CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-180

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology & Biopharmaceutics Review

NDA:	21-180
Product Trade Name:	ORTHO EVRA™ (norelgestromin & ethinyl estradiol transdermal system)
Active Ingredient/s:	Norelgestromin and ethinyl estradiol (6.0 mg/0.75 mg)
Indication:	Contraception
Submission Dates:	12/21/00 (original NDA)
Sponsor:	R. W. Johnson PRI
Submission/Priority Type:	Original/1S
Reviewer:	Dhruba J. Chatterjee, Ph.D.
Team Leader:	Ameeta Parekh, Ph.D.

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Synopsis

The subject of this submission is ORTHO EVRA™ (referred in this document also as EVRA) a transdermal delivery system for the contraceptive steroid hormones 17-deacetylnorgestimate (norelgestromin, 17d-NGM), the primary active metabolite of the progestin norgestimate (NGM), and ethinyl estradiol (EE). The 7-day EVRA transdermal contraceptive system (the first transdermal contraceptive system seeking market access) is a square, flexible 20 cm^2 system with radius corners. The system contains 6 mg of 17d-NGM and 0.75 mg of EE and designed to deliver to the systemic circulation 0.15 mg 17d-NGM and 0.02 mg EE daily. Three active patches during first three weeks of a cycle (rotated at different application sites) followed by a 'no-patch' week is the recommended regimen. The laminated matrix transdermal system is composed of three distinct layers: a backing layer, a contact adhesive layer containing the active ingredients and excipients, and a disposable film with a release coating.

RECOMMENDATION

From an OCPB perspective, the application is acceptable. There are no outstanding issues at this time.

COMMENTS TO THE SPONSOR

The sponsor is hereby requested to submit data justifying choice of the current dissolution medium (eg. how would the dissolution profile/results appear using conventional aqueous media, or that containing a surfactant, or containing lower concentrations of HP-ß-CD). More data may also be collected describing the complete dissolution profile of the drugs from the patches justifying choice of the time points to set dissolution specifications.

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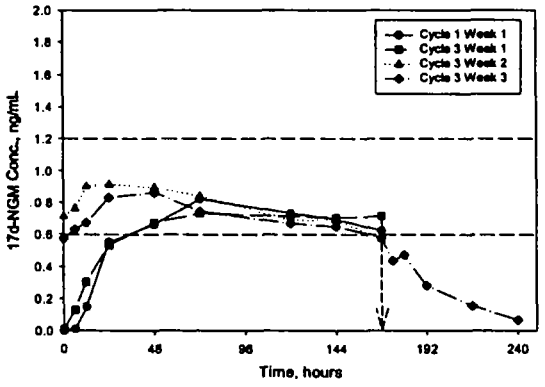
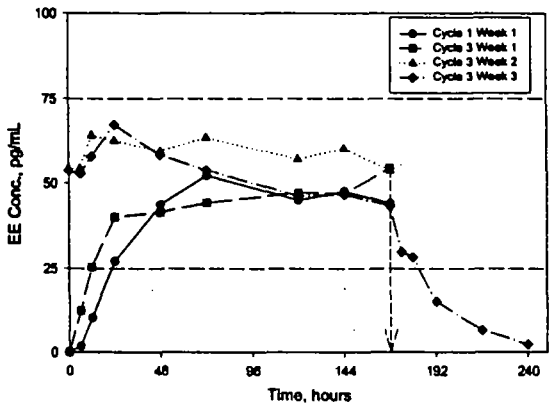
Overall Summary of Clinical Pharmacology and Biopharmaceutics Findings

- The sponsor has submitted satisfactory data to accept 150 µg (for 17d-NGM) and 20 µg (for EE) as daily amounts of drug that are delivered *in vivo*. It may be noted that following the application of the patches, the expected variability in the PK parameters (C_{ss} and AUC) are generally 25 - 45% (CV). Following 7 days of patch wear, approximately 20% of the total amount of drug loaded in the patches is absorbed systemically and approximately 40% is delivered to the skin surface.

- The sponsor has submitted data following administration of combination oral contraceptives (ORTHO-CYCLEN® & ORTHO TRI-CYCLEN®) and has established 'target' C_{ss} values for 17d-NGM and EE for the combination contraceptive to be effective. Those C_{ss} values following administration of ORTHO EVRA™ were within the established target ranges. In addition, independent clinical trials have been conducted in support of safety/efficacy of EVRA.

- Mean 17d-NGM and EE Serum Concentrations (ng/mL) in healthy female volunteers following application of ORTHO EVRA™ on the buttock for three consecutive cycles are shown below. (Dotted horizontal lines indicate the reference 'target' range. Dotted vertical arrow indicates time of patch removal)





- Based on the instructions to the patients, the longest time a patient may be on one patch is 9 days during weeks 2 and 3 of a cycle (for unavoidable circumstances). The sponsor conducted a study to show that a patch worn for 10 days instead of the prescribed 7 days might maintain the necessary contraceptive efficacy. A section in the label claims that continuing on a patch beyond day 7 (till day 10) may not be associated with a clinical difference in efficacy. While the above may be true, the *mean* C_{ss} levels on day 10 are at the lower end of the established targets. Therefore, necessary changes are made in this section of the label to reflect that, under any circumstances, patch use beyond day 9 may not ensure continued efficacy.

- One study comparing the relative exposures of the drugs from different sites showed lower exposure from the abdomen when compared to the other three sites (buttocks, torso and the arm were bioequivalent among themselves). However, sponsor's claim that applying the patches either on the buttocks, abdomen, torso or the arm may be insignificant, is acceptable based on the following:
  - another study comparing the exposure from the abdomen and the buttocks showed appreciably higher exposure from the abdomen (higher than the buttock),
  - C_{ss} values following application in the abdomen is comparable to those obtained at the other sites, and
  - among over 70,000 patches used in the pivotal clinical trials, approximately 30 % of those were used in the abdomen and 50 % in the buttocks. The Medical Officer confirms that the few pregnancies occurring in these pivotal trials could not be associated with any specific trend based on the site of application.

- Use of the patches under different external conditions (commonly found in health clubs) such as normal activity, sauna (10 minutes), whirlpool (10 minutes), cool water bath (up to 30 minutes), treadmill (20 to 30 minutes), and combination may not affect the pharmacokinetic performance of the patches. Marginally higher exposure only for EE was observed for most of the conditions.

- The adhesion of the patches from the phase 3 and phase 1 studies appear acceptable. A relatively low % of patients had either partial or complete 'falling-off' of patches. If the patient experiences problems with adhesion, a new replacement patch may immediately be applied without any expected differences in contraceptive efficacy/safety.

- There is a decreasing trend of exposure to the drugs with increasing age, body weight and body surface area. Five of the 15 pregnancies that occurred in the clinical trials were observed in women weighing > 198 lbs. (90 Kgs.) [this information is in the label]. Since only one dose was studied in the pivotal clinical trials, dose adjustment is neither an option, nor recommended.

- The clinical trial and to-be-marketed formulations (manufactured by) were identical. The alternate manufacturing site ( ) is not acceptable, as the formulation was not bioequivalent to the clinical trial (to-be-marketed) formulation for EE (90% CI for C_{max}, AUC and C_{ss} ranged between .

- Significant changes in sponsor-proposed dissolution specifications have been recommended in this review. These specifications have been accepted by the sponsor as of 11/16/2001.

Background

Questions addressed in this section:

- ***What are the highlights of chemistry and formulation of the drug and drug product?***
- ***What is the mechanism of action, proposed indication and main goal of therapy?***
- ***What are other drugs available in this class?***
- ***What are some highlights of claims for this product in the proposed label?***

The subject of this submission is EVRA™, a transdermal delivery system for the contraceptive steroid hormones 17-deacetylnorgestimate (17d-NGM), the primary active metabolite of the progestin norgestimate (NGM), and ethinyl estradiol (EE). The 7-day EVRA transdermal contraceptive system is a square, flexible 20 cm^2 system with radius corners. The system contains 6 mg of 17d-NGM and 0.75 mg of EE and designed to deliver to the systemic circulation 0.15 mg 17d-NGM and 0.02 mg EE daily. The laminated matrix system is composed of three distinct layers: a backing layer, a contact adhesive layer containing the active ingredients and excipients, and a disposable film with a release coating. The composition of the 20 cm^2 of EVRA™ Transdermal Contraceptive System follows:

Table 1.

Quantitative Target Composition				
			Unit Formula	
Component	*Reference*	*Role*	*% w/w*	*Weight/Patch*
Drug Substances				
Norelgestromin (17d-NGM)	In-House	Progestogen		
Ethinyl Estradiol, micronized	USP and EP	Estrogen		
Excipients				
Polyisobutylene/Polybutene	In-House	Adhesive		
Lauryl Lactate[b]	In-House	Solvent/		
Crospovidone, micronized	NF and EP	Hydrophilic		
Total Adhesive Matrix				
Polyester Non-Woven	In-House	Structural		
Polyester Backing Film	In-House	Backing		
Total Patch Weight				
Polyester Release Liner	In-House	Protection		

[a] are evaporated during the manufacturing process and do not contribute substantially to the final composition of the transdermal system.
[b] Quantity refers to the lauryl lactate mixture in the final product.

The formulation used in the Phase 3 studies is identical to the formulation proposed for marketing. Based on the data submitted, approximately 18 % (17d-NGM) - 19 % (EE) of the total drug in the patches is absorbed *in vivo* in the 7 days of patch wear.

Combinations of progestins and estrogens act as contraceptives by preventing ovulation. The inhibition of ovulation is achieved by blocking the release of both follicular stimulating hormone (FSH) and luteinizing hormone (LH) by means of negative feedback effects on both the pituitary gland and hypothalamus. The predominant effect of estrogen is to inhibit the secretion of FSH while continued action of progestogen serves to inhibit the release of LH. Ovulation can possibly be prevented either by inhibiting the ovulatory stimulus or by preventing the growth of follicles.

Measurements of circulating FSH and LH show that estrogen-progestogen combinations suppress both hormones. The estrogen also stabilizes the uterine lining (the endometrium) so that irregular shedding and unwanted breakthrough bleeding does not occur. The progestogen ensures that withdrawal bleeding will be prompt, brief, and essentially physiological. Hence, serum levels of the drug molecules and their metabolites were monitored for PK parameters. LH, FSH and progesterone levels are often monitored to evaluate PD characteristics (surrogate for suppression of ovulation). The clinical end point, as monitored in the pivotal trials, is prevention of pregnancy.

The proposed indication for this product is contraception. Healthy females during their reproductive age are the target population for this product. Goal of this product is to preclude pregnancy with an acceptable safety profile.

The majority of the oral contraceptive 'pills' available in the market consists of a combination of estrogens and progestins. With time, the doses of both the components have reduced. The same sponsor has a two such marketed pills available for contraception - ORTHO-CYCLEN® and ORTHO TRI-CYCLEN®. The uniqueness of this current product under review is that this is the first transdermal hormonal system that is designed for contraception.

The sponsor claims high effectiveness from this product (0.6 – 0.8 % users experienced unintended pregnancy in the first year of use, depending on typical or perfect use), comparable to combination oral contraceptives and certain intra-uterine devices available for the same indication. Additionally, sponsor claims that applications of this transdermal delivery system applied to the buttock, abdomen, upper outer arm or upper torso (excluding breast) were therapeutically equivalent. Labeling also claims no performance differences following use of this product in the sauna, whirlpool, on a treadmill and during a cold water bath.

Information from 10 clinical pharmacology studies and additional literature reports have been submitted in support of this NDA. This CPB review follows a 'Question-Based' format, addressing questions relevant to this application.

Clinical Pharmacology

Q1. ***Were appropriate clinical endpoints, surrogate endpoints or pharmacodynamic (PD) biomarkers selected, adequately measured and used to assess efficacy and safety in clinical pharmacology studies?***

The clinical end point for the pivotal clinical trials were occurrence of pregnancy. In general, the level of serum progesterone (whether < or > 3-5 ng/ml) serves as a surrogate end point for indication of ovulation suppression. Although no formal exposure-response analysis report was submitted to Section 6 of this NDA, in one study report submitted only to the clinical section, the sponsor has evaluated the effect of transdermal dose (from different patch sizes) on the serum levels of progesterone and general markers of efficacy and safety.

Q2. ***Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?***

Yes. 17-d NGM and its primary active metabolite, NG, and EE were adequately identified and measured in all PK studies. A summary of the analytical validations is presented in a later section.

Q3. ***What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?***

a) Based on PK parameters, what is the degree of linearity or non-linearity in the dose-concentration relationship?

A randomized, open-label, single-center, three-way crossover study (# NRGEEP-PHI-006) was conducted to assess the dose proportionality of three sizes of the transdermal contraceptive system, namely 10 cm^2 (containing 3.0 mg 17d-NGM and 0.38 mg EE), 15 cm^2 (containing 4.5 mg 17d-NGM and 0.56 mg EE), and 20 cm^2 (containing 6.0 mg 17d-NGM and 0.75 mg EE). Data from the study is presented below:

Table 2a: Mean (±SD) Pharmacokinetic Parameters for 17d-NGM, NG, and EE by Transdermal Contraceptive System Size (Study NRGEEP-PHI-006)

Parameter	10 cm^2		15 cm^2		20 cm^2	
17d-NGM						
C_{max} (ng/mL)	0.54	(0.20)	0.71	(0.25)	0.95	(0.26)
t_{max} (h)	111	(41.7)	108	(45.9)	95.4	(42.2)
$C^{ss}_{48\text{-}168h}$ (ng/mL)	0.46	(0.16)	0.62	(0.21)	0.83	(0.21)
$AUC_{0\text{-}168h}$ (ng·h/mL)	68.8	(24.1)	92.5	(33.2)	123	(32.3)
$AUC_{0\text{-}240h}$ (ng·h/mL)	81.2	(27.7)	110	(37.9)	146	(37.9)
$t_{½}$ (h)	30.8	(10.6)	32.9	(20.2)	28.3	(9.97)
NG						
C_{max} (ng/mL)	0.88	(0.48)	1.28	(0.51)	1.84	(0.69)
t_{max} (h)	168	(18.8)	175	(7.22)	173	(13.2)
C_{avg} (ng/mL)	0.48	(0.24)	0.65	(0.25)	0.92	(0.37)
$AUC_{0\text{-}168h}$ (ng·h/mL)	67.8	(39.3)	91.8	(40.7)	137	(59.2)
$AUC_{0\text{-}240h}$ (ng·h/mL)	112	(63.0)	155	(66.4)	232	(93.4)
$t_{½}$ (h)	63.6	(39.1)	49.3	(31.2)	52.3	(27.9)
EE						
C_{max} (pg/mL)	34.0	(14.5)	47.8	(18.9)	70.7	(33.2)
t_{max} (h)	78.0	(40.4)	82.8	(38.8)	71.2	(30.4)
$C^{ss}_{48\text{-}168h}$ (pg/mL)	28.1	(10.7)	40.2	(13.9)	56.7	(22.6)
$AUC_{0\text{-}168h}$ (pg·h/mL)	4253	(1668)	6022	(2181)	8543	(3488)
$AUC_{0\text{-}240h}$ (pg·h/mL)	4663	(1786)	6657	(2372)	9395	(3828)
$t_{½}$ (h)	18.9	(8.77)	16.7	(4.23)	17.4	(4.07)

