CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-180

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA NUMBER:	21-180
DATE RECEIVED BY CENTER:	December 21, 2000
NAME OF DRUG:	Ortho Evra™ (Norelgestromin/Ethinyl Estradiol)
INDICATION:	Contraception
SPONSOR:	The R.W. Johnson Pharmaceutical Research Institute
STATISTICAL REVIEWER:	Moh-Jee Ng (HFD-715)
STATISTICAL TEAM REVIEWER:	Michael Welch (HFD-715)
BIOMETRICS DIVISION DIRECTOR:	S. Edward Nevius (HFD-715)
CLINICAL REVIEWER:	Daniel Davis, M.D. (HFD-580)
PROJECT MANAGER:	Jennifer Mercier (HFD-580)

1. Introduction

The sponsor presented the results of 3 clinical studies to establish the efficacy of Ortho Evra™ for prevention of pregnancy. These clinical studies are open-label to evaluate contraceptive efficacy and safety of the transdermal contraceptive system of 17-deacetylnorgestimate (17d-NGM) and ethinyl estradiol (EE). The studies were of 13 cycles with each cycle consisting of a 21-day patch period followed by a 7-day patch-free period. The studies required at least 20,000 cycles of exposure to EVRA, and at least 500 women completing all 13 cycles. Table 1summaries these three clinical trials.

Table 1
Summary of all Clinical Trials

Study # Start Date	# of Centers	Trial Design	Treatment Groups Application Times	Subjects evaluable for efficacy /Total on-therapy cycles
NRGEEP-CONT-004 10/17/97	45centers/ (39 US 6 Canada)	Multicenter, randomized, open-label, parallel study, compared EVRA with triphasic regimen of levonorgestrel and EE	**EVRA:** 250 µg 17d-NGM, 25 µg EE, days 1-21 patch –free, days 22-28 **Triphasil:** 50 µg levonorgestrel / 30 µg EE, days 1-6 75 µg levonorgestrel / 40 µg EE, days 7-11 125 µg levonorgestrel / 30 µg EE, days 12-21 placebo, days 22-28	811/5,244 605/4,169
NRGEEP-CONT-003 10/17/97	65 outside US	Multicenter, randomized, open-label, parallel study, compared EVRA with a marketed monophasic regimen of desogestrel and EE (Mercilon)	**EVRA:** 250 µg 17d-NGM, 25 µg EE, days 1-21 patch –free, days 22-28 **Mercilon:** 150 µg desogestrel / 20 µg EE, days 1-21 drug-free, days 22-28	844/5,921 640/4,667
NRGEEP-CONT-002 10/18/97	73 centers/ (31 in US 42 outside US)	Multicenter, non-randomized, open-label, noncomparative study.	**EVRA:** 250 µg 17d-NGM, 25 µg EE, days 1-21 patch –free, days 22-28	1,664/10,994

Keywords: Clinical studies, NDA review

2. Clinical studies

2.1 NRGEEP-CONT-004

This was a randomized, open label, parallel and multicenter study. Subjects were treated with either EVRA or Triphasil (containing 50 µg levonorgestrel/30 µg EE [Days 1-6], 75 µg levonorgestrel/40 µg EE [Days 7-11], and 125 µg levonorgestrel/30 µg EE [Days 12-21]). The ratio of subjects randomized to the EVRA group versus the Triphasil group was 4:3. Among 1,495 subjects enrolled in 45 centers (6 in Canada and 39 in US), 1,416 subjects took study drug, 811 subjects to receive EVRA and 605 to receive Triphasil. One-third of subjects were to be treated for 13 28-day cycles, the remaining were to be treated for 6 28-day cycles.

2.2 Clinical studies – NRGEEP-CONT-003

This was a randomized, open label, parallel and multicenter study. Subjects were treated with either EVRA or Mercilon (containing 150 µg desogestrel/20 µg EE). The ratio of subjects randomized to the EVRA group versus the Mercilon group was 4:3. Among 1,517 subjects enrolled in 65 centers (10 countries), 1,484 subjects took study drug, 844 to receive EVRA and 640 to receive Mercilon. One-third of subjects were to be treated for 13 28-day cycles, the remaining were to be treated for 6 28-day cycles.

2.3 Clinical studies – NRGEEP-CONT-002

This was a non-randomized, non-comparative, open label, multicenter study. Subjects were treated with EVRA. Among 1,754 subjects enrolled in 73 centers (31 in US and 42 outside United States), 1672 subjects took the study drug and were evaluable for safety analyses. One-third of subjects were to be treated for 13 28-day cycles, the remaining were to be treated for 6 28-day cycles.

