.
[b] Using tablet as reference.
* AUC from time zero until the last measured time point.

Table 6: Estrone Sulfate Mean (SD) Pharmacokinetic Data Summary For Thirty-Six Healthy Postmenopausal Women Following a Single Oral Dose of two 1.0 mg 17β-Estradiol/ 90.0 µg Norgestimate RWJPRI Process Tablets, Process Tablets and the Oral Solution (Baseline Corrected) (Protocol ESTNRG-PHI-008)

Parameter	Solution	
C_{max} (ng/mL)	19.4	(11.3)
C_{max} Ratio [a]	NA	
C_{max} Ratio [b]	NA	
t_{max} (h)	2.2	(1.1)
AUC 0-* (ng· h/mL)	294.9	(269.0)
AUC 0-* Ratio [a]	NA	
AUC 0-* Ratio [b]	NA	
AUC 0-∞ (ng· h/mL)	321.8	(307.4)
AUC 0-∞ Ratio [a]	NA	
AUC 0-∞ Ratio [b]	NA	
k_e (h^{-1})	0.040	(0.021)
$t_{½}$ (h)	22.21	(10.99)

[a] Using Solution as reference.
[b] Using tablet as reference.
* AUC from time zero until the last measured time point.

Table 7: 17-Deacetylnorgestimate Mean (SD) Pharmacokinetic Data Summary For Thirty-Six Healthy Postmenopausal Women Following a Single Oral Dose of Two 1.0 mg 17β-Estradiol/ 90.0 µg Norgestimate RWJPRI Process Tablets, Process Tablets and the Oral Solution (Protocol ESTNRG-PHI-008)

Parameter	Solution	
C_{max} (pg/mL)	1396.8	(338.8)
C_{max} Ratio [a]	NA	
C_{max} Ratio [b]	NA	
t_{max} (h)	1.1	(0.2)
AUC 0-* (pg· h/mL)	10913.7	(2821.7)
AUC 0-* Ratio [a]	NA	
AUC 0-* Ratio [b]	1.14	(0.28)
AUC 0-∞ (pg· h/mL)	14181.9	(4448.9)
AUC 0-∞ Ratio [a]	NA	
AUC 0-∞ Ratio [b]	NA	
k_e (h^{-1})	0.023	(0.013)
$t_{½}$ (h)	37.01	(16.54)

[a] Using Solution as reference.
[b] Using tablet as reference.
* AUC from time zero until the last measured time point.

Table 8: Norgestrel (SD) Mean Pharmacokinetic Data Summary For Thirty-Six Healthy Postmenopausal Women Following a Single Oral Dose of Two 1.0 mg 17β-Estradiol/ 90.0 µg Norgestimate RWJPRI Process Tablets Process Tablets and the Oral Solution (Protocol ESTNRG-PHI-008)

Parameter	Solution	
C_{max} (pg/mL)	304.4	(123.8)
C_{max} Ratio [a]	NA	
C_{max} Ratio [b]	NA	
t_{max} (h)	1.2	(0.4)
AUC 0-* (pg· h/mL)	6577.3	(3040.9)
AUC 0-* Ratio [a]	NA	
AUC 0-* Ratio [b]	NA	

[a] Using Solution as reference.
[b] Using tablet as reference.
* AUC from time zero until the last measured time point.

Table 9: 90% Confidence Intervals For the Ratio of the Means from Process Tablets to Process Tablets For Thirty-Six Healthy Postmenopausal Women Following a Single Oral Dose of two 1.0 mg 17β-Estradiol/90.0 µg Norgestimate RWJPRI Process Tablets, Process Tablets and the Oral Solution (Protocol ESTNRG-PHI-008)