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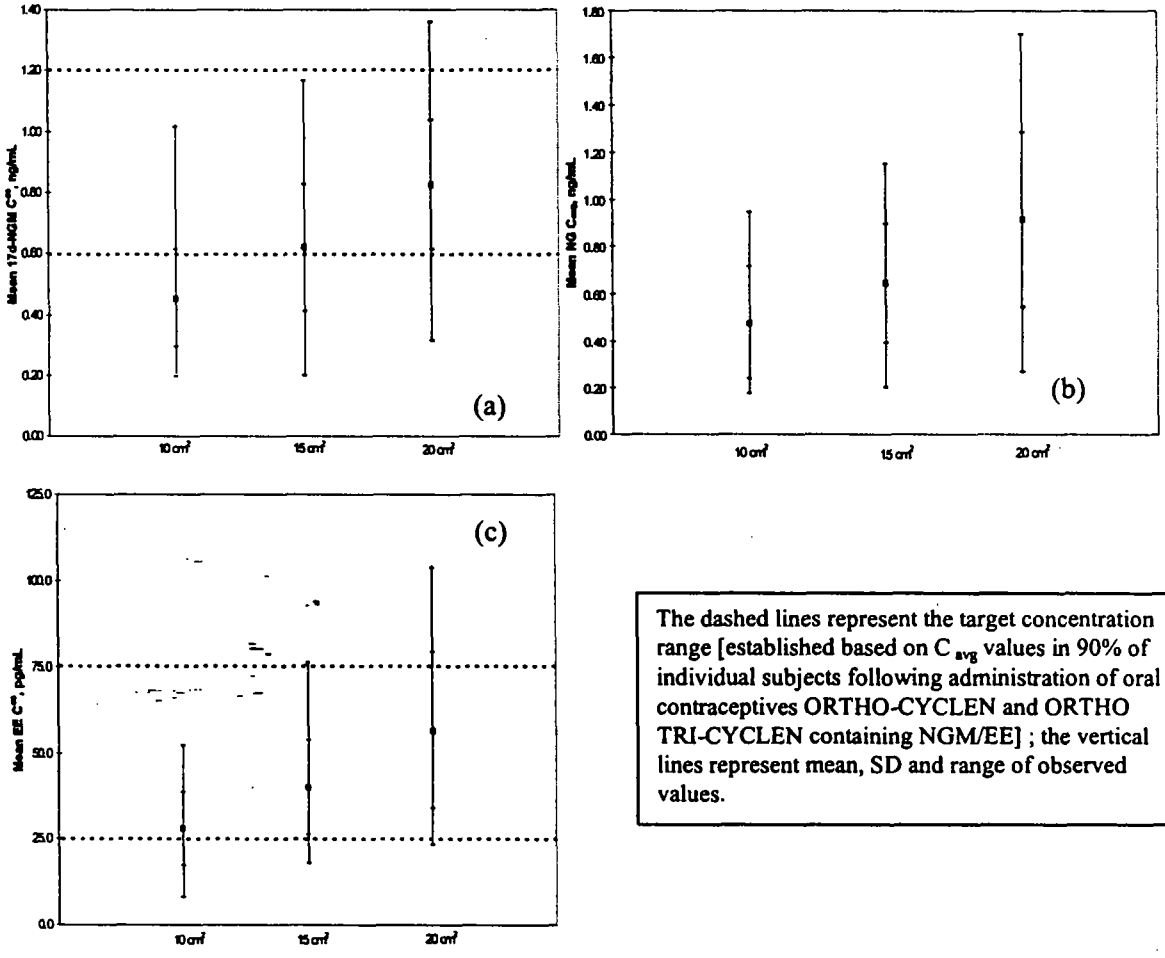
Table 2b: 90% Confidence Intervals for the Ratio of Means (Study NRGEEP-PHI-006)

Analyte	Normalized Parameter[a]	Ratio[b] (%)	($10\ cm^2/20\ cm^2$) Lower and Upper Confidence Intervals (%)	Ratio[b] (%)	($15\ cm^2/20\ cm^2$) Lower and Upper Confidence Intervals (%)	Ratio[b] (%)	($10\ cm^2/15\ cm^2$) Lower and Upper Confidence Intervals (%)
17d-NGM	AUC_{0-240h}	111.44	103.51	99.17	92.11	112.38	104.38
			119.99		106.77		121.00
	C^{ss}	110.41	102.56	99.43	92.36	111.04	103.14
			118.87		107.05		119.55
NG	AUC_{0-240h}	93.54	84.53	89.96	81.30	103.98	93.96
			103.51		99.55		115.06
	C_{avg}	103.96	94.53	96.2	87.47	108.07	98.26
			114.33		105.80		118.85
EE	AUC_{0-240h}	100.09	93.25	97.67	91.00	102.50	95.48
			107.42		104.82		109.99
	C^{ss}	99.65	92.83	97.28	90.62	102.43	95.42
			106.98		104.44		109.96

[a] Geometric means are normalized to a size of $20\ cm^2$.
[b] Ratio of geometric means.

Figure 1: Mean (a) 17d-NGM, (b) NG and (c) EE Steady-State Serum Concentrations in 28 Healthy Female Volunteers Following Single Application of a Transdermal Contraceptive System of 17d-NGM and EE for One Week (Study NRGEEP-PHI-006)



The dashed lines represent the target concentration range [established based on C_{avg} values in 90% of individual subjects following administration of oral contraceptives ORTHO-CYCLEN and ORTHO TRI-CYCLEN containing NGM/EE] ; the vertical lines represent mean, SD and range of observed values.

Based on the above information, and plots presented by the sponsor on normalized AUC values (not included herein), it may be concluded that the three sizes of the transdermal systems exhibit linear PK, but does not appear to be truly proportional. The proposed product for the market being only the 20 cm^2 patch (evaluated separately for clinical safety and efficacy), linearity and/or proportionality may not be a critical issue.

b) How do PK parameters change with time following chronic dosing?

With the final formulation, sponsor presented results from one single-dose and two multiple-dose studies.

Study NRGEEP-PHI-003 was a single-center, open-label study to determine the safety and pharmacokinetics of 17d-NGM, NG, and EE in 18 healthy female volunteers following a single application of EVRA™ for 1 week. Serial blood sampling was performed from day 1 – 13. The patches were removed after the 168-h sampling point. Following are the results:

Figure 2: Mean 17d-NGM, NG and EE Serum Concentrations (ng/mL) vs. Time in Healthy Female Volunteers Following a Single Application of a Transdermal Contraceptive System of 17d-NGM and EE (Study NRGEEP-PHI-003)

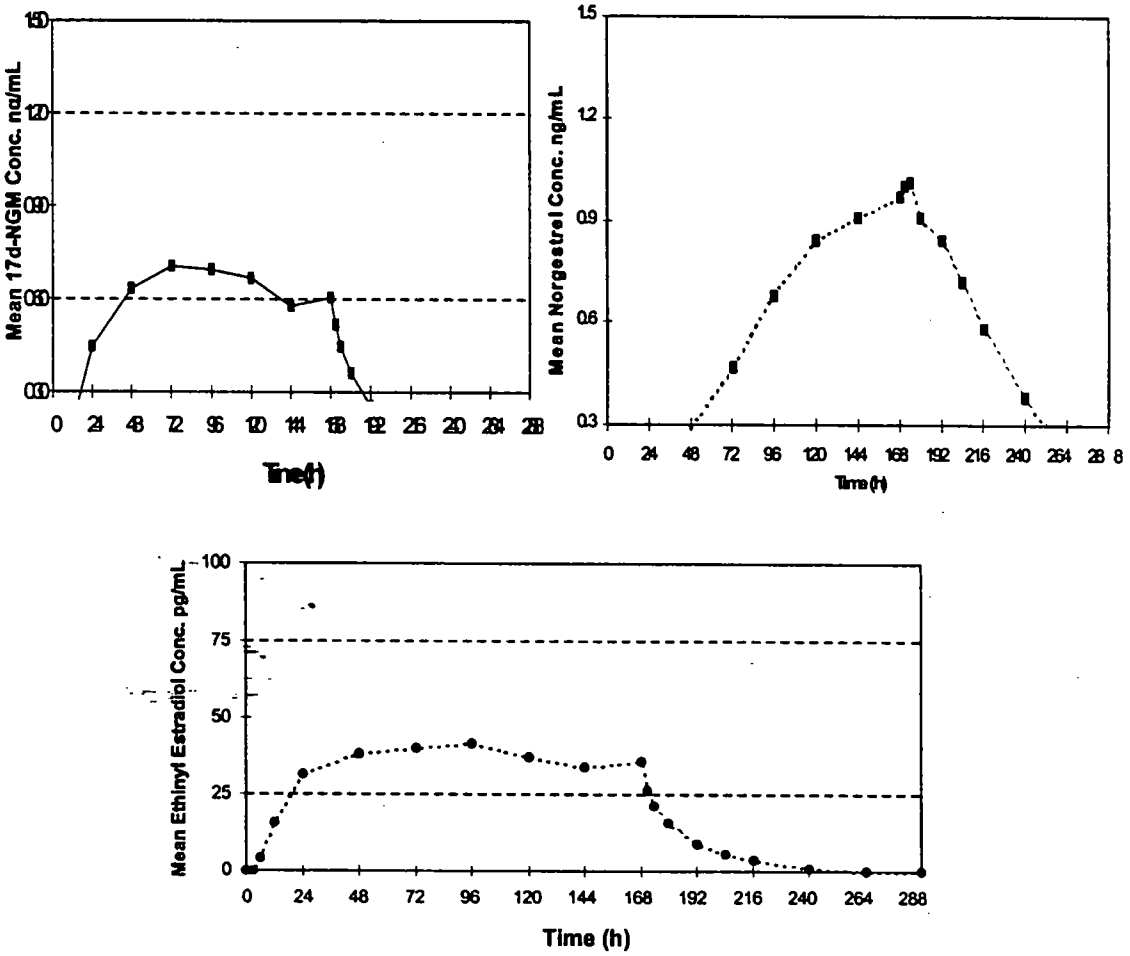


Table 3: Mean Pharmacokinetic Parameters in Healthy Female Volunteers Following a Single Application of a Transdermal Contraceptive System of 17d-NGM and EE for One Week (Study NRGEEP-PHI-003)

	C^{ss} [a] (ng/mL)	AUC_{0-168} (ng·h/mL)	AUC_{0-288} (ng·h/mL)	$t_{1/2}$ (h)
17d-NGM				
Mean	0.65	96.0	111	24.5
SD	0.20	31.1	35.2	6.77
% CV	30.0	32.4	31.7	27.6
NG				
Mean	0.68[b]	89.6	152	39.0
SD	0.34	49.7	86.0	17.2
% CV	50.2	55.4	56.7	44.0
EE				
Mean	38.1[c]	5749[d]	6383[d]	16.8
SD	12.7	1960	2119	4.22
% CV	33.4	34.1	33.2	25.1

[a] Average serum concentrations at plateau (48/72-168 h) .
[b] Steady state not attained; value is mean of all measurable concentrations .
[c] pg/mL
[d] pg·h/mL

In Study NRGEEP-PHI-005, 12 non-pregnant women were studied with multiple doses of the EVRA patch: first patch for 7 days, the second for 10 days. The following are the results:

Figure 3: Mean Serum Concentrations of 17d-NGM, NG, and EE vs. Time in Healthy Female Volunteers Following Consecutive Application of TD Contraceptive Systems of 17d-NGM/EE for 7 and 10 Days (Study NRGEEP-PHI-005)

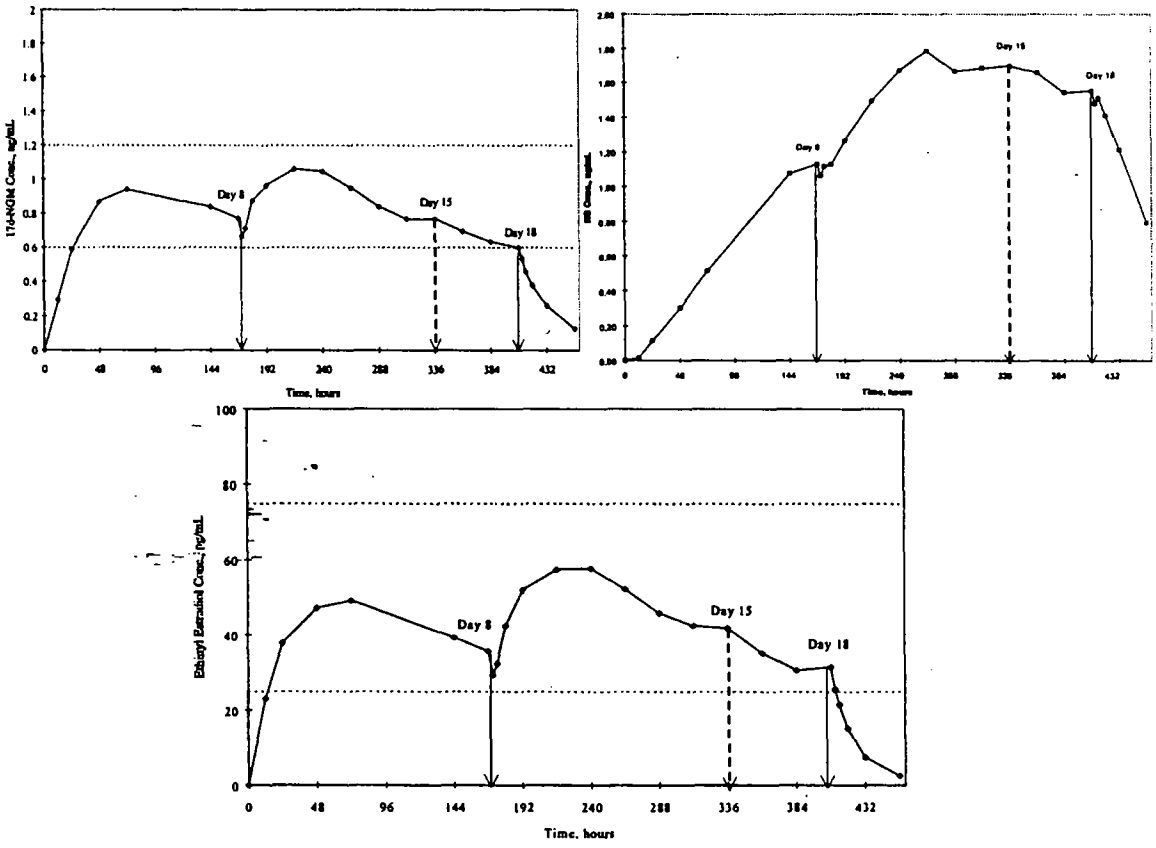


Table 4: Mean (SD) Pharmacokinetic Parameters Obtained from 12 Healthy Women Wearing Two Consecutive EVRA™ Patches[a] (Study NRGEEP-PHI-005)

	C^{ss}(ng/mL)			AUC (ng·h/mL)				
	48-168 (h)	192-336 (h)	192-408 (h)	0-456 (h)	0-168 (h)	168-336 (h)	168-408 (h)	$t_{½}$ (h)
17d-NGM	0.85	0.93	0.84	347	130	155	203	25.8
	(0.39)	(0.35)	(0.30)	(140)	(63.2)	(58.7)	(74.3)	(14.9)
NG	0.45[b]	1.43[c]	1.46[d]	538	100	265	381	47.1
	(0.25)	(0.68)	(0.67)	(249)	(56)	(124)	(171)	(22.7)
EE	42.9[e]	50.7[e]	45.0[e]	18108[f]	6769[f]	8353[f]	10816[f]	13.7
	(18.1)	(18.6)	(15.0)	(6754)	(3083)	(3098)	(3695)	(3.30)