3. Summary Withdrawal from Study

Table 2 summarizes the reason for subject discontinuation by treatment group.

Table 2
Enrollment and Reasons for withdrawal of Study Subjects

	CONT-004		CONT-003		CONT-002
	EVRA	Triphasil	EVRA	Mercilon	EVRA
Number randomized	571	458	844	640	1210
Number discontinued	240 (29.6%)	147(24.3%)	168 (20%)	93 (15%)	462 (28%)
Lost to Follow-up	32 (3.9%)	48 (7.9%)	14 (2%)	14 (2.2%)	84 (5%)
Adverse Event	102 (12.6%)	33(5.5%)	81 (10%)	29 (5%)	213 (13%)
Subject Choice	77(9.5%)	40(6.6%)	49 (6%)	29 (5%)	108 (7%)
Protocol Violation	6(0.7%)	5(0.8%)	6 (.7%)	3 (0.5%)	18 (1%)
Pregnancy	4(0.5%)	7(1.2%)	3 (.4%)	4 (.6%)	5 (.3%)
Other	19(2.3%)	13(2.1%)	15 (1.8%)	13 (2%)	33 (2%)
Unknown	1(0.1%)	0	0	1 (.2%)	1 (.1%)

Source: Study CONT-004, Vol 1.076, Table 7.1
Study CONT-003, Vol 1.079, Table 7.1
Study CONT-002, Vol 1.082, Table 6

For studies CONT-004 and CONT-003, the rates of withdrawal due to adverse events and subject choice were higher in the EVRA group; lost to Follow-up was higher in the Triphasil group. However in the study CONT-002, the rates of withdrawal due to lost to follow-up and adverse events were the highest among these 3 studies.

4. Summary of Pregnancies

There were 35 on-therapy pregnancies reported (See Table 3) in the 3 studies. Each on-therapy pregnancy was classified as either a method failure or a user failure. Pregnancies were designated as user failures only if there was documentation that the subjects did not use the study drug correctly. Pregnancies were designated as Method failure for those with no documentation.

Thirty five pregnancies were reported (see Table 2)

- Pre-therapy Pregnancies – those in which conception occurred prior to intake of study drug: none
- In-therapy Pregnancies – those in which conception occurred after the first tablet was taken and prior to discontinuation of the study drug: 12 in CONT-004, 6 in CONT-003, and 6 in CONT-002.
- Post-therapy Pregnancies – those in which deception occurred after discontinuation of study drug: 4 in CONT-004, 4 in CONT-003, and 3 in CONT-002.

Table 3
Summary of Pregnancies

	CONT-004	CONT-003	CONT-002	TOTAL
Pre-therapy Pregnancies	0	0	0	0
On-therapy Pregnancies	12	6	6	24
Method Failure	8	4	5	17
User Failure	4	2	1	7
Post-therapy Pregnancies	4	4	3	11
Total Pregnancies	16	10	9	35

5. Sponsor's Contraceptive Efficacy Method

Contraceptive efficacy was determined by pregnancy results estimated from the Pearl indices (Higgins and Wilkens, 1985) and life table analyses (Procedure Lifetest of SAS). Pregnancy rates included subjects who took the study drug for at least one day and who had no pre-therapy pregnancies. The primary contraceptive efficacy parameter was determined by the Overall Pearl Index which is based only on-therapy pregnancies. The endpoints of interest for the life table method were the 6-cycle and 13-cycle with 2-sided 95% confidence intervals.

The Pearl Index is defined as the number of in-treatment pregnancies per 100 woman-years times 1300 divided by the total number of cycles of exposure. The contraceptive efficacy was measured by the overall and method failure Pearl indices, with 95% confidence interval and standard error were calculated for each of the indices. Pearl Index was based on data collected through Cycle 13.

The sponsor used SAS procedure Lifetest to estimate the probability of pregnancies in a fixed time period for on-therapy pregnancy subjects. The endpoints of interest were the 6-cycle and 13-cycle cumulative probabilities of pregnancy, with 95% confidence intervals.

6. Sponsor's Efficacy Results

Contraceptive effectiveness was based on pregnancy rates using the Pearl Index and Life-Table analysis.