Analyte	Baseline Correction	Parameter	Geometric Mean Wet	Geometric Mean Dry	Unadjusted			Adjusted for Drug Content		
					Ratio of the Geometric Mean (%)	90% Conf. Limits Lower (%)	90% Conf. Limits Upper (%)	Ratio (%)	90% Conf. Limits Lower (%)	90% Conf. Limits Upper (%)
Estradiol	No	AUC (0-∞)	1580.26	1562.52	98.88	92.50	105.69	99.80	93.37	106.68
		AUC (0-t)	1372.18	1334.27	97.24	91.00	103.90	98.15	91.85	104.87
		C_{max}	57.45	43.06	74.95	66.37	84.65	75.65	66.99	85.45
	Yes	AUC (0-∞)	1367.58	1317.06	96.31	89.51	103.62	97.21	90.34	104.59
		AUC (0-t)	1236.78	1188.97	96.13	89.52	103.23	97.03	90.36	104.20
		C_{max}	55.20	40.90	74.10	65.49	83.85	74.80	66.10	84.64
Estrone	No	AUC (0-∞)	9548.41	9239.82	96.77	92.48	101.26	97.67	93.34	102.20
		AUC (0-t)	8433.11	8171.21	96.89	92.66	101.32	97.80	93.53	102.27
		C_{max}	357.65	340.46	95.19	89.82	100.89	96.08	90.66	101.83
	Yes	AUC (0-∞)	7403.80	7222.80	97.56	92.30	103.11	98.47	93.17	104.07
		AUC (0-t)	7083.16	6866.80	96.95	91.92	102.25	97.85	92.78	103.20
		C_{max}	340.02	324.27	95.37	89.61	101.49	96.26	90.45	102.44
Estrone Sulfate	No	AUC (0-t)	279.76	281.21	100.52	94.16	107.31	101.46	95.04	108.31
		C_{max}	16.35	14.65	89.58	83.97	95.57	90.42	84.76	96.46
	Yes	AUC (0-∞)	273.44	272.46	99.64	92.14	107.76	100.57	93.00	108.76
		AUC (0-t)	241.45	242.82	100.57	93.76	107.87	101.51	94.63	108.88
		C_{max}	15.82	14.12	89.25	83.48	95.42	90.09	84.26	96.31
17d NGM	No	AUC (0-∞)	13263.60	12178.09	91.82	84.98	99.21	90.68	83.93	97.98
		AUC (0-t)	9533.58	8807.69	92.39	86.04	99.20	91.24	84.97	97.98
		C_{max}	1359.09	1001.72	73.70	69.61	78.04	72.79	68.75	77.07
	Yes	AUC (0-∞)	13046.01	11614.53	89.03	81.61	97.11	87.93	80.61	95.91
		AUC (0-t)	9460.53	8542.97	90.30	83.57	97.58	89.19	82.54	96.37
		C_{max}	1357.94	999.01	73.57	69.48	77.89	72.66	68.62	76.93
Norgestrel	No	AUC (0-t)	5711.58	5777.30	101.15	92.82	110.23	99.90	91.67	108.87
		C_{max}	311.78	273.10	87.59	81.46	94.18	86.51	80.46	93.02
	Yes	AUC (0-t)	5341.06	5777.30	108.17	95.88	122.04	106.83	94.69	120.53
		C_{max}	307.94	273.10	88.69	82.74	95.06	87.59	81.72	93.89

Table 10: 90% Confidence Intervals for the Ratio of the Means From Process Tablets to the Mean From Solution For Thirty-Six Healthy Postmenopausal Women Following a Single Oral Dose of two 1.0 mg 17β-Estradiol/ 90.0 µg Norgestimate RWJPRI Process Tablets, Process Tablets and the Oral Solution (Protocol ESTNRG-PHI-008)