[a] First patch worn for 7 days; second for 10 days, [b] 0-168 h, [c] 168-336 h, [d] 168-408 h, [e] pg/mL, [f] pg·h/mL

In Study NRGEEP-PHI-013, 24 healthy women were studied with multiple doses of the EVRA patches for three consecutive weeks per cycle for three cycles. Additionally, volunteers were randomized to apply the patches either to the abdomen or the buttocks. Results follow:

Table 5: Mean (±SD) Pharmacokinetic Parameters in Healthy Female Volunteers Following Application of a Transdermal Contraceptive System of 17d-NGM and EE for Three Consecutive Cycles; Subjects Randomized to **Abdomen** (Study NRGEEP-PHI-013)

Parameter	Week 1 of Cycle 1	Week 1 of Cycle 3	Week 2 of Cycle 3	Week 3 of Cycle 3
17d-NGM				
t_{max} (h)	72.0 (33.9)	85.2 (37.8)	44.7 (18.7)	45.8 (44.4)
C_{max} (ng/mL)	0.87 (0.44)	1.08 (0.87)	1.17 (0.76)	1.14 (0.52)
$C^{ss}_{48\text{-}168h}$ (ng/mL)	0.65 (0.27)	0.82 (0.56)	0.80 (0.37)	0.81 (0.32)
C_{min} (ng/mL)	0.50 (0.24)	0.67 (0.41)	0.64 (0.27)	0.67 (0.27)
$AUC_{0\text{-}168h}$ (ng·h/mL)	102 (40.6)	130 (93.3)	142 (73.2)	141 (59.0)
NG				
t_{max} (h)	147 (49.1)	153 (19.4)	125 (42.2)	85.1 (60.1)
C_{max} (ng/mL)	1.04 (0.73)	1.56 (1.06)	2.70 (1.81)	2.99 (1.70)
C_{avg} (ng/mL)	0.66 (0.36)	1.05 (0.71)	2.18 (1.44)	2.46 (1.27)
C_{min} (ng/mL)	1.03 (0.74)	1.50 (0.97)	2.22 (1.22)	2.28 (1.08)
$AUC_{0\text{-}168h}$ (ng·h/mL)	91.5 (59.4)	165 (124)	367 (242)	414 (213)
EE				
t_{max} (h)	101 (39.2)	83.1 (39.3)	68.7 (55.3)	53.5 (39.9)
C_{max} (pg/mL)	74.0 (20.3)	72.6 (23.8)	79.4 (29.2)	95.7 (25.7)
$C^{ss}_{48\text{-}168h}$ (pg/mL)	57.7 (8.64)	56.7 (17.3)	61.6 (19.8)	71.1 (20.4)
C_{min} (pg/mL)	49.5 (9.72)	50.1 (15.5)	54.1 (17.7)	57.4 (18.5)
$AUC_{0\text{-}168h}$ (pg·h/mL)	8728 (1495)	8935 (3088)	10407 (3683)	12139 (3241)

Table 6: Mean Sex Hormone Binding Globulin Concentrations (nmol/L) in Healthy Female Volunteers Following Application of a Transdermal Contraceptive System of 17d-NGM and EE for Three Consecutive Cycles; Subjects Randomized to Abdomen (Study NRGEEP-PHI-013)

	Prestudy	Cycle 1 Day 1	Cycle 1 Day 22	Cycle 2 Day 1	Cycle 2 Day 22	Cycle 3 Day 1	Cycle 3 Day 22
Mean	18.5	32.2	147	108	146	104	148
SD	12.8	17.2	40.9	35.1	45.8	34.5	44.8
% CV	69.0	53.3	27.9	32.6	31.5	33.0	30.3

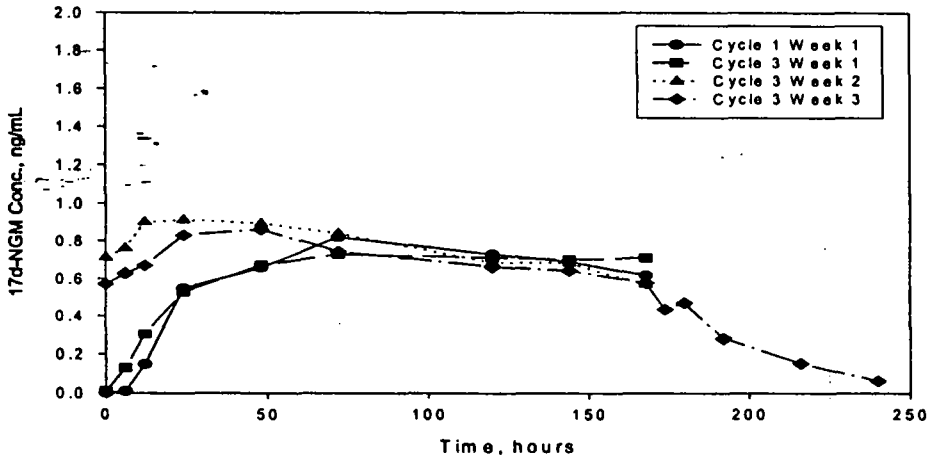
Table 7: Mean (±SD) Pharmacokinetic Parameters in Healthy Female Volunteers Following Application of a Transdermal Contraceptive System of 17d-NGM and EE for Three Consecutive Cycles; Subjects Randomized to **Buttock** (Study NRGEEP-PHI-013)

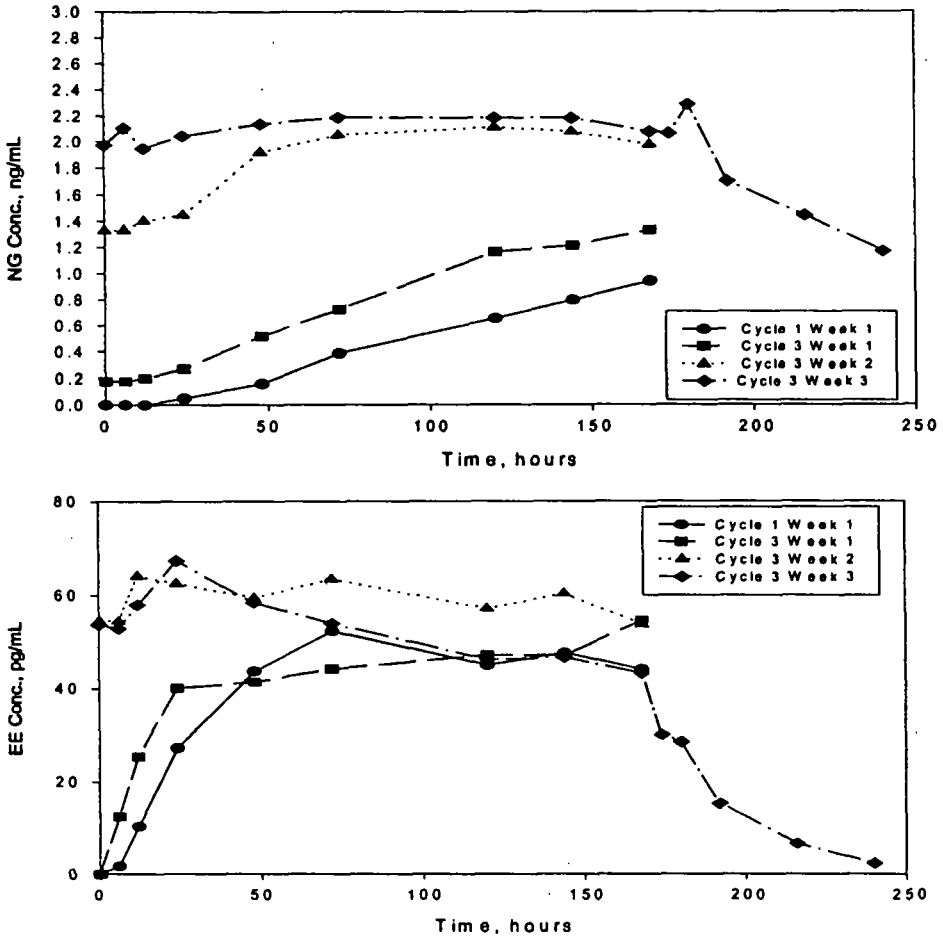
Parameter	Week 1 of Cycle 1	Week 1 of Cycle 3	Week 2 of Cycle 3	Week 3 of Cycle 3
17d-NGM				
t_{max} (h)	105 (34.7)	122 (45.1)	41.0 (40.1)	51.0 (41.6)
C_{max} (ng/mL)	0.86 (0.38)	0.89 (0.31)	1.08 (0.42)	0.96 (0.36)
$C^{ss}_{48\text{-}168h}$ (ng/mL)	0.70 (0.28)	0.70 (0.29)	0.80 (0.23)	0.70 (0.32)
C_{min} (ng/mL)	0.62 (0.27)	0.71 (0.30)	0.57 (0.25)	0.58 (0.32)
$AUC_{0\text{-}168h}$ (ng·h/mL)	107 (44.2)	105 (45.5)	132 (57.1)	120 (52.8)
NG				
t_{max} (h)	157 (28.8)	154 (19.0)	115 (53.5)	106 (60.7)
C_{max} (ng/mL)	1.00 (0.30)	1.37 (0.78)	2.34 (1.32)	2.78 (1.50)
C_{avg} (ng/mL)	0.57 (0.15)	0.90 (0.42)	1.88 (1.07)	2.14 (1.22)
C_{min} (ng/mL)	0.94 (0.33)	1.33 (0.76)	1.97 (1.17)	2.07 (1.30)
$AUC_{0\text{-}168h}$ (ng·h/mL)	72.4 (20.5)	131 (77.0)	315 (180)	359 (207)
EE				
t_{max} (h)	113 (38.9)	128 (47.3)	49.1 (46.1)	60.0 (59.2)
C_{max} (pg/mL)	56.8 (23.1)	64.3 (20.0)	83.8 (26.5)	78.0 (43.2)
$C^{ss}_{48\text{-}168h}$ (pg/mL)	46.4 (17.9)	47.6 (17.3)	59.0 (25.1)	49.6 (27.0)
C_{min} (pg/mL)	44.0 (17.9)	54.5 (19.0)	53.6 (24.0)	43.2 (19.0)
$AUC_{0\text{-}168h}$ (pg·h/mL)	6796 (2673)	7160 (2893)	10054 (4205)	8840 (5176)

Table 8: Mean Sex Hormone Binding Globulin Concentrations (nmol/L) in Healthy Female Volunteers Following Application of a Transdermal Contraceptive System of 17d-NGM and EE for Three Consecutive Cycles; Subjects Randomized to Buttock (Study NRGEEP-PHI-013)

	Prestudy	Cycle 1 Day 1	Cycle 1 Day 22	Cycle 2 Day 1	Cycle 2 Day 22	Cycle 3 Day 1	Cycle 3 Day 22
Mean	21.9	34.7	139	107	129	95.4	143
SD	12.0	20.5	21.3	24.7	40.8	31.5	29.7
% CV	55.0	59.2	15.4	23.0	31.7	33.0	20.8

Figure 4: Mean Serum Concentrations of 17d-NGM (ng/mL), NG (ng/ml) and EE (pg/ml) in Healthy Female Volunteers Following Application of a Transdermal Contraceptive System of 17d-NGM and EE for Three Consecutive Cycles; Subjects Randomized to Buttock (Study NRGEEP-PHI-013)





Reviewer's comments:

The following may be concluded from a comparison of the three studies above:

- No significant accumulation was observed for 17d-NGM and EE beyond 1 week of application.
- Observed PK parameters for 17d-NGM and EE did not differ much between each of the 3 weeks of cycle 3.
- SHBG levels increased each cycle between weeks 1 and 3, and dropped during the 4th week.
- Metabolite NG levels show signs of accumulation between weeks 1 of cycle 1 and 3 (< 2 folds). Since the study was not designed to continue till all the metabolites achieved steady state, it was difficult to assess the time for NG to achieve steady state. Moreover, due to significant binding of NG to SHBG (unlike 17d-NGM), the NG levels elevated with the elevation of SHBG between weeks 1 – 3 of each cycle. This was a direct result of induction of SHBG levels by EE.
- Exposure of the drug and metabolites was observed to be partially higher following administration in the abdomen as compared to the buttocks. However, this may not be of significant clinical relevance (see later for Study NRGEEP-PHI-004 conclusions).
- From figure 3 it is evident that the *mean* serum levels of EE and particularly 17d-NGM are just around the lower range for optimum efficacy on days 9-10. Hence, it may not be advisable to

suggest that contraceptive efficacy will be optimum beyond day 7 if a patient uses a patch for 10 days instead of the intended 7 days.

c) *Is the dose and dosing regimen consistent with the known relationship between dose-concentration-response?*

No formal dose/concentration-response studies were conducted with this product. The sponsor has re-submitted two studies describing the PK of 17d-NGM and EE following administration of oral tablets containing either a) 250 mg of NGM (*not 17d-NGM*) & 0.035 mg EE administered daily for 21 days (ORTHO-CYCLEN®; protocol NRGMON-OC-402) or b) 0.180 mg NGM/0.035 mg EE for days 1-7, 0.215 mg NGM/0.035 mg EE for days 8-14 and 0.250 mg NGM/0.035 mg EE for days 15-21 (ORTHO TRI-CYCLEN®; protocol NRGTRI-OC-115). From these two studies they have attempted to identify the effective serum concentration range for both 17d-NGM and EE ensuring optimum efficacy. The following were the results:

Table 9: Mean (±SD) Pharmacokinetic Parameters of 17d-NGM in Normal Female Volunteers Following Oral Administration of ORTHO-CYCLEN ® for Three Cycles (Study NRGMON-OC-402)

	Day 1 of Cycle 1	Day 21 of Cycle 3
17d-NGM		
C_{max} (ng/mL)	1.78 (±0.397)	2.19 (±0.655)
t_{max} (h)	1.19 (±0.250)	1.43 (±0.680)
$AUC_{0\text{-}24h}$ (ng·h/mL)	9.90 (±3.25)	18.1 (±5.53)
$AUC_{0\text{-}\infty}$ (ng·h/mL)	14.8 (±5.10)	33.6 (±13.8)
CL/F (L/h)	18.4 (±5.09)	15.1 (±4.78)
CL/F (L/h/kg)	0.31 (±0.084)	0.25 (±0.071)
Vd/F (L)	135 (±34.5)	129 (±42.2)
Vd/F (L/kg)	2.28 (±0.531)	2.17 (±0.545)
$t_{½}$ (h)	18.4 (±5.91)	24.9 (±9.04)
NG		
C_{max} (ng/mL)	0.649 (±0.485)	2.65 (±1.11)
t_{max} (h)	1.42 (±0.690)	1.67 (±1.32)
$AUC_{0\text{-}24h}$ (ng·h/mL)	6.22 (±2.46)	48.2 (±20.5)
$AUC_{0\text{-}\infty}$ (ng·h/mL)	17.2 (±8.65)	148 (±66.4)
CL/F (L/h)	17.6 (±7.23)	6.30 (±3.21)
CL/F (L/h/kg)	0.29 (±0.109)	0.11 (±0.059)
Vd/F (L)	181 (±75.8)	69.5 (±33.4)
Vd/F (L/kg)	2.96 (±1.18)	1.18 (±0.600)
$t_{½}$ (h)	37.8 (±14.0)	45.0 (±20.4)
EE		
C_{max} (pg/mL)	92.2 (±24.5)	147.(±41.5)
t_{max} (h)	1.2 (±0.26)	1.13 (±0.23)
$AUC_{0\text{-}24h}$ (pg·h/mL)	629 (±138)	1210 (±294)
$AUC_{0\text{-}\infty}$ (pg·h/mL)	728.(±179)	1770.(±572)
CL/F (L/h)	51.7 (±17.2)	31.1 (±9.96)
CL/F (L/h/kg)	0.87 (±0.236)	0.53 (±0.17)
Vd/F (L)	355 (±75.8)	250 (±63.3)
Vd/F (L/kg)	6.03 (±1.17)	4.26 (±1.14)
$t_{½}$ (h)	10.1 (±1.90)	15.0 (±2.36)