For study CONT-004, the method failure Pearl Indices are 0.99 [0.02, 1.96] for EVRA and 1.25 [0.02,2.47] for Triphasil. The overall Pearl Indices are 1.24 [.15,2.33] in EVRA and 2.18 [0.57,13.8] in Triphasil. The life-table pregnancy rates of method failure through 13 cycles are 1.1% for EVRA and 1.3% for Triphasil. The overall life table pregnancy rates through 13 cycles are 1.3% for EVRA and 1.8% for Triphasil group. The sponsor concluded that the life-table analyses indicated the probabilities of pregnancy through 13 cycles are similar for both treatment groups. The relative risk of pregnancy using EVRA as compared with the Triphasil group is 0.57 which in not statistically significant (p=0.332),

For study CONT-003, the method failure Pearl Indices are 0.66[0, 1.4] for EVRA and 0.28 [0, .83] for Mercilon. The overall Pearl Indices are 0.88[.02,1.74] for EVRA, and 0.56 [0,1.33] for Mercilon group. The life-table pregnancy rates of method failure through 13 cycles are 0.4% for EVRA and 0.2% for Mercilon. The overall life table pregnancy rates through 13 cycles are 0.5% for EVRA and 0.3% for Mercilon. The Life Table analyses indicated the probability of pregnancy through 13 cycles are similar for both treatment groups. The relative risk of pregnancy using EVRA as compared with Mercilon is 1.55 which is not statistically significant (p=0.613).

For study CONT-002, the method failure and overall Pearl Indices are 0.59[.07, 1.11] and 0.71[.14,1.28], respectively. The life-table pregnancy rates of method failure and overall through 13 cycles were 0.4% and 0.7%, respectively.

Table 4
Sponsor's Efficacy Result
Pearl Index and Life Table Pregnancy Rate

	CONT-004		CONT-003		CONT-002	Total
	EVRA	Triphasil	EVRA	Mercilon	EVRA	EVRA
Total # of Subject	811	605	844	640	1,664	3,319
Total Cycle of Exposure	5,240	4,167	5,921	4,667	10,994	22,155
# women year	403	321	455	359	846	1,704
Method Failure						
On-therapy Pregnancies	4	4	3	1	5	12
Pearl Index/100 women years (95% CI)	0.99 (0.02,1.96)	1.25 (0.02,2.47)	0.66 (0, 1.4)	0.28 (0, .83)	0.59 (.07,1.1)	0.7 (0.31,1.1)
Life-Table at Cycle 6 (95% CI)	0.4% (0,1.0%)	0.6% (0,1.2%)	0.4% (0, 0.9%)	0.2% (0,0.5%)	0.4% (0,0.7%)	0.4% (0.2%,0.6%)
Life-Table at Cycle 13 95% CI)	1.1% (0,2.5%)	1.3% (0,2.7%)	0.4% (0, 0.9%)	0.2% (0,0.5%)	0.4% (0,0.7%)	0.6% (0.2%,.9%)
Overall						
On-therapy Pregnancies	5	7	4	2	6	15
Pearl Index/100 women years (95% CI)	1.24 (0.15,2.33)	2.18 (0.57,3.8)	0.88 (0.02, 1.74)	0.56 (0, 1.33)	0.71 (.14,1.28)	0.88 (0.44,1.33)
Life-Table at Cycle 6 (95% CI)	0.6% (0,1.2%)	1.2% (0.2%2.1%)	0.5% (0, 1%)	0.3% (0,0.8%)	0.4% (0,0.7%)	0.5% (0.2%,0.7%)
Life-Table at Cycle 13 95% CI)	1.3% (0,2.7%)	1.8% (0.2%,3.4%)	0.5% (0, 1%)	0.3% (0,0.8%)	0.7% (0,1.4%)	0.8% (0.3%,1.3%)
Relative Risk for pregnancy compared with market drug (p-value)	0.567 (p=0.332)		1.55 (p=0.613)			

7. Reviewer's Analysis and Comments

This reviewer's analyses are based on the data provided in the electronic submission. The results of this reviewer's analysis are consistent with the sponsor's efficacy results (see Table 4). The medical reviewer requested to change 1 post-pregnancy (patient # is 20018) to on-therapy pregnancy of CONT-002. Therefore increasing the number of on-therapy pregnancies from 6 to 7 and the overall Pearl index from 0.71 to 0.83.

For study CONT-004, the overall and method failure Pearl Indices are higher in the Triphasil group than in the EVRA group. The observed relative risk for all on-therapy pregnancies who received EVRA is less than one (.567), indicating that a subject in the EVRA group would be less likely to become pregnant than a subject in the Triphasil treatment group. However, the differences are not statistically significant.

For study CONT-003, the overall and method failure Pearl Indices are lower in the Mercilon group than in the EVRA group. The observed relative risk for all on-therapy pregnancies who received EVRA is greater that one (1.55), indicating that a subject in the

EVRA would be more likely to become pregnant that a subject in the Mercilon treatment group. However, the differences are not statistically significant.