					Unadjusted			Adjusted for Drug Content		
						90% Conf. Limits			90% Conf. Limits	
Analyte	Baseline Correction	Parameter	Geometric Mean Solution	Geometric Mean Wet	Ratio (%)	Lower (%)	Upper (%)	Ratio (%)	Lower (%)	Upper (%)
Estradiol	No	AUC (0-∞)	2236.36	1580.26	70.66	66.11	75.53	68.18	63.78	72.88
		AUC (0-t)	2000.90	1372.18	68.27	63.89	72.95	65.87	61.64	70.38
		C_{max}	488.15	57.45	11.77	10.42	13.29	11.35	10.05	12.82
	Yes	AUC (0-∞)	2053.09	1367.58	66.61	61.91	71.67	64.27	59.73	69.15
		AUC (0-t)	1897.52	1236.78	65.18	60.70	69.99	62.89	58.56	67.53
		C_{max}	486.19	55.20	11.35	10.03	12.85	10.95	9.68	12.40
Estrone	No	AUC (0-∞)	9585.92	9548.41	99.61	95.19	104.23	96.10	91.84	100.56
		AUC (0-t)	8489.28	8433.11	99.34	95.00	103.88	95.84	91.66	100.22
		C_{max}	390.87	357.65	91.50	86.34	96.98	88.28	83.30	93.56
	Yes	AUC (0-∞)	7551.44	7403.80	98.04	92.77	103.62	94.60	89.50	99.98
		AUC (0-t)	7212.14	7083.16	98.21	93.12	103.58	94.76	89.84	99.94
		C_{max}	373.76	340.02	90.97	85.48	96.82	87.77	82.47	93.41
Estrone Sulfate	No	AUC (0-t)	278.63	279.76	100.41	94.06	107.18	96.87	90.75	103.41
		C_{max}	17.78	16.35	91.99	86.23	98.14	88.75	83.20	94.69
	Yes	AUC (0-∞)	268.57	273.44	101.82	94.15	110.11	98.23	90.83	106.23
		AUC (0-t)	239.67	241.45	100.74	93.92	108.06	97.20	90.62	104.26
		C_{max}	17.26	15.82	91.67	85.75	98.01	88.45	82.73	94.56
17d NGM	No	AUC (0-∞)	14280.56	13263.60	92.88	85.96	100.35	90.73	83.97	98.04
		AUC (0-t)	10534.19	9533.58	90.50	84.28	97.18	88.41	82.34	94.93
		C_{max}	1361.68	1359.09	99.81	94.27	105.68	97.50	92.09	103.23
	Yes	AUC (0-∞)	14260.12	13046.01	91.49	83.87	99.80	89.37	81.93	97.49
		AUC (0-t)	10534.19	9460.53	89.81	83.11	97.04	87.73	81.19	94.80
		C_{max}	1361.68	1357.94	99.73	94.19	105.59	97.42	92.01	103.15
Norgestrel	No	AUC (0-t)	5738.02	5711.58	99.54	91.34	108.47	97.24	89.23	105.97
		C_{max}	281.30	311.78	110.84	103.08	119.18	108.28	100.70	116.43
	Yes	AUC (0-t)	5738.02	5341.06	93.08	82.50	105.02	90.93	80.60	102.59
		C_{max}	281.30	307.94	109.47	102.13	117.34	106.94	99.77	114.63

Table 11: 90 % Confidence Intervals For the Ratio of the Means From Process Tablets to the Mean From Solution For Thirty-Six Healthy Postmenopausal Women Following a Single Oral Dose of two 1.0 mg 17β-Estradiol/ 90.0 µg Norgestimate RWJPRI Process Tablets, Process Tablets and the Oral Solution (Protocol ESTNRG-PHI-008)