Table 10: Mean (±SD) Pharmacokinetic Parameters in Normal Female Volunteers Following Oral Administration of ORTHO TRI-CYCLEN ® for Three Cycles (Study NRGTRI-OC-115)

NGM Dose	Day 7 (Cycle 3) 0.180 mg Days 1-7	Day 14 (Cycle 3) 0.215 mg Days 8-14	Day 21 (Cycle 3) 0.250 mg Days 15-21
17d-NGM			
C_{max} (ng/mL)	1.80 (±0.46)	2.12 (±0.56)	2.66 (±0.47)
t_{max} (h)	1.42 (±0.73)	1.21 (±0.26)	1.29 (±0.26)
$AUC_{0\text{-}24\,h}$ (ng·h/mL)	15.0 (±3.88)	16.1 (±4.97)	21.4 (±3.46)
CL/F (L/h)	12.6 (±3.49)	14.9 (±5.45)	12.0 (±1.79)
CL/F (L/h/kg)	0.21 (±0.05)	0.25 (±0.08)	0.20 (±0.04)
Terminal $t_{½}$ (h)	NC	NC	22.3 (±6.54)
NG			
C_{max} (ng/mL)	1.94 (±0.82)	3.00 (±1.04)	3.66 (±1.15)
t_{max} (h)	3.15 (±4.05)	2.21 (±2.03)	2.58 (±2.97)
$AUC_{0\text{-}24\,h}$ (ng·h/mL)	34.8 (±16.5)	55.2 (±23.5)	69.3 (±23.8)
CL/F (L/h)	6.54 (±3.46)	4.98 (±3.07)	4.10 (±1.64)
CL/F (L/h/kg)	0.10 (±0.04)	0.08 (±0.04)	0.07 (±0.03)
Terminal $t_{½}$ (h)	NC	NC	40.2 (±15.4)
EE[a]			
C_{max} (pg/mL)	124 (±39.5)	128 (±38.4)	126 (±34.7)
t_{max} (h)	1.27 (±0.26)	1.32 (±0.25)	1.31 (±0.56)
$AUC_{0\text{-}24\,h}$ (pg·h/mL)	1130 (±420)	1130 (±324)	1090 (±359)
CL/F (L/h)	35.0 (±12.9)	32.9 (±7.95)	36.0 (±13.5)
CL/F (L/h/kg)	0.57 (±0.22)	0.56 (±0.16)	0.60 (±0.22)
Terminal $t_{½}$ (h)	NC	NC	15.9 (±4.39)

[a] 0.035 mg EE on Days 1 to 21

NC = not calculated

Figure 5: Mean 17d-NGM, NG and EE Serum Concentrations vs. Time on Days 7, 14, and 21 of Cycle 3 Following Oral Administration of ORTHO TRI-CYCLEN ® for Three Cycles (Study NRGTRI-OC-115)

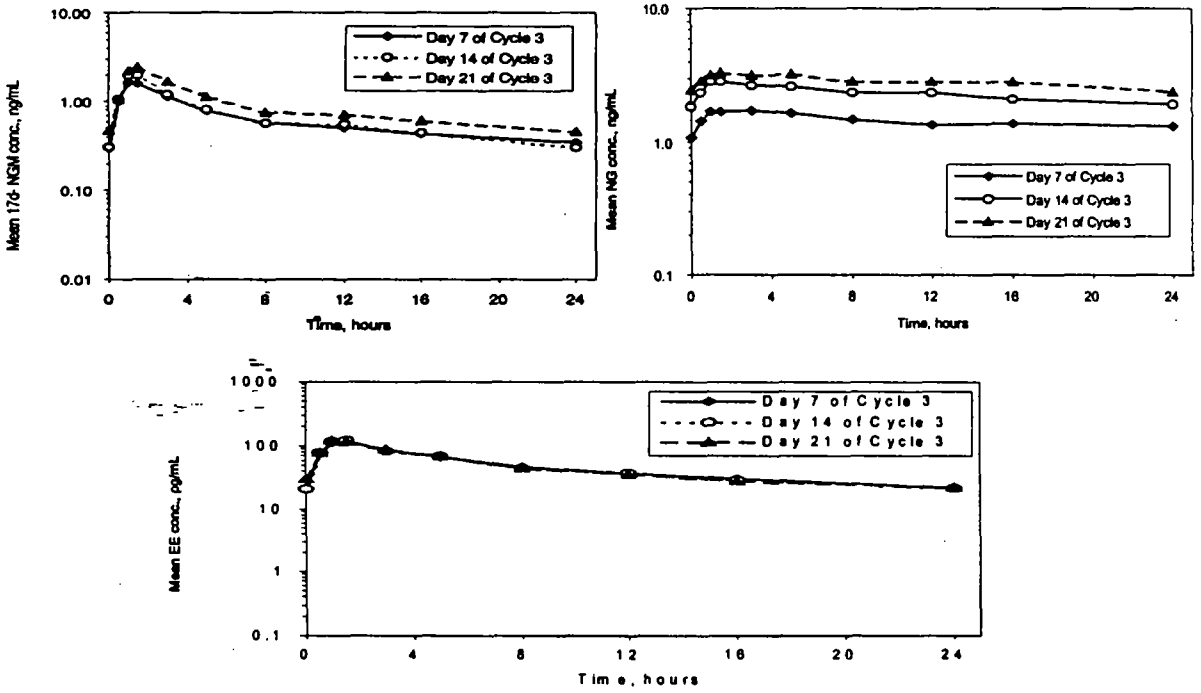


Table 11: Mean (±SD) C_{min} Levels (ng/mL) in Normal Female Volunteers Following Oral Administration of ORTHO TRI-CYCLEN ® for Three Cycles (Study NRGTRI-OC-115)

	Day 6	Day 7	Day 8	Day 13	Day 14	Day 15	Day 20	Day 21	Day 22
17d-NGM									
Mean	0.30	0.30	0.35	0.34	0.31	0.31	0.45	0.59	0.46
SD	0.09	0.09	0.13	0.09	0.13	0.15	0.13	0.40	0.11
CV %	30.4	28.7	36.3	25.7	41.1	46.6	29.9	67.3	23.5
NG									
Mean	0.99	1.08	1.33	1.88	1.85	1.92	2.33	2.24	2.41
SD	0.47	0.50	0.62	0.66	0.80	0.99	0.67	0.94	0.96
CV %	47.7	46.0	47.1	35.4	43.3	51.5	28.8	41.8	39.8
EE (pg/mL)									
Mean	22.8	21.9	23.9	24.7	21.1	22.0	21.3	31.2	25.4
SD	11.4	10.2	10.2	8.10	8.45	9.20	9.85	26.4	17.6
CV %	49.8	46.7	42.1	32.8	40.1	41.8	46.4	84.4	69.2

Reviewer's comments:

The sponsor identified the C_{ss} target ranges of 0.6 – 1.2 ng/mL for 17d-NGM and 25 – 75 pg/mL of EE for optimum efficacy. From a review of data from the above studies, these ranges are acceptable due to the following:

- All C_{min} values for both 17d-NGM and EE were approximately similar to the lower boundary of the target range. With the oral formulation, the C_{max} values were, as expected, higher than those obtained with the TD formulation.
- Majority of the serum levels between 4 – 12 hours at steady state (as observed in Figure 5) was within the target ranges.
- AUC values for 7 days following the TD formulations were comparable to those obtained following the oral administration (multiplying the 0-24 hour AUC values by 7). However, it is to be noted that weekly exposure following TD administration were minimally higher than those observed with the oral formulation. This was expected, as TD delivery ensures more sustained and less fluctuating serum drug levels.
- The phase 3 trials that utilized the TD formulation showed an acceptable efficacy profile.

Dose Finding

Although no information of 'dose-finding' or other PK-PD studies were submitted to Section 6 of the NDA, Study NRGEEP-CONT-001 results (containing significant CPB information) were reported under Section 8 of the NDA. A portion of the study was to assess extent of ovulation suppression following 10, 15 and 20 cm^2 patches in comparison to ORTHO CYCLEN (oral), and also report serum levels of the drug and metabolites within 48 hours of administration during cycle 3. This study provided valuable data on dose-finding and confirmatory PK performance of the patches relative to the oral tablets. Approximately 100 subjects participated in this part of the study (25 per treatment groups of 10 cm^2, 15 cm^2, 20 cm^2 patches and ORTHO CYCLEN containing 250 µg NGM/35 µg EE). On 9/28/01 sponsor notified (upon inquiry) that the formulation in this study used contained 5.5% lauryl lactate and was *different* from the final 'to-be-marketed' formulation (containing 3.78% lauryl lactate). However, the results (below) were valuable for dose-finding.

Table 12: Summary Statistics of Serum Concentrations Within 48 Hours of Application of Patch or Administration of Pill during Cycle 3 (Protocol NRGEEP-CONT-001)

Regimen		Elapsed Sample Time(h)	17d-NGM (ng/mL)	NG (ng/mL)	EE (pg/mL)
10 cm^2 Patch	Mean	11.6[a]	0.36	0.97	25.3
	SD	22.2	0.18	1.35	14.0
	% CV	-191	50.6	139	55.4
	Min				
	Max				
	N	23	23	23	23
15 cm^2 Patch	Mean	-10.9[a]	0.42	1.13	40.6
	SD	18.7	0.19	0.46	27.6
	% CV	-171.0	44.9	41.1	68.1
	Min				
	Max				
	N	21	21	21	21
20 cm^2 Patch	Mean	-14.2[a]	0.62	1.89	45.6
	SD	19.7	0.23	1.02	18.0
	% CV	-139	37.5	53.7	39.4
	Min				
	Max				
	N	24	24	24	23
ORTHO-CYCLEN	Mean	3.21[b]	0.70	1.85	53.8
	SD	3.39	0.54	0.88	41.5
	% CV	106	76.3	47.4	77.2
	Min				
	Max				
	N	28	28	28	26

[a] Time from application of third patch.
[b] Time from last oral dose.

Figure 6: Mean 17d-NGM, NG and EE Serum Concentrations Within 48 Hours of Patch or Oral Pill Administration during Cycle 3 (Protocol NRGEEP-CONT-001)

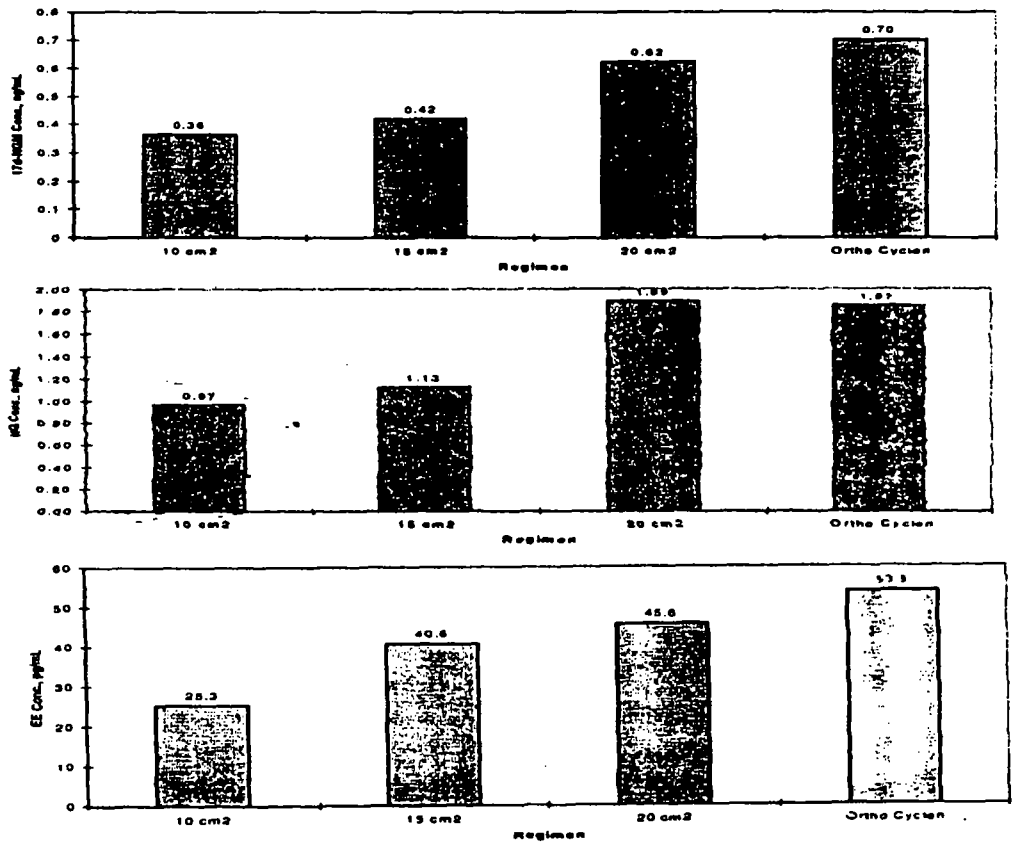


Table 13: Incidence of Ovulation, Luteal Activity, and Anovulation By Treatment Group: (A) Cycles 1 and 3 & (B) Cycle 4 (Protocol NRGEEP-CONT-001)

(A)

	10 cm² Patch			15 cm² Patch			20 cm² Patch			ORTHO-CYCLEN/CILEST		
	Prop	%	(Pu)	Prop	%	(Pu)	Prop	%	(Pu)	Prop	%	(Pu)
Subjects With at Least 3 Progesterone Measurement(s) During Cycle(s) 1 & 3												
Ovulate	57/133	42.9	(49.9)	16/139	11.5	(16.0)	8/129	6.2	(9.7)	10/138	7.2	(10.9)
Luteal Activity	13/133	9.8		13/139	9.4		7/129	5.4		6/138	4.3	
Anovulate	63/133	47.4		110/139	79.1		114/129	88.4		122/138	88.4	
Subjects With at Least 3 Valid Progesterone Measurement(s) During Cycle(s) 1 & 3												
Ovulate	54/129	41.9	(49.0)	14/137	10.2	(14.5)	7/128	5.5	(8.8)	8/131	6.1	(9.5)
Luteal Activity	13/129	10.1		13/137	9.5		7/128	5.5		6/131	4.6	
Anovulate	62/129	48.1		110/137	80.3		114/128	89.1		117/131	89.3	

Notes: Pu – upper limit of the one-sided 95% confidence interval;
All (scheduled or repeated) progesterone measurements are used. If there are two or more measurements, then the maximum progesterone level is used.