This reviewer performs subgroup analysis by ages less than 35 years old and women with baseline body weight less than 90 kg. (See Table 5)

Table 5
Reviewer's Pearl Index Result
Overall Evaluation Group

	CONT-004		CONT-003	
	EVRA	Triphasil	EVRA	Mercilon
Subjects less than < 35 years old				
Total # of Subject	686	520	694	544
Total Cycle of Exposure	4363	3543	4836	3914
# women-cycle	336	273	372	301
On-therapy pregnancies	5	7	3	2
Pearl Index	1.5	2.6	.8	.6
Odds Ratio P-value for pregnancy compared with control drug (95% CI)	.5381 p=.4355(.1339,4.983)		1.177 P=1.000 (.1343,14.13)	
Subjects with Baseline Body Weight < 90 kg				
Total # of Subject	794	586	830	629
Total Cycle of Exposure	5121	4057	5814	4590
# women-cycle	394	312	447	353
On-therapy pregnancies	4	6	4	2
Pearl Index	1.1	1.9	.9	.6
Odds Ratio P-value for pregnancy compared with control drug (95% CI)	.4895 p=.419 (.1012, 2.076)		1.518 p=.9598 (.2167, 16.83)	

There is only 1 on-therapy pregnancy in women greater than 35 years old. This on-therapy pregnancy is in study CONT-003 EVRA treatment group.

There are 6 on-therapy pregnancies in women with baseline body weight $\geq$ 90 kg. All subjects are less than 35 years old.

- 2 in CONT-004 (1 in EVRA and the other 1 in Triphasil group)
- 4 in CONT-002 EVRA group

The pregnancy odds ratios pertain to the Pearl Index estimate for EVRA relative to Triphasil and Mercilon. The odds ratios are higher in the CONT-003 than in the CONT-004 for both subgroups. However, the differences are not statistically significant (p=1.000 and =0.9598). The odd ratios suggest the risk for pregnancy was about the same as that for women under 35 years of age and for women whose baseline body weight is less than 90 kg. This reviewer did not perform subgroup analyses for study CONT-002 as there is no control group in this study.

Moh-Jee Ng, M.S.
Mathematical Statistician

Concur: Mike Welch, Ph.D.

Ed Nevius, Ph.D.

cc. Original NDA 21-180
HFD-580 / Division file
HFD-580 / DDavis, JMercier
HFD-715/ENevius,MWelch, CAnello, MNg,

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Moh-Jee Ng
11/9/01 07:57:41 AM
BIOMETRICS

Mike Welch
11/9/01 09:37:21 AM
BIOMETRICS
Concur with review
Need signoffs by 11/9

S. Edward Nevius
11/13/01 11:44:59 AM
BIOMETRICS
Concur with review.

APPEARS THIS WAY
ON ORIGINAL

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-180	Brand Name	ORTHO-EVRA
OCPB Division	II	Generic Name	Norelgestromin/ethinylestradiol
Medical Division	DRUDP	Drug Class	Sterold hormone combination
OCPB Reviewer	DJ Chatterjee (filled by Johnny Lau)	Indication(s)	Contraception
OCPB Team Leader	Ameeta Parekh	Dosage Form	Transdermal system
Date of Submission	12/21/2000	Dosing Regimen	(7-day/patch)x3 ; 7 days off
Estimated Due Date of OCPB Review	9/7/2000	Route of Administration	Transdermal
PDUFA Due Date	10/21/2001	Sponsor	RW Johnson
Division Due Date	9/21/2001	Priority Classification	1S

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x		/	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	x			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	2		
multiple dose:	x	2		
Patients-				
single dose:				
multiple dose:				
Dose proportionality -	[redacted]	[redacted]		
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	1		
In-vivo effects of primary drug:				
In-vitro:	x	1		
Subpopulation studies -		[redacted]		
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:		[redacted]		
Phase 2:				
Phase 3:				

PK/PD:		[redacted]		
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	[redacted]	[redacted]		
Data rich:	x	1		
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted]			

Filability and QBR comments

	"X" if yes	*Comments*
Application filable ?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Briefing (on 11/9/01, 9:30 – 10.30 AM) attended by: DJ Chatterjee, A. Parekh, J. Hunt, H. Malinowski, J. Lazor, S. Haidar, M. Kim (all from OCPB), J. Mercier (PM), A. Mitra (CMC) & D. Davis (MO).

CC: NDA 21-180, HFD-850 (Electronic Entry or Lee), HFD-580 (CSO), HFD-870 (TL, DD, DDD), CDR (B. Murphy)

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

Statistical Review (Carci Studies)

N/A