Analyte	Baseline Correction	Parameter	Geometric Mean Solution	Geometric Mean Dry	Unadjusted Ratio (%)	Unadjusted 90% Conf. Limits Lower (%)	Unadjusted 90% Conf. Limits Upper (%)	Adjusted for Drug Content Ratio (%)	Adjusted for Drug Content 90% Conf. Limits Lower (%)	Adjusted for Drug Content 90% Conf. Limits Upper (%)
Estradiol	No	AUC (0-∞)	2236.36	1562.52	69.87	65.36	74.69	68.04	63.65	72.73
		AUC (0-t)	2009.90	1334.27	66.38	62.13	70.94	64.65	60.50	69.08
		C_{max}	488.15	43.06	8.82	7.18	9.96	8.59	7.61	9.70
	Yes	AUC (0-∞)	2053.09	1317.06	64.15	59.62	69.02	62.47	58.06	67.22
		AUC (0-t)	1897.52	1188.97	62.66	58.35	67.29	61.02	56.82	65.53
		C_{max}	486.19	40.90	8.41	7.44	9.52	8.19	7.24	9.27
Estrone	No	AUC (0-∞)	9585.92	9239.82	96.39	92.12	100.86	93.87	89.70	98.22
		AUC (0-t)	8489.28	8171.21	96.25	92.05	100.65	93.73	89.64	98.02
		C_{max}	390.87	340.46	87.10	82.19	92.32	84.83	80.04	89.90
	Yes	AUC (0-∞)	7551.44	7222.80	95.65	90.50	101.09	93.15	88.13	98.44
		AUC (0-t)	7212.14	6866.80	95.21	90.28	100.42	92.72	87.91	97.79
		C_{max}	373.76	324.27	86.76	81.52	92.33	84.49	79.39	89.92
Estrone Sulfate	No	AUC (0-t)	278.63	281.21	100.93	94.55	107.74	98.29	92.07	104.92
		C_{max}	17.78	14.65	82.41	77.25	87.92	80.25	75.23	85.61
	Yes	AUC (0-∞)	268.57	272.46	101.45	93.81	109.71	98.79	91.35	106.84
		AUC (0-t)	239.67	242.82	101.31	94.45	108.67	98.66	91.98	105.83
		C_{max}	17.26	14.12	81.82	76.53	87.48	79.68	74.53	85.19
17d NGM	No	AUC (0-∞)	14280.56	12178.09	85.28	78.93	92.14	82.28	76.15	88.90
		AUC (0-t)	10534.19	8807.69	83.61	77.86	89.78	80.67	75.13	86.62
		C_{max}	1361.68	1001.72	73.56	69.48	77.89	70.98	67.04	75.15
	Yes	AUC (0-∞)	14260.12	11614.53	81.45	74.66	88.85	78.58	72.04	85.72
		AUC (0-t)	10534.19	8542.97	81.10	75.05	87.63	78.25	72.41	84.55
		C_{max}	1361.68	999.01	73.37	69.29	77.68	70.79	66.85	74.95
Norgestrel	No	AUC (0-t)	5738.02	5777.03	100.68	92.39	109.72	97.14	89.14	105.86
		C_{max}	281.30	273.10	97.08	90.29	104.39	93.67	87.11	100.72
	Yes	AUC (0-t)	5738.02	5777.03	100.68	89.24	113.59	97.14	86.10	109.60
		C_{max}	281.30	273.10	97.08	90.57	104.06	93.67	87.39	100.40

Adverse experiences and safety monitoring

Treatment with 17β-estradiol/norgestimate (2 mg/180 µg) administered as process tablets, process tablets, and oral solution was well-tolerated by postmenopausal female subjects. Three (8%) of 36 subjects reported one treatment-emergent adverse event, one in each treatment group. Two subjects reported headaches and one reported breast pain (see Table 12). All three of the adverse events were rated by the investigator as mild in severity; none were serious or necessitated the discontinuation of treatment.
There were no clinically significant prestudy to poststudy changes in physical or gynecological examination findings or in the vital sign measurements. Clinical laboratory abnormalities were unremarkable.

Table 12: Incidence of Treatment-Emergent Adverse Events (Protocol ESTNRG-PHI-008)

Adverse Event	Process Tablet (N=36)	Process Tablet (N=36)	Oral Solution (N=36)	Total (N=36)
Headache	1 (3%)	0 (0%)	1 (3%)	2 (6%)
Female Breast Pain	0 (0%)	1 (3%)	0 (0%)	1 (3%)
Total Number of Subjects With at Least One Adverse Event	1 (3%)	1 (3%)	1 (3%)	3 (8%)

Conclusions: . The rate of absorption of E_2 was much faster from the alcoholic oral solution as compared to the process tablet formulations, resulting in C_{max} values approximately 8 to 12-fold higher than from the tablet formulations, depending on the tablet and whether or not data was baseline corrected. The extent of absorption of E_2 from the tablets relative to the oral solution averaged from 66 to 73% depending on the formulation and whether data was baseline corrected. Similarly, E_2 from the wet process tablet formulation was absorbed more rapidly than from the dry process tablet formulation, resulting in higher C_{max} but not AUC values. Similar results were obtained for 17d-NGM although the difference between the solution and the tablet dosage forms were not as large. Less marked differences were observed for E_1 and E_1S, and essentially no differences between dosage forms were noted for NG.