(B)

	10 cm² Patch			15 cm² Patch			20 cm² Patch			ORTHO-CYCLEN/CILEST		
	Prop	%	(Pu)	Prop	%	(Pu)	Prop	%	(Pu)	Prop	%	(Pu)
Subjects With at Least 3 Progesterone Measurement(s) During Cycle 4												
Ovulate	49/135	36.3	(43.1)	21/136	15.4	(20.5)	10/129	7.8	(11.6)	10/133	7.5	(11.3)
Luteal Activity	11/135	8.1		6/136	4.4		4/129	3.1		3/133	2.3	
Anovulate	75/135	55.6		109/136	80.1		115/129	89.1		120/133	90.2	
Subjects With at Least 3 Valid Progesterone Measurement(s) During Cycle 4												
Ovulate	44/123	35.8	(42.9)	19/128	14.8	(20.0)	9/122	7.4	(11.3)	8/123	6.5	(10.2)
Luteal Activity	9/123	7.3		6/128	4.7		3/122	2.5		3/123	2.4	
Anovulate	70/123	56.9		103/128	80.5		110/122	90.2		112/123	91.1	

Notes: Pu – upper limit of the one-sided 95% confidence interval;
All (scheduled or repeated) progesterone measurements are used. If there are two or more measurements, then the maximum progesterone level is used.

Reviewer's comments:

The following key conclusions regarding the validity of dose selection can be derived from this study and the results presented above:

- Among the 2 patch sizes, selection of the 20 cm² was optimum based on the following:
  a) Drug and metabolite profiles from the 20 cm² patch was comparable to the oral pill (Table 12, Figure 6)
  b) Efficacy (progesterone levels and suppression) was almost identical between the 20 cm² patch and the oral pill for cycles 1, 3 and 4 (Table 13)
  c) Suppressed serum LH and Estradiol levels were most comparable between the 20 cm² patch and the ORTHO CYCLEN treatment groups
  d) Breakthrough bleeding incidences (safety) were also comparable between the oral pill and the 20 cm² patch groups, and higher with the lower size patches
  e) Among the 4 treatment group, development of follicle (based on diameter) was the lowest in the 20 cm² patch group

[Results for items b, c and d above are not included in this review, and in available in Item 8, Volume 2 of 27 (overall volume 69 of 94) of the archival copy of the NDA.]

Based on the above information, the choice of dose (the 20-cm² patch size) was optimal.

Q4. What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Since normal "subjects" use oral contraceptives, patients and volunteers are not considered different. From a review of literature, it is evident that the PK parameter values of EE is highly variable (typical CVs range between 25 – 75% for AUC and oral clearance). This is attributed to variable high first pass, gut wall metabolism, enterohepatic recirculation and genetic factors. However, progesterones have been associated with lower variability values due to the fact that the oral absorption is almost complete. In both cases, inter-individual variability values have been found to be higher than intra-individual variability, especially for EE.

From data presented in earlier sections (Tables 3 – 8) for this submission, PK parameters following transdermal administration show a trend towards lowered variability for EE (25 – 40% CV), but higher for 17d-NGM (25 – 45% CV) when compared to either literature data following administration of OCs in general, or ORTHO CYCLEN. This might be because the reduced variability of EE is due to a reduction in various factors related to oral administration (first pass, gut metabolism etc.). Both the drugs now show a similar level of variability – a value dictated probably by the inter-individual variability of drug absorption via the skin.

Q5. What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

This product is intended for healthy women during age of menarche. Studies in pediatric and geriatric population, or subjects with hepatic or renal insufficiencies have not been conducted. With the help of population pharmacokinetics (data pooled from 9 phase 1 studies), the effects of race, age, body weight, and body surface area on the pharmacokinetics of 17d-NGM and EE were evaluated in 263 subject data sets obtained from 230 healthy women. Regression models were used to evaluate the relationship of pharmacokinetics estimates ($AUC_{0\text{-}168h}$ and C_{ss}) to demographic covariates (race, age, and body weight or body surface area). Results follow:

Table 14: Ratio of Predicted Values and 90% Confidence Intervals for an Increase of 0.3 m^2 of BSA[a]

			Change in Estimate (BSA)		
Analyte	Parameter	BSA	Estimate	Lower Limit	Upper Limit
17d-NGM	$AUC_{0\text{-}168h}$	1.40	123	111	137
		1.70[b]	100		
		2.00	81	73	90
	C^{ss}	1.40	121	109	134
		1.70[b]	100	100	
		2.00	83	75	91
EE	$AUC_{0\text{-}168h}$	1.40	122	109	136
		1.70[b]	100		
		2.00	82	74	92
	C^{ss}	1.40	122	110	135
		1.70[b]	100		
		2.00	82	74	91

[a] Assumes the other effects in the model are fixed.
[b] Assumed as fixed at 100%. All reported values are percentages of the value at 0.3 m^2 of BSA.
Mean = 1.70 m^2

Table 15: Ratio of Predicted Values and 95% Confidence Intervals for an Increase of Five Years of Age[a]

		Change in Estimate (BWT)			
Analyte	Parameter	Age	Estimate	Lower Limit	Upper Limit
17d-NGM	AUC_{0-168h}	25	107	104	110
		30[b]	100		
		35	94	91	97
		40	88	83	93
		45	82	76	90
	C^{ss}	25	106	104	109
		30[b]	100		
		35	94	91	97
		40	88	84	93
		45	83	76	90
EE	AUC_{0-168h}	25	105	102	108
		30[b]	100		
		35	96	93	98
		40	91	86	97
		45	87	80	95
	C^{ss}	25	104	101	107
		30[b]	100		
		35	96	93	99
		40	92	87	97
		45	88	81	96

[a] Assumes the other effects in the model are fixed.
[b] Assumed as fixed at 100%. All reported values are percentages of the value at 30 yr of age. Mean = 32 yr

Table 16: Ratio of Predicted Values and 95% Confidence Intervals for an Increase of 10 kg of Body Weight[a]

		Change in Estimate(BWT)			
Analyte	Parameter	BWT	Estimate	Lower Limit	Upper Limit
17d-NGM	AUC_{0-168h}	45	121	110	133
		55	110	105	115
		65[b]	100		
		75	91	87	96
		85	83	75	91
		95	75	65	87
	C^{ss}	45	118	108	130
		55	109	104	114
		65[b]	100		
		75	92	88	96
		85	85	77	93
		95	78	67	90
EE	AUC_{0-168h}	45	119	107	133
		55	109	104	115
		65[b]	100		
		75	92	87	97
		85	84	75	93
		95	77	65	90
	C^{ss}	45	119	107	131
		55	109	104	115
		65[b]	100		
		75	92	87	97
		85	84	76	93
		95	77	67	90

[a] Assumes the other effects in the model are fixed.

Race: According to the sponsor, race (assessed in data sets as 164 Caucasians, 60 Hispanics, 25 Blacks, and 14 "Other Subjects" which included Asians and American Indians) accounted for a smaller proportion of the inter-individual variability. For EE, no significant differences in C_{ss} or AUC due to race were found. For 17d-NGM, statistically significant differences in C_{ss} due to race

were apparent, while the significance of the AUC differences depended upon other factors. The statistically significant differences in 17d-NGM C_{ss} due to race appeared to be due primarily to a 28 to 33% increase for the "Other Subjects" compared to Caucasians.

Reviewer's comments:

- There is a decreasing trend of exposure to the drugs with increasing age, body weight and body surface area.
- Majority of the 95% CI boundaries around the point estimate ratio for AUC and C_{ss} were within 80 – 125%. Some values were as low as 65% (lower boundary) for body weights > 85 kgs, indicating that exposure decreased with increasing body weight. Five of the 15 pregnancies that occurred in the pivotal clinical trials were observed in women weighing > 198 lbs. (90 Kgs.).
- Possible increase in C_{ss} of 17d-NGM (approximately 30%) in 'Other Subjects' as compared to Caucasians may not have pose significant safety concerns as long as the total exposure (AUC) is comparable to currently marketed OCs.

Although PK parameters have been shown to be partially affected by intrinsic parameters, it may be recalled that these parameters (for both 17d-NGM and EE) showed a higher inter-individual variability as high as 40% (CV). No clinical significance may be inferred from these effects, and hence, no dose adjustment is recommended.

Site of Application: Sponsor conducted a study focused to assess the effect of application of the patch at different anatomic sites on the absorption and PK of the drugs (Study NRGEEP-PHI-004). Thirty-six healthy non-pregnant subjects wore one single patch for 7 days for each of the four treatment periods. Subjects were randomly assigned to wear the patch on the abdomen, buttock, upper outer arm, or upper torso. After a 1-month washout, subjects applied the patch at a different site alternately. The following are the results from the study:

Table 17: Mean (SD) Pharmacokinetic Parameters Obtained from 36 Women Wearing the 20-cm² Seven-Day EVRA™ Patch at Different Application Sites (Study NRGEEP-PHI-004)

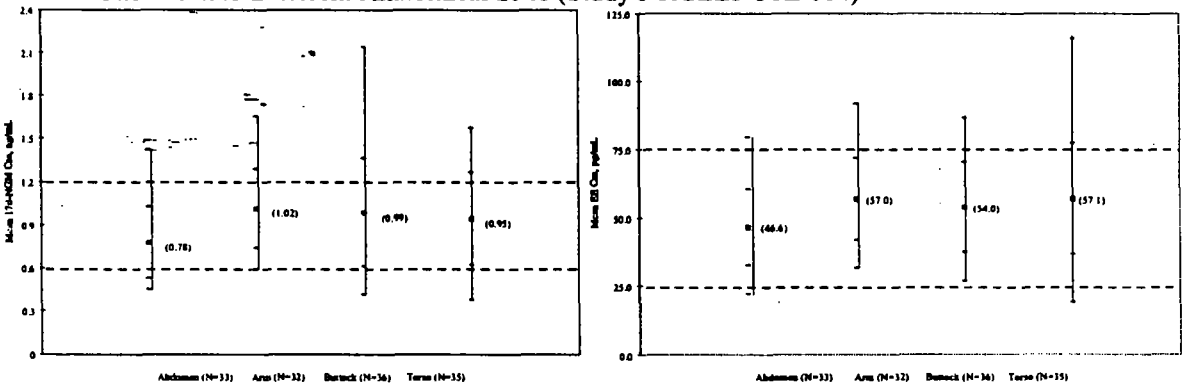
Parameter	Abdomen	Arm	Buttock	Torso
17d-NGM				
C_{max} (ng/mL)	0.88 (0.28)	1.18 (0.35)	1.17 (0.50)	1.07 (0.38)
t_{max} (h)	73.5 (32.3)	69.8 (34.1)	78.8 (43.0)	79.6 (42.5)
C^{ss} (ng/mL)	0.78 (0.25)	1.02 (0.27)	0.99 (0.38)	0.95 (0.32)
AUC_{0-168h} (ng·h/mL)	117 (37.6)	155 (44.3)	150 (57.9)	143 (50.4)
AUC_{0-240h} (ng·h/mL)	136 (43.6)	177 (46.4)	174 (64.6)	166 (56.7)
$t_{1/2}$ (h)	27.6 (10.4)	26.1 (6.95)	28.0 (6.90)	30.1 (21.4)
NG				
C_{max} (ng/mL)	1.32 (0.57)	1.71 (0.65)	1.60 (0.69)	1.59 (0.88)
t_{max} (h)	173 (7.85)	170 (19.5)	176 (11.3)	175 10.3)
C^{ss} (ng/mL)	0.72 (0.31)	0.98 (0.43)	0.86 (0.40)	0.86 (0.50)
AUC_{0-168h} (ng·h/mL)	106 (49.0)	146 (66.9)	131 (65.1)	132 (79.6)
AUC_{0-240h} (ng·h/mL)	169 (73.9)	225 (90.8)	208 (94.7)	208 (117)
$t_{1/2}$ (h)	43.4 (22.3)	45.4 (22.0)	45.1 (17.6)	51.6 (48.1)
EE				
C_{max} (pg/mL)	58.7 (19.9)	69.5 (20.6)	66.3 (23.9)	71.2 (32.2)
t_{max} (h)	56 (27.3)	57.8 (32.7)	52.7 (32.4)	56.2 (26.6)
C^{ss} (pg/mL)	46.6 (14.0)	57.0 (14.9)	54.0 (16.5)	57.1 (20.3)
AUC_{0-168h} (pg·h/mL)	7163 (2211)	8751 (2272)	8391 (2622)	8599 (3161)
AUC_{0-240h} (pg·h/mL)	7766 (2332)	9540 (2437)	9189 (2755)	9523 (3354)
$t_{1/2}$ (h)	16.1 (3.02)	16.4 (3.47)	18.1 (6.43)	17.1 (3.81)

Table 18: Bioequivalence Testing Results for Pharmacokinetic Parameters Obtained from 31[a] Women Wearing the 20-cm^2 Seven-Day EVRA™ Patch at Different Application Sites (Study NRGEEP-PHI-004)

				90% Confidence Intervals for the Ratio of the Means (Test/Reference)				
Analyte	Reference	Test	Parameter	Geometric Mean for Reference	Geometric Mean for Test	Ratio (%)	Lower Limit (%)	Upper Limit (%)
17d-NGM	Abdomen	Arm	AUC_{0-240}	128.57	167.38	130.19	119.59	141.72
			C^{ss}	0.73	0.96	130.35	120.02	141.97
	Abdomen	Buttock	AUC_{0-240}	128.57	161.69	125.75	115.52	136.90
			C^{ss}	0.73	0.92	124.96	114.90	135.91
	Abdomen	Torso	AUC_{0-240}	128.57	160.25	124.64	114.49	135.68
			C^{ss}	0.73	0.92	125.16	115.26	136.33
	Buttock	Arm	AUC_{0-240}	161.69	167.38	103.52	95.10	112.70
			C^{ss}	0.92	0.96	104.46	96.05	113.61
	Buttock	Torso	AUC_{0-240}	161.69	160.25	99.11	91.04	107.89
			C^{ss}	0.92	0.92	100.31	92.24	109.10
	Arm	Torso	AUC_{0-240}	167.38	160.25	95.74	87.95	104.22
			C^{ss}	0.96	0.92	96.03	88.30	104.44
NG	Abdomen	Arm	AUC_{0-240}	156.87	205.69	131.12	112.65	146.18
			C^{ss}	0.67	0.89	133.07	119.51	148.15
	Abdomen	Buttock	AUC_{0-240}	156.87	191.10	121.82	109.30	135.76
			C^{ss}	0.67	0.79	118.70	106.61	132.17
	Abdomen	Torso	AUC_{0-240}	156.87	188.78	120.34	107.98	134.12
			C^{ss}	0.67	0.79	118.71	106.61	132.18
	Buttock	Arm	AUC_{0-240}	191.09	205.69	107.64	96.58	119.97
			C^{ss}	0.79	0.89	112.11	100.68	124.83
	Buttock	Torso	AUC_{0-240}	191.09	188.78	98.79	88.64	110.10
			C^{ss}	0.79	0.79	100.01	89.82	111.36
	Arm	Torso	AUC_{0-240}	205.69	188.78	91.78	82.35	102.29
			C^{ss}	0.89	0.79	89.21	80.12	99.33
EE	Abdomen	Arm	AUC_{0-240}	7314.26	9172.91	125.41	116.03	136.03
			C^{ss}	43.88	54.67	124.59	113.95	136.22
	Abdomen	Buttock	AUC_{0-240}	7314.26	8769.69	119.90	109.97	130.72
			C^{ss}	43.88	51.45	117.26	107.25	128.20
	Abdomen	Torso	AUC_{0-240}	7314.26	9101.52	124.44	114.13	135.67
			C^{ss}	43.88	54.59	124.42	113.80	136.03
	Buttock	Arm	AUC_{0-240}	8769.69	9172.91	104.60	95.94	114.04
			C^{ss}	51.45	54.67	106.25	97.18	116.17
	Buttock	Torso	AUC_{0-240}	8769.69	9101.52	103.78	95.19	113.15
			C^{ss}	51.45	54.59	106.11	97.05	116.01
	Arm	Torso	AUC_{0-240}	9172.91	9101.52	99.22	91.01	108.18
			C^{ss}	54.67	54.59	99.87	91.34	109.19

[a] Only those 31 subjects who completed all four treatments were included in the statistical analysis.

Figure 7: Mean 17d-NGM & EE Steady-State Serum Concentrations vs. Time in Healthy Female Volunteers Following Single Application of a Transdermal Contraceptive System of 17d-NGM and EE for One Week to Different Anatomical Sites (Study NRGEEP-PHI-004)



[The dashed lines represent the target concentration range; vertical lines represent mean, SD and range of observed values.]

Reviewer's comments:

- Exposure following administration of the patches in the abdomen is less compared to the other sides (refer to the highlighted sections in Table 18). However, Study NRGEEP-PHI-013 (Tables 5 and 7) comparing the exposure from the abdomen and the buttocks showed appreciably higher exposure from the abdomen (higher than the buttock).
- The mean C_{ss} levels from all anatomic sites are all within the established target range for both the drugs.
- As is observed in Figure 7 above, although the mean serum level of 17d-NGM is lower from the abdomen, the probability of the levels being lower than 0.6 ng/ml following administration at either the abdomen, buttock or torso sites is almost equal. A much lesser proportion of patients showed EE serum levels below the target range from application to any site.
- Among over 70,000 patches used in the pivotal clinical trials, approximately 30 % of those were used in the abdomen and 50 % in the buttocks. The Medical Officer confirms that the few pregnancies occurring in these pivotal trials could not be associated with any specific trend based on site of application. Efficacy was *not* affected due the site of application.

Based on the above, the 4 anatomical sites may be switched interchangeably (as in the clinical trials) without appreciable clinical consequences.

Q6. What extrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

It has been long known and accepted that agents such as rifampicin and anticonvulsants such as phenobarbitone, phenytoin and carbamazepine induce liver enzymes leading to a reduction in plasma levels of the contraceptive steroids and an overall reduction in contraceptive efficacy. Broad spectrum antibiotics have also been implicated in causing contraceptive failures or excessive bleeding. These contraceptive drugs are hydrolyzed by the intestinal microorganisms, and are then reabsorbed back into the system (entero-hepatic recirculation). In the presence of the antibiotics, the flora is possibly absent, and the reabsorption of the drugs might be hampered. Theoretically, this may lead to a reduction of the serum levels and hence, efficacy. Although focussed studies conducted so far have not clearly shown that such drug-drug interaction may be clinically significant, with lowering of contraceptive doses in the recent years, this phenomenon can not be ignored. In this NDA, the sponsor has submitted results of a study conducted to address this issue.

Study NRGEEP-PHI-012 was conducted in 20 healthy adult women (age 18 to 48 years). Each subject wore a 20-cm^2 17d-NGM/EE EVRA™ contraceptive patch on the abdomen for 1 week alone and for 1 week with coadministered tetracycline HCl (500 mg q.i.d. for 3 days prior to and 7 days during wear). A 1-month washout period separated the two-wear periods. Serial blood samples were collected at 0, 6, 12, 24, 48, 72, 120, 144, 168, 171, 174, 180, 192, 204, 216, and 240 hours after patch application. Results are detailed in Tables 17, 18 and Figure 8. Additionally, the sponsor also conducted *in vitro* investigation to delineate the potential of 17d-NGM and EE (and metabolites) to inhibit other drugs. It was found that with the extremely low serum concentrations of the drug (pM – nM range) following application of the patch, any inhibition of the enzymes is likely to be clinically insignificant due to their high inhibitory constants ($K_i > 0.5\ \mu M$).

Table 19: Mean (±SD) Pharmacokinetic Parameters in Healthy Female Volunteers Following Application of a Transdermal System of 17d-NGM and EE with and without Tetracycline HCl (Study NRGEEP-PHI-012)

Parameter	EVRA™ Contraceptive Patch Only	EVRA™ Contraceptive Patch + Tetracycline HCl
17d-NGM		
t_{max} (h)	92.4 (38.4)	112 (37.4)
C_{max} (ng/mL)	0.72 (0.28)	0.69 (0.23)
C^{ss} (ng/mL)	0.58 (0.16)	0.58 (0.20)
$AUC_{0\text{-}168h}$ (ng·h/mL)	86.5 (27.1)	82.7 (29.3)
$AUC_{0\text{-}240h}$ (ng·h/mL)	100 (27.8)	101 (35.3)
$AUC_{0\text{-}\infty}$ (ng·h/mL)	107 (29.6)	106 (36.2)
$t_{½}$ (h)	31.7 (12.3)	29.8 (13.0)
NG		
t_{max} (h)	167 (26.9)	173 (19.0)
C_{max} (ng/mL)	0.82 (0.29)	0.94 (0.31)
C_{avg} (ng/mL)	0.52 (0.17)	0.53 (0.20)
$AUC_{0\text{-}168h}$ (ng·h/mL)	63.9 (30.2)	57.7 (29.7)
$AUC_{0\text{-}240h}$ (ng·h/mL)	105 (43.8)	107 (45.6)
$AUC_{0\text{-}\infty}$ (ng·h/mL)	142 (45.6)	161 (66.4)
$t_{½}$ (h)	61.8 (30.2)	76.1 (59.0)
EE		
t_{max} (h)	112 (46.2)	109 (47.8)
C_{max} (pg/mL)	50.8 (20.3)	50.8 (16.1)
C^{ss} (pg/mL)	42.2 (12.9)	44.1 (13.5)
$AUC_{0\text{-}168h}$ (pg·h/mL)	6204 (2198)	6256 (1911)
$AUC_{0\text{-}240h}$ (pg·h/mL)	7003 (2337)	7307 (2222)
$AUC_{0\text{-}\infty}$ (pg·h/mL)	7093 (2362.)	7426 (2240)
$t_{½}$ (h)	19.5 (5.47)	20.0 (4.07)

Table 20: 90% Confidence Intervals for the Ratio of the Means from EVRA ™ Contraceptive Patch plus Tetracycline HCl (Test) to EVRA ™ Contraceptive Patch Alone (Reference) for Each Analyte (Study NRGEEP-PHI-012)

Analyte	Parameter	Geometric Mean Reference	Geometric Mean Test	Ratio (%)	90% Confidence Limits Lower (%)	90% Confidence Limits Upper (%)
17d-NGM	$AUC_{0\text{-}240h}$	96.80	94.20	97.31	88.65	106.81
	C^{ss}	0.56	0.54	96.72	88.24	106.01
NG	$AUC_{0\text{-}240h}$	97.81	94.91	97.04	85.06	110.70
	C_{avg}	0.50	0.48	96.97	86.75	108.38
EE	$AUC_{0\text{-}240h}$	6684.60	6990.00	104.57	95.04	115.05
	C^{ss}	40.52	42.14	103.99	94.80	114.08

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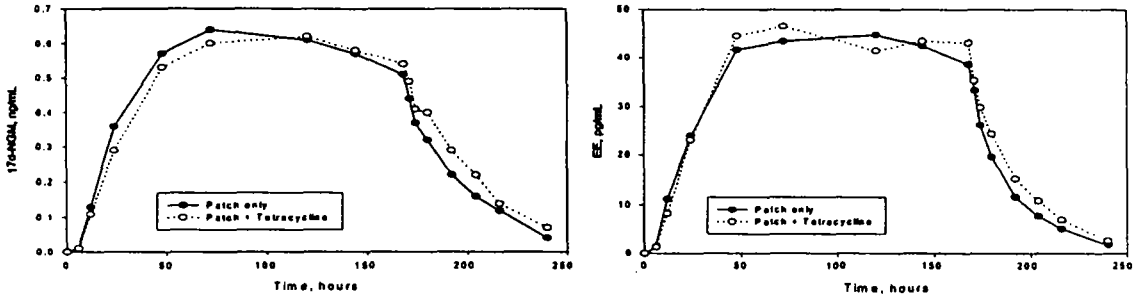
Figure 8: Mean 17d-NGM and EE Serum Concentrations (ng/mL) in Healthy Female Volunteers Following Application of an EVRA™ Patch With and Without Tetracycline HCl (Study NRGEEP-PHI-012)



Reviewer's comments:

Results from the above study suggest that concomitant administration of ORTHO EVRA transdermal system and tetracycline should not result in any clinically relevant differences in exposure of 17d-NGM and EE. Hence, no alteration in efficacy is expected.

Q7. Do other factors affect the delivery of the drugs from the patches?

Due to the nature of the product, sponsor conducted a study to evaluate the pharmacokinetic parameters of 17d-NGM, NG, and EE following application of EVRA™ when worn under conditions of heat, humidity, cold, and exercise as compared to the normal activity.

Thirty healthy adult women, aged 19 to 47 years (mean = 32.7 ± 7.65) and weighing 50.4 to 81.3 kg (mean = 64.1 ± 8.32), were enrolled and 29 completed the study. Each subject wore a 20-cm^2 17d-NGM/EE EVRA™ patch on the abdomen for 7 days under specified conditions during each of three treatment periods: each treatment period separated by a 1-month washout period. The total study duration was 12 weeks. Subjects participated in the following once daily activities in the order determined by a computer-generated schedule: normal activity, sauna (10 minutes), whirlpool (10 minutes), cool water bath (up to 30 minutes), treadmill (20 to 30 minutes), and combination. Serial blood samples were collected till 10 days after patch application for the determination of 17d-NGM, NG, and EE. Additionally, blood was collected at 1, 3, and 6 hours after completion of the test activity on Day 3 of each treatment period (except for normal activity).

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Table 21:	Mean (SD) Pharmacokinetic Parameters in Healthy Female Volunteers Following Application of an EVRA ™ Contraceptive Patch of 17d-NGM and EE Under Conditions Found in a Health Club (Study NRGEEP-PHI-015)					
Parameter	Combination	Cool Water	Normal	Sauna	Treadmill	Whirlpool
17d-NGM						
t_{max} (h)	51.6 (2.40)	59.7 (20.9)	74.5 (31.0)	47.8 (7.76)	48.6 (13.3)	65.4 (20.7)
C_{max} (ng/mL)	1.02 (0.26)	0.93 (0.33)	0.94 (0.32)	1.07 (0.36)	0.97 (0.20)	1.05 (0.39)
C^{ss} (ng/mL)	0.67 (0.15)	0.73 (0.22)	0.73 (0.27)	0.73 (0.24)	0.63 (0.13)	0.73 (0.31)
$AUC_{0\text{-}168h}$ (ng·h/mL)	113 (27.0)	116 (37.3)	116 (43.8)	119 (42.6)	107 (21.4)	122 (51.2)
$AUC_{0\text{-}240h}$ (ng·h/mL)	124 (31.2)	129 (39.2)	129 (49.4)	132 (44.4)	117 (26.0)	134 (55.8)
$AUC_{0\text{-}\infty}$ (ng·h/mL)	127 (30.7)	133 (38.4)	135 (49.1)	135 (44.5)	120 (22.1)	141 (54.4)
$t_{½}$ (h)	24.2 (8.45)	25.0 (14.9)	28.2 (15.9)	19.5 (9.18)	32.9 (22.3)	32.6 (26.9)
N	12	12	29	12	12	11
NG						
t_{max} (h)	155 (38.2)	143 (50.2)	161 (21.1)	149 (34.4)	159 (23.9)	151 (20.7)
C_{max} (ng/mL)	1.28 (0.93)	1.32 (0.48)	1.39 (0.90)	1.60 (1.03)	1.28 (0.32)	1.30 (0.73)
C_{ave} (ng/mL)	0.89 (0.51)	0.87 (0.30)	0.90 (0.48)	1.10 (0.69)	0.84 (0.25)	0.90 (0.49)
$AUC_{0\text{-}168h}$ (ng·h/mL)	131 (83.6)	126 (51.0)	127 (79.7)	166 (111)	124 (41.5)	131 (80.0)
$AUC_{0\text{-}240h}$ (ng·h/mL)	197 (147)	184 (66.7)	193 (129)	248 (174)	180 (54.7)	188 (113)
$AUC_{0\text{-}\infty}$ (ng·h/mL)	267 (296)	216 (69.1)	232 (180)	330 (261)	218 (74.3)	221 (136)
$t_{½}$ (h)	52.4 (27.1)	47.5 (27.8)	45.2 (15.5)	49.3 (18.1)	49.9 (16.2)	44.5 (18.1)
N	12	12	29	12	12	11
EE						
t_{max} (h)	42.9 (17.6)	84.0 (48.1)	86.9 (48.5)	65.4 (35.3)	60.9 (36.8)	76.5 (52.0)
C_{max} (pg/mL)	89.9 (32.2)	63.9 (18.1)	64.5 (21.6)	85.4 25.8	81.3 21.2	80.8 (39.8)
C^{ss} (pg/mL)	59.3 (19.0)	52.3 (16.8)	53.0 (18.7)	61.7 (20.0)	60.8 (17.0)	55.2 (16.8)
$AUC_{0\text{-}168h}$ (pg·h/mL)	10343 (3293)	8186 (2458)	8237 (3047)	10172 (3428)	10378 (2534)	8987 (2749)
$AUC_{0\text{-}240h}$ (pg·h/mL)	11132 (3600)	9109 (2796)	9055 (3377)	11155 (3631)	11246 (3034)	9716 (2865)
$AUC_{0\text{-}\infty}$ (pg·h/mL)	11229 (3612)	9225 (2727)	9416 (3131)	11679 (3867)	11345 (3026)	9807 (2875)
$t_{½}$ (h)	15.2 (3.48)	14.9 (3.58)	15.0 (2.67)	25.7 (30.9)	17.7 (9.51)	18.0 (7.34)
N	12	12	29	12	12	11

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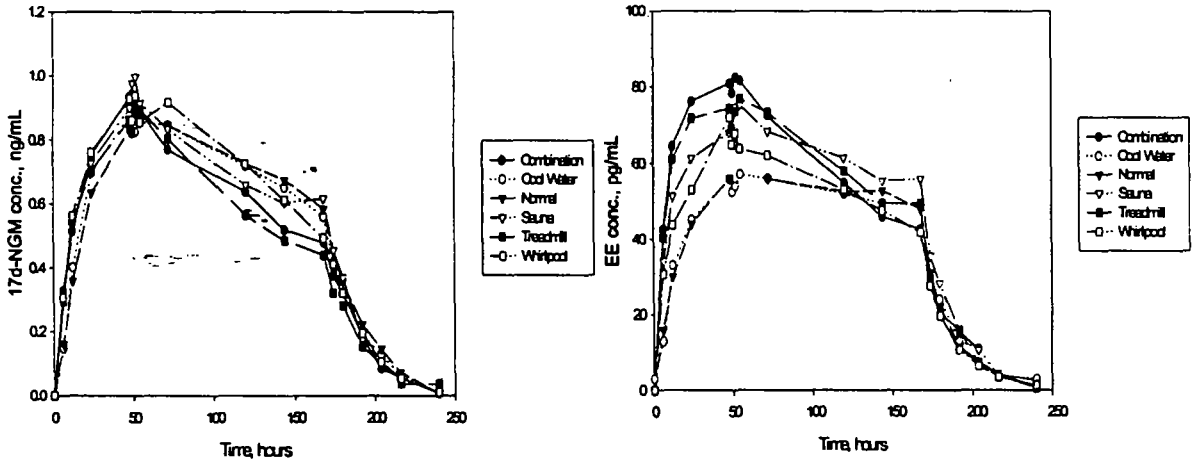
Table 22: 90% Confidence Intervals for the Ratio of the Mean from Test Activity to Normal Conditions (Reference) for 17d-NGM , NG, and EE (Study NRGEEP-PHI-015)