Bioequivalence between the process tablets relative to the process tablets was not shown in this study.

The results of this study indicate that administration of 17β-estradiol/norgestimate (2 mg/180 µg) as either process tablets, process tablets, or oral solution was safe and well-tolerated by healthy, postmenopausal women.

APPEARS THIS WAY
ON ORIGINAL

DRUG METABOLISM
Department #: DM98355

A SIMULATION OF 17-DEACETYLNORGESTIMATE SERUM CONCENTRATION PROFILES FOR THE CYCLOPHASIC HORMONE REPLACEMENT REGIMEN OF 17β-ESTRADIOL GIVEN ORALLY ONCE DAILY FOR 3 DAYS, FOLLOWED BY THE COMBINATION 17β-ESTRADIOL / NORGESTIMATE REGIMEN GIVEN ONCE DAILY FOR 3 DAYS

SUMMARY

The objective of performing these simulations was to obtain estimates of the 17-deacetylnorgestimate (17d-NGM) serum concentrations which would result from the pulsed dosing of norgestimate (NGM) for 3 days on and 3 days off during the continuous cyclophasic hormone replacement therapy regimen. The cyclophasic regimen consists of 17β-estradiol (E_2) tablets given orally once daily for 3 days, followed by the combination of E_2/NGM tablets given orally once daily for 3 days. The 6-day regimen is repeated continuously in hormone replacement therapy.

Data for the simulations were obtained from the 90-day multiple dose study, ESTNRG-PHI-001, which was conducted in postmenopausal female subjects.[1] Specifically, the mean 17d-NGM serum concentration data from the first dose of NGM given in the study (Study Day 4), and the mean 17d-NGM serum concentration data obtained from the last of the 3-day pulsed NGM doses on the 90th day of the study were utilized to perform the simulations.

In the study, 12 postmenopausal females in each of three dose groups received pulsed NGM dosing regimens of either 30 µg, 90 µg, or 180 µg given together with E_2 in the cyclophasic hormone replacement regimens. The simulation excludes the 180 µg NGM dose group since it has been dropped from development. The simulation analysis centers on the 90 µg NGM dose group because it is the 1 mg/90 µg E_2/NGM tablet strength which will be filed with regulatory agencies for approval. However, the analysis also includes the 30 µg NGM dose group for comparison of 17d-NGM serum concentration profiles.

Simulations were performed by the method of superposition[2] using Microsoft® Excel® software.[3] Declining concentrations of the terminal phases were estimated by regression simulation.

SYNOPSIS

NAME OF SPONSOR/COMPANY: The R.W. Johnson Pharmaceutical Research Institute NAME OF FINISHED PRODUCT: CYCLOPHASIC HRT NAME OF ACTIVE INGREDIENT(S): 17β-estradiol and norgestimate	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: Not Applicable

Title of Study: Effects of Race, Age, and Body Weight on the Pharmacokinetics of 17β-Estradiol, Norgestimate, and Their Metabolites - An Analysis of Data Pooled From Five CYCLOPHASIC HRT Clinical Pharmacokinetic Studies (ESTNRG-PHI-002, 004, 006, 007, and 008).

Investigators: (see individual study reports of clinical studies ESTNRG-PHI-002, 004, 006, 007, and 008).

Study Center(s): (see individual study reports of clinical studies ESTNRG-PHI-002, 004, 006, 007, and 008).

Publication (Reference): Individual study reports of clinical studies ESTNRG-PHI-002, 004, 006, 007, and 008.

Studied Period (years): (see individual study reports of clinical studies ESTNRG-PHI-002, 004, 006, 007, and 008).