		Geometric Mean	Geometric Mean	Ratio	90% Confidence Limits Lower	Upper
17d-NGM						
Sauna	AUC_{0-240h}	127.9	120.01	93.83	82.79	106.34
	C^{ss}	0.73	0.68	93.19	82.45	105.33
Whirlpool	AUC_{0-240h}	127.9	127.12	99.39	87.72	112.60
	C^{ss}	0.73	0.69	94.20	83.37	106.44
Treadmill	AUC_{0-240h}	127.9	120.39	94.13	83.49	106.13
	C^{ss}	0.73	0.66	89.99	80.02	101.19
Cool Water	AUC_{0-240h}	127.9	126.99	99.29	88.48	111.42
	C^{ss}	0.73	0.72	99.00	88.43	110.82
Combination	AUC_{0-240h}	127.9	118.46	92.62	82.16	104.41
	C^{ss}	0.73	0.64	87.86	78.13	98.79
NG						
Sauna	AUC_{0-240h}	174.81	179.31	102.57	89.23	117.91
	C_{ave}	0.84	0.87	103.43	90.75	117.89
Whirlpool	AUC_{0-240h}	174.81	195.99	112.11	97.56	128.84
	C_{ave}	0.84	0.92	109.23	95.86	124.46
Treadmill	AUC_{0-240h}	174.81	185.11	105.89	92.66	121.02
	C_{ave}	0.84	0.88	104.28	92.00	118.21
Cool Water	AUC_{0-240h}	174.81	173.40	99.20	87.26	112.76
	C_{ave}	0.84	0.82	98.06	86.94	110.6
Combination	AUC_{0-240h}	174.81	166.86	95.45	83.53	109.07
	C_{ave}	0.84	0.79	93.98	82.92	106.51
EE						
Sauna	AUC_{0-240h}	8752.27	10141.04	115.87	101.20	132.66
	C^{ss}	51.64	56.73	109.85	95.70	126.09
Whirlpool	AUC_{0-240h}	8752.27	9825.43	112.26	98.09	128.49
	C^{ss}	51.64	55.85	108.14	94.25	124.09
Treadmill	AUC_{0-240h}	8752.27	11044.29	126.19	110.84	143.66
	C^{ss}	51.64	59.68	115.56	101.25	131.89
Cool Water	AUC_{0-240h}	8752.27	8666.88	99.02	87.42	112.17
	C^{ss}	51.64	49.88	96.59	85.06	109.68
Combination	AUC_{0-240h}	8752.27	11074.91	126.54	111.16	144.05
	C^{ss}	51.64	58.63	113.53	99.48	129.56

Figure 15: Mean 17d-NGM and EE Serum Concentrations in Healthy Female Volunteers Following Application of an EVRA™ Contraceptive Patch of 17d-NGM and EE Under Conditions Found in a Health Club (Study NRGEEP-PHI-015)



Reviewer's comments:

- Results suggest that PK of EE is affected more than of 17d-NGM. Marginally higher exposure of EE from this low dose product may be considered clinically insignificant.
- The serum levels of the both the drugs under all the conditions are within the "target" ranges.
- The variability of the exposure of the drugs is not greater than the inherent PK variability as observed in the single and multiple dose studies.
- No clinically significant effect of any of the environmental conditions on the drug delivery profiles can be established.
- Sponsor reports that from in this study only one EVRA™ contraceptive patch became detached; adhesion for all others was >90%.

The sponsor also performed some *simulations* to determine how certain deviations from the recommended dosing regimen may affect the efficacy of the patches. This reviewer draws the following conclusions from those simulations and results of the actual PK studies:

- Wearing patches beyond the suggested 7-day period should be avoided, and if such overuse is unavoidable, backup contraception is recommended.
- If patches are changed more frequently than every 7 days (eg. due to adhesion issues), backup contraception may not be necessary.
- Back-up contraception is required when there is a delayed dosing start or early dosing finish.
- Back-up contraception may not be required when there is up to 1 day of no patch wear on days other than 1 or 21.
- Backup contraception is needed when there is more than 1 day of no-patch-wear.

Q8. Are there issues related to adhesion of the patches?

From the results of all the clinical pharmacology studies the adhesion of the patches to the skin was found to be acceptable. Few patches actually fell off in the studies combined and the rest of the patches showed > 75% adhesion (edges lifted off). In the pivotal phase 3 clinical trials, approximately 2% of the total number of patches actually fell off. The % of subjects with at least 1 patch that fell off ranged from 1% – 8 %, with a reduction in the number from Cycle 1 (7%) to Cycle 13 (1%) (improved with time). Note that any patch showing signs of 'falling-off' may immediately be replaced with a fresh patch probably without any clinical consequences.

Q9. Are there any unresolved clinical pharmacology issues?

The medical officer observed incidences of pulmonary emboli in two patients at different cycles (with no obvious trend) following use of EVRA™ patches. This may pose as a safety issue. Although embolism has been very infrequently associated with combination oral contraceptives (with some newer generation progesterones), in this current case, no serum levels of the drugs were obtained around the time when the emboli were detected. Hence, no specific drug exposure related reasons be assigned to explain this phenomenon. In this context, it may be recalled that application of EVRA™ reduces the peaks and troughs of the drugs, while minimally increasing the weekly total drug exposure (AUC) when compared to a combination OC at comparable dosage strengths.

Biopharmaceutics

Q1. Is the proposed to-be-marketed formulation identical to the pivotal clinical trial formulation?

According to the sponsor, the proposed to-be-marketed formulation is *identical* to formulation used in all the Phase 3 studies.

The sponsor conducted a bioequivalence study to support a formulation essentially similar, but from an alternative manufacturer [redacted] . (potentially for the future). The study was conducted to compare the performance of this new formulation to that used in the pivotal clinical trials [redacted]

The results of the study indicate that the new formulation was bio-equivalent for 17d-NGM (90% CI for C_{max}, AUC and C_{ss} were all within 86 – 99 %), but *not* bio-equivalent for EE (90% CI for C_{max}, AUC and C_{ss} were within 116 - 131 %). Hence, this new formulation ([redacted]) may neither be substituted to the one used in the pivotal clinical trials, nor be marketed. Further details of the results of this bioequivalence study are not discussed herein.

Q2. What are the specifications and methods for dissolution?

Table 23: Proposed Product Cumulative Release Method and Specification

Applicant:	The R.W. Johnson Pharmaceutical Research Institute
Drug:	EVRA™ (17-Deacetylnorgestimate/Ethinyl Estradiol)
NDA No.:	21-180
Dosage Form	20 cm^2 Transdermal Patch
Strength(s)	6.0 mg 17d-NGM, 0.75 mg EE
Apparatus Type	
Media	[redacted]
Volume	
Speed of Rotation (rate of flow for flow-through apparatus)	
Sampling Time(s)	
Brief Description of Cumulative Release Analytical Method	[redacted]
Recommended Cumulative Release Specification	[redacted]

Number of Pages Redacted 2

❖❖❖

Confidential,
Commercial Information

Q3. What is the actual rate of <u>in vivo</u> drug release, and how was it determined?

Sponsor conducted a randomized, parallel-group, open-label, two-way crossover study to evaluate the bioavailability of 17d-NGM and EE from a transdermal contraceptive system versus intravenous infusion in 26 adult females. Each subject wore one EVRA™ on either the abdomen or the buttock (randomized) for 7 days, or they received a single intravenous infusion, 252 µg of 17d-NGM and 25 µg of EE over a 1-hour period (1 mL/min). One month after receiving the first treatment, they crossed over to the other treatment. The total study duration was approximately 6 weeks. All relevant PK parameters were estimated for each subject and the absorbed dose per day (k_0) was calculated as (CL) (C^{ss}) for 17d-NGM and (CL^{ss}) (C^{ss}) EE. Results follow:

Table 25: Mean (SD) Pharmacokinetic Parameters Following Intravenous Infusion of 17d-NGM and EE and Application of EVRA ™ Contraceptive Patch (Study NRGEEP-PHI-014)

Parameter	Infusion	Abdomen	Buttock	Abdomen + Buttock
17d-NGM				
t_{max} (h)	0.99 (0.20)	96.0 (42.7)	60.9 (23.2)	78.5 (38.1)
C_{max} (ng/mL)	3.65 (1.05)	0.90 (0.40)	1.20 (0.17)	1.05 (0.34)
$t_{½}$ (h)	29.2 (14.5)	25.9 (8.15)	30.9 (16.1)	28.4 (12.8)
$AUC_{0\text{-}77h}$ (ng·h/mL)	27.8 (5.77)	NC	NC	NC
$AUC_{0\text{-}168h}$ (ng·h/mL)	NC	109 (45.3)	151 (24.5)	130 (41.5)
$AUC_{0\text{-}240h}$ (ng·h/mL)	NC	126 (53.6)	172 (32.1)	149 (49.2)
$AUC_{0\text{-}\infty}$ (ng·h/mL)	33.2 (6.41)	132 (56.4)	182 (39.5)	157 (54.2)
CL (L/h)	7.89 (1.63)	NC	NC	NC
ke (h^{-1})	0.029 (0.013)	0.029 (0.007)	0.028 (0.014)	0.028 (0.011)
C^{ss} (ng/mL)	NA	0.71 (0.28)	0.96 (0.17)	0.84 (0.26)
FI (%)	NA	88.1 (21.7)	105 (15.5)	96.8 (20.5)
k_0 (µg/day)	NA	139 (44.1)	159 (28.1)	149 (38.0)
NG				
t_{max} (h)	NA	163 (16.6)	163 (19.4)	163 (17.7)
C_{max} (ng/mL)	NA	0.94 (0.34)	1.43 (0.55)	1.18 (0.51)
$t_{½}$ (h)	NA	58.4 (49.7)	45.9 (16.7)	52.1 (36.9)
$AUC_{0\text{-}77h}$ (ng·h/mL)	NA	NC	NC	NC
$AUC_{0\text{-}168h}$ (ng·h/mL)	NA	74.1 (28.6)	128 (53.3)	101 (50.1)
$AUC_{0\text{-}240h}$ (ng·h/mL)	NA	116 (41.1)	195 (81.5)	156 (75.0)
$AUC_{0\text{-}\infty}$ (ng·h/mL)	NA	154 (87.0)	242 (117)	198 (110)
ke (h^{-1})	NA	0.017 (0.008)	0.017 (0.006)	0.017 (0.007)
C_{ave} (ng/mL)	NA	0.59 (0.20)	0.92 (0.36)	0.76 (0.33)
FI (%)	NA	125 (23.7)	134 (25.8)	130 (24.7)
EE				
t_{max} (h)	0.92 (0.19)	94.2 (44.3)	90.5 (49.1)	92.3 (45.9)
C_{max} (pg/mL)	186 (58.8)	50.8 (20.3)	71.0 (22.0)	60.9 (23.2)
$t_{½}$ (h)	14.1 (3.67)	15.2 (3.76)	15.3 (2.96)	15.2 (3.32)
$AUC_{0\text{-}77h}$ (pg·h/mL)	834 (213)	NC	NC	NC
$AUC_{0\text{-}last}$ (pg·h/mL)	NC	6713 (2603)	10141 (2639)	8427 (3106)
$AUC_{0\text{-}168h}$ (pg·h/mL)	NC	6059 (2395)	9101 (2241)	7580 (2751)
$AUC_{0\text{-}240h}$ (pg·h/mL)	NC	6742 (2605)	10167 (2642)	8454 (3108)
$AUC_{0\text{-}\infty}$ (pg·h/mL)	885 (215)	6797 (2603)	10256 (2649)	8526 (3119)
CL^{ss} (L/h)	18.3 (5.09)	NC	NC	NC
ke (h^{-1})	0.053 (0.02)	0.049 (0.01)	0.047 (0.01)	0.048 (0.011)
C^{ss} (pg/mL)	NA	40.1 (14.9)	59.6 (16.1)	49.8 (18.1)
FI (%)	NA	115 (20.8)	111 (16.9)	113 (18.7)
k_0 (µg/day)	NA	18.3 (7.23)	22.9 (5.08)	20.5 (6.59)

NC = not calculated; NA = not applicable

Since the effect of anatomical site may be considered clinically insignificant, computed mean delivery rates are149 and 20.6 µg/day for 17d-NGM and EE respectively, and hence sponsor's labeled dose of 150 µg/day (17d-NGM) and 20 µg/day (EE) are acceptable. These *average* values were, however, associated with mean variability of ≈ 25% CV for 17d-NGM and ≈ 30% CV for EE.

Analytical

Q1. Which metabolites have been selected for analysis and why?

Based on information available from combination OCs, *in vivo* literature and *in vitro* experimental evidence of metabolic pathways of NGM, 17d-NGM and EE, and the consideration that ORTHO EVRA is a transdermal system, total 17d-NGM (17 deacetylnorgestimate), NG (norgestrel) and EE were primarily assayed from all serum samples. Other metabolites of 17d-NGM and EE were in insignificant levels in serum for analysis.

Q2. What bioanalytical methods are used to assess concentrations, and how reliable are the methods?

APPEARS THIS WAY
ON ORIGINAL

Number of Pages Redacted 5

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Draft Labeling
(not releasable

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dhruba Chatterjee
11/16/01 02:26:00 PM
BIOPHARMACEUTICS
Nothing outstanding
Final CPB review for original NDA 21-180

Ameeta Parekh
11/19/01 12:50:52 PM
BIOPHARMACEUTICS
I concur

APPEARS THIS WAY
ON ORIGINAL

NDA 21-180

ORTHO EVRA®
(norelgestromin/ethinyl estradiol) Transdermal Patch

R.W. Johnson Pharmaceutical Research Institute
1, 4S

PM: Jennifer Mercier
HFD-580
7-4260

Submission Date: December 21, 2000
Primary Goal Date: October 21, 2001
Secondary Goal Date: December 21, 2001

/S/

Abuse Liability Review

N/A

NDA 21-180

ORTHO EVRA®
(norelgestromin/ethinyl estradiol) Transdermal Patch

R.W. Johnson Pharmaceutical Research Institute
1, 4S

PM: Jennifer Mercier
HFD-580
7-4260

Submission Date: December 21, 2000
Primary Goal Date: October 21, 2001
Secondary Goal Date: December 21, 2001

/S/

Micro Review (Efficacy)

N/A

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: October 5, 2001

TO: Jennifer L. Mercier, Project Manager
Daniel Davis, M.D., Clinical Reviewer
Division of Reproductive and Urologic Drug Products, HFD-580

THROUGH: John R. Martin, M.D., Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Constance Lewin, M.D.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-180

APPLICANT: R. W. Johnson Pharmaceutical Research Institute

DRUG: Ortho-Evra (transdermal 17-deacetylnorgestimate and ethinyl estradiol)

CHEMICAL CLASSIFICATION: 3

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Prevention of pregnancy

CONSULTATION REQUEST DATE: February 22, 2001

ACTION GOAL DATE: October 21, 2001

I. BACKGROUND:

Routine clinical inspections were conducted in support of the above-noted application and focused on the conduct of protocols NRGEEP-CONT-002 and NRGEEP-CONT-004. Doctors John P. Lenihan, Jr.; Mary L. Meador; and Steven Rosenfeld were chosen for inspection. Goals of the inspections included validation of the primary efficacy endpoint data and safety data, as well as an evaluation of the adequacy of informed consent.

II. RESULTS (by protocol/site):

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Lenihan	Tacoma	Washington	March 22, 2001	June 6, 2001	VAI-R
Meador	Bend	Oregon	March 22, 2001	June 4, 2001	NAI
Rosenfeld	Tucson	Arizona	March 22, 2001	October 4, 2001	NAI

Protocol NRGEEP-CONT-002

1. Site #1 (John P. Lenihan, Jr., M.D. – Tacoma, Washington):

Sixty-nine subjects were enrolled at this site, 35 of whom completed the study. Records for all subjects were reviewed. Inspection revealed a number of regulatory violations; a Form FDA 483 was issued for inadequate reporting of several non-serious adverse events, protocol violations, and recordkeeping inadequacies/inaccuracies. Dr. Lenihan has responded in writing and has adequately addressed all of the inspectional findings.

Data appear acceptable.

2. Site #2 (Mary L. Meador, M.D. – Bend, Oregon):

Sixty-one subjects were enrolled at this site, 37 of whom completed the study. Records were reviewed for nine subjects. No regulatory violations were noted; a Form FDA 483 was not issued.

Data appear acceptable.

Protocol NRGEEP-CONT-004

Site #3 (Steven Rosenfeld, M.D. – Tucson, Arizona):

Sixty subjects were enrolled at this site, 28 of whom completed the study. Records were reviewed for 32 subjects. No regulatory violations were noted; a Form FDA 483 was not issued.

It is noted that initially at this site, Jose M. Ruiz III, M.D., was the principal investigator, and Dr. Steven Rosenfeld was a sub-investigator. Dr. Rosenfeld became principal investigator, and assumed primary responsibility for the study, after Dr. Ruiz moved out of the state of Arizona. Dr. Ruiz's conduct of the protocol was inspected as part of the inspection of Dr. Rosenfeld.

Data appear acceptable.

APPEARS THIS WAY
ON ORIGINAL

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Routine clinical inspections conducted in support of NDA #21-180 focused on protocol NRGEEP-CONT-002 as conducted by Drs. John P. Lenihan, Jr., and Mary L. Meador; and protocol NRGEEP-CONT-004 as conducted by Drs. Jose Ruiz and Steven Rosenfeld. Drs. Ruiz and Rosenfeld were successive principal investigators at the same site in Tucson, Arizona. Dr. Ruiz's conduct of protocol NRGEEP-CONT-004 was evaluated as part of the inspection of Dr. Rosenfeld.

Inspection of Drs. Meador and Rosenfeld revealed that they and Dr. Ruiz appear to have conducted their respective protocols in compliance with federal regulations. Inspection of Dr. Lenihan revealed a number of regulatory violations, but these have been adequately addressed and do not adversely impact acceptability of the data generated by Dr. Lenihan in protocol NRGEEP-CONT-002. These inspections did not specifically investigate the reasons for study discontinuation in large numbers of subjects at each of these sites.

It appears that the data generated by Drs. Lenihan, Meador, Ruiz and Rosenfeld may be used in support of the pending application.

Key to Classification:

NAI = No deviation from regulations. Data acceptable
VAI = Minor deviation(s) from regulations. Data acceptable
VAI-r = Deviation(s) from regulations, response requested. Data acceptable
OAI = Significant deviations from regulations. Data unreliable

/S/

Constance Lewin, M.D.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

/S/

John R. Martin, M.D.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

DISTRIBUTION:
NDA 21-180
Division File
HFD-45/Program Management Staff (electronic copy)
HFD-47/Pratt /Lewin
HFD-47/GCP I Branch Chief
HFD-47/Reading File

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Mercier

Food and Drug Administration
Rockville MD 20857

OCT - 9

Steven Rosenfeld, M.D.
El Rio Ob/Gyn Associates
445 N. Silverbell Road, Suite 201
Tucson, Arizona 85745

Dear Dr. Rosenfeld:

Between August 14 and 17, 2001, Mr. Randall N. Johnson, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol NRGEEP-CONT-004) of the investigational drug Ortho-Evra (transdermal 17-deacetylnorgestimate and ethinyl estradiol), performed for R. W. Johnson Pharmaceutical Research Institute. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did adhere to pertinent federal regulations and good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Johnson during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address listed below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, Maryland 20855

FEI: 3003424231
Field Classification: NAI
Headquarters Classification:
__X__1)NAI
_____2)VAI-no response required
_____3)VAI-response requested

Deficiencies noted: None

cc:
HFA-224
HFD-580 Doc.Rm. NDA#21-180
HFD-580 Review Div.Dir./Allen
HFD-580 MO/Davis
HFD-580 PM/Mercier
HFD-45 Reading File
HFD-46 Chron File
HFD-46 GCP File #10474
HFD-46 GCP Reviewer/Lewin
HFD-46 GCP Br Chief/Martin
HFD-46 CSO/Ibarra-Pratt
HFR-PA250 DIB/Kozick
HFR-PA2565 Bimo Monitor/Koller
HFR-PA2530 Field Investigator/Johnson

r/d: CL:10-05-01
reviewed:JM:10-05-01
f/t:jau:10-09-01

APPEARS THIS WAY
ON ORIGINAL

Reviewer Note to Rev. Div. M.O.

This routine inspection was conducted in support of pending NDA #21-180 and focused on the conduct of protocol NRGEEP-CONT-004. Please note that initially at this site, Jose M. Ruiz III, M.D., was the principal investigator, and Dr. Steven Rosenfeld was a sub-investigator. Dr. Rosenfeld became principal investigator, and assumed primary responsibility for the study, after Dr. Ruiz moved out of the state of Arizona. Dr. Ruiz's conduct of the protocol was inspected as part of the inspection of Dr. Rosenfeld.

Sixty subjects were enrolled at this site, 28 of whom completed the study. Reasons for discontinuation are not discussed in the establishment inspection report. Records were reviewed for 52 subjects. No regulatory violations were noted; a Form FDA 483 was not issued.

Please note that due to its nature, the primary efficacy endpoint could not be validated. For this study, the primary efficacy endpoint was contraceptive efficacy as assessed by the Pearl Index and lift table analysis. The Pearl Index is an estimate of the number of pregnancies per 100 women-years of product use. The endpoints of interest in the life table analysis were the 6-cycle and 13-cycle gross cumulative probabilities of pregnancy. Although these parameters could not be validated, individual subject pregnancy results were reviewed at the inspection.

Data appear acceptable.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Mercier

Food and Drug Administration
Rockville MD 20857

SEP 14

John P. Lenihan, M.D.
314 Martin Luther King Jr. Way, Suite 104
Tacoma, Washington 98405

Dear Dr. Lenihan:

We acknowledge receipt of your August 22, 2001, letter in response to our August 2, 2001, letter regarding observations made during our inspection conducted between May 17 through May 25, 2001. In our letter, we summarized observations that were in violation of FDA regulations, and we requested your written response to these violations, with regard to actions you had taken, or would take, to achieve compliance with FDA regulations. In addition, we acknowledge your June 5, 2001, written response to the Form FDA 483, Inspectional Observations. Please note that our letter dated August 2, 2001 was sent to you prior to the receipt of your June 5, 2001, response letter.

We trust that the actions described in your letter will provide adequate measures to bring your site into compliance with FDA regulations. We will keep this and all related correspondence on file for future reference.

Should you desire to receive a copy of the FDA regulations that apply to clinical investigators, or have other questions regarding FDA regulations, please do not hesitate to contact me in writing at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, Maryland 20855

cc:
HFA-224
HFD-580/Doc. Rm.: NDA 21-180
HFD-580/Mercier
HFD-580/Davis
HFD-580/Dixon
HFD-45/Reading File
HFD-46/Chron File
HFD-46/GCP file #10389
HFD-46/Pratt
HFD-46/Lewin
HFD-46/Martin
HFR-PA3540/Anderson
HFR-PA350/Corcoran
HFR-PA3540/Mattson

Field Classification: VAI
Headquarters Classification:
_____1)NAI
_____2)VAI (no response required)
___x__3)VAI-R (response requested)
_____4)VAI-RR (adequate response received)
_____5)OAI-WL

Deficiencies noted:

____inadequate consent form
____inadequate drug accountability
__x__deviation from protocol
__x__inadequate records
__x__failure to report ADRs
____failure to obtain IRB approval
____failure to personally conduct or supervise study
____other

r/d: drafted:pratt:9/13/01
reviewed:jrm:9/13/01
final type:jau:9/13/01

DEPARTMENT OF HEALTH & HUMAN SERVICES

Mercier

Food and Drug Administration
Rockville MD 20857

AUG - 2 2001

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

John P. Lenihan, M.D.
314 Martin Luther King Jr. Way, Suite 104
Tacoma, Washington 98405

Dear Dr. Lenihan:

Between May 17 through May 25, 2001, Mr. Carl Anderson representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study, Protocol # NRGEEP-CONT-002, of the investigational drug, transdermal 17-deacetylnorgestimate and ethinyl estradiol (Ortho-Evra), performed for the R.W. Johnson Pharmaceutical Research Institute. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected. At the conclusion of the inspection, Mr. Anderson discussed his findings with you.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to all U.S. Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects. We wish to emphasize the following:

1. You failed to report adverse events. Your records show that:
   A. Subject #28015 withdrew from the study for increased menstrual flow and cramping, although the case report form (CRF) lists the reason for withdrawal as "subject choice," and not "adverse event." The adverse events were also not listed as Adverse Events on the CRFs for visits 1 and 2.

   In addition, the following events were not recorded as Adverse Events on the CRFs:
   B. Subject #s16028, and 36038 experienced patch application site irritation,
   C. Subject # 16038 experienced headaches, and
   D. Subject # 36040 experienced very heavy menstrual flow.

2. You failed to conduct your study in accordance with the approved protocol.
   A. Subject # 31018 missed her Cycle 6 appointment scheduled for 9/8/98, and this appointment was not kept until 12/17/98, due to incarceration. According to the protocol, she should have been listed as "lost to follow-up" in the CRF.
   B. Subject #s 16041 and 36029 did not have urine pregnancy tests performed prior to dispensing study drug as required by the protocol.
   C. The post-study pregnancy test for subject # 36030 was performed outside of the protocol-specified time frame.
   D. Documentation of a post-study pregnancy test for subject # 28022 was not found.

3. You failed to maintain adequate and accurate records, in that entries were made in subjects' diaries by the study coordinator without subjects' initials as required by the protocol-specific worksheets. In addition, the inspection found evidence that for subject #16029, a lost diary was recreated by the coordinator, based on a conversation with the subject, without the subject dating and initialing the diary.

Because of the violations of FDA regulations discussed above, we request that you inform this office, in writing, of the actions you have taken or plan to take to assure that the findings noted above are not repeated in any ongoing or future studies and to bring your procedures in compliance with FDA regulations.

We appreciate the cooperation shown Mr. Anderson during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, Maryland 20855

APPEARS THIS WAY
ON ORIGINAL

cc:
HFA-224
HFD-580/Doc. Rm.: NDA 21-180
HFD-580/Mercier
HFD-580/Davis
HFD-580/Dixon
HFD-45/Reading File
HFD-46/Chron File
HFD-46/GCP file #10389
HFD-46/Molchan
HFD-46/Martin
HFR-PA3540/Anderson
HFR-PA350/Corcoran
HFR-PA3540/Mattson

Field Classification: VAI
Headquarters Classification:
_____1)NAI
_____2)VAI (no response required)
__x__3)VAI-R (response requested)
_____4)VAI-RR (adequate response received)
_____5)OAI-WL

Deficiencies noted:

____inadequate consent form
____inadequate drug accountability
__x__deviation from protocol
__x__inadequate records
__x__failure to report ADRs
____failure to obtain IRB approval
____failure to personally conduct or supervise study
____other

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r/d: drafted/sem/07.30.01
reviewed:jrm:7/31/01
final type:jau:8/1/01

Note to Review Division:

Our review of the information provided to us regarding the inspection of this clinical investigator concludes that there were some problems with the data at this site. One that is concerning is the inadequate reporting of adverse events. Although the adverse events that were not reported were not serious, the numbers of problems such as headaches, increased menstrual flow, and patch application site irritation are not accurate. Also, as reported by the field investigator, numerous entries in subjects' diaries were made by the study coordinator without the subjects' initialing.

Sixty-nine subjects were enrolled at this site; 35 completed the study. The inspector reviewed all records for the presence of signed informed consent forms and the primary efficacy endpoint (post study urine pregnancy test). Fifty charts were also examined to check the accuracy and clarity of various records. Our final classification of this inspection is VAI-R.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Mercier

Food and Drug Administration
Rockville MD 20857

JUN 13 2001

Mary L. Meador, M.D.
Bend Memorial Clinic
1501 NE Medical Center Dr.
Bend, Oregon 97701

Dear Dr. Meador:

Between April 23-26, 2001, Mr. James Henry representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol NRGEEP-CONT-002, NDA 21-180) of the investigational drug, transdermal 17-deacetylnorgestimate and ethinyl estradiol (Ortho-Evra), performed for the R.W. Johnson Pharmaceutical Research Institute. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all U.S. Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects. At the conclusion of the inspection, Mr. Henry discussed his findings with you and your staff.

We appreciate the cooperation shown Mr. Henry during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, Maryland 20855

cc:
HFA-224
HFD-580/Doc. Rm.: NDA 21-180
HFD-580/Mercier
HFD-580/Davis
HFD-580/Dixon
HFD-45/Reading File
HFD-46/Chron File
HFD-46/GCP file #10383
HFD-46/Molchan
HFR-PA3515/Henry
HFR-PA350/Corcoran
HFR-PA3540/Mattson

Field Classification: Referred to Center
Headquarters Classification: NAI

___x__1)NAI
_____2)VAI (no response required)
_____3)VAI-R (30 day response requested)
_____4)VAI-RR (adequate response received)
_____5)OAI-WL

Deficiencies noted:

____inadequate consent form
____inadequate drug accountability
____deviation from protocol
____inadequate records
____failure to report ADRs
____failure to obtain IRB approval
____failure to personally conduct or supervise study
____other

r/d: drafted/sem/06.12.01
reviewed:jrm:6.12.01
final type:jau:6.13.01

APPEARS THIS WAY
ON ORIGINAL

Note to Review Division:

Our review of the information provided to us regarding the inspection of this clinical investigator concludes that the data at this site appears to be acceptable for use in support of the NDA submission. Sixty-one subjects were enrolled at this site; 37 completed the study. The inspector reviewed all records for the presence of signed informed consent forms and reviewed medical records and case report forms in depth for 9 subjects. Our final classification of this inspection is No Action Indicated (NAI).

Although none of the audited subjects became pregnant during the study, note that the formal primary efficacy endpoint, defined as contraceptive efficacy as assessed by the Pearl Index and life table analysis, was not evaluated.

APPEARS THIS WAY
ON ORIGINAL