Phase of development: 1

Objectives: To evaluate the effects of race, age, and body weight on the pharmacokinetics of 17β-estradiol (E_2) and its metabolites (estrone E_1, estrone sulfate E_1S), norgestimate (NGM) and its metabolites (17deacetyl norgestimate 17d-NGM, and norgestrel NG).

Methodology: The two-stage approach to population pharmacokinetic analysis was used. Individual pharmacokinetics estimates obtained from five single-dose data-rich clinical pharmacokinetics studies were pooled. The pharmacokinetic estimates served as dependent variables in the second stage to evaluate the relationship to the demographic covaraites. The relation between pharmacokinetics and covariates (race, age, and body weight) was analyzed using regression models.

Number of Subjects (planned and analyzed): Data pooled from 161 subjects from 5 studies.

Diagnosis and Main Criteria for Inclusion: Single-dose pharmacokinetic estimates (C_{max} and $AUC_{0\text{-}last}$), with serum drug levels measured from the time study drug was given to 72 hours after dose administration. The diagnosis and main criteria of subject inclusion can be found in individual study reports of clinical studies ESTNRG-PHI-002, 004, 006, 007, and 008.

Test Product, Dose and Mode of Administration, Batch No.: (see individual study reports of clinical studies ESTNRG-PHI-002, 004, 006, 007, and 008).

Duration of Treatment: (see individual study reports of clinical studies ESTNRG-PHI-002, 004, 006, 007, and 008).

Reference Therapy, Dose and Mode of Administration, Batch No.: (see individual study reports of clinical studies ESTNRG-PHI-002, 004, 006, 007, and 008).

Criteria for Evaluation:

Single-dose pharmacokinetics data (C_{max} and $AUC_{0\text{-}last}$) of E_2, NGM, and their metabolites.

Statistical Methods:

Race, age group, and body weight group were used in the analysis as categorical variables. Analysis of variance (ANOVA) models were fitted to the log-transformed pharmacokinetics data with race, age group, and body weight group as factors and the main effects were tested.

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: The R.W. Johnson Pharmaceutical Research Institute NAME OF FINISHED PRODUCT: CYCLOPHASIC HRT NAME OF ACTIVE INGREDIENT(S): 17β-estradiol and norgestimate	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

SUMMARY - CONCLUSIONS

PHARMACOKINETIC RESULTS:

Subjects' age and body weight were similar across studies indicating the feasibility of pooling the data for the population pharmacokinetics analysis. The analysis of the effect of race was restricted to Whites and Hispanics due to the limited number of Blacks and Asians in the five studies. At a 5% level of significance, analysis of variance modeling for E_2, E_1, and E_1S showed no significant race, weight group or age group effects for either $AUC_{0\text{-last}}$ or C_{max}. The analysis of C_{max} of 17d-NGM showed that the race and age group effects were not significant whereas the weight group effect was significant. Analysis of $AUC_{0\text{-last}}$ of 17d-NGM and $AUC_{0\text{-last}}$ and C_{max} of NG showed that the age group effect was not significant, whereas the weight group effect was significant at the 5% level.

PHARMACODYNAMIC RESULTS (If Applicable): Not Applicable.

PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES (If Applicable): Not Applicable.

SAFETY RESULTS (If Applicable): Not Applicable.

CONCLUSION: The analysis results demonstrated that race did not have significant effects on the pharmacokinetics of E_2, NGM, and their metabolites. Postmenopausal women of various age groups (40-50, 51-55, 56-60, 61-70 years) showed no significant difference on the pharmacokinetics of E_2, NGM, and their metabolites. Postmenopausal women of various body weights (<60, 60-80, >80 kg) also showed no significant difference in the pharmacokinetics of E_2 and its metabolites. With respect to the pharmacokinetics of 17d-NGM and NG, there was no significant difference between women of body weight <60 kg and of 60-80 kg; women with body weight higher than 80kg, however, had approximately 40% lower peak serum 17d-NGM and approximately 30% lower peak serum NG concentrations levels. NGM was not measurable in subjects' serum at the doses used in the studies.

Date of the report: