SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: ORTHO EVRA® NAME OF ACTIVE INGREDIENT(S): 17-deacetylnorgestimate/ethinyl estradiol	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: NRGEEP P01-1026

Title of Study: A Study of the Pharmacokinetics of ORTHO EVRA® Exhibiting Faster Equilibration Profile Compared With the Pharmacokinetics of Currently Marketed ORTHO EVRA® in Healthy Female Volunteers

Principal Investigator: Lawrence A. Galitz, M.D., SFBC International, Miami, FL, USA

Publication (Reference): None

Studied Period (years): Clinical Conduct: 21 May 2004 to 18 August 2004
Sample Analysis: NGMN/NG: 13 July 2004 to 17 September 2004;
EE: 13 July 2004 to 01 October 2004

Phase of development: 1

Objectives: The primary objective was to compare the pharmacokinetics of ORTHO EVRA exhibiting a faster equilibration profile with a currently marketed ORTHO EVRA lot, after application to the buttock. Safety was also assessed.

Methodology: This was a single-center, randomized, open-label, 2-way crossover study. Healthy, adult, nonpregnant women were randomized to wear either ORTHO EVRA with a faster equilibration profile or currently marketed ORTHO EVRA for 7 days during the open-label phase, washing out for 21 days and then crossing over to the other treatment for 7 days. Total study participation time was 7 weeks.

Number of Subjects (planned and analyzed): 40 subjects were planned for randomization; 42 were analyzed for safety, and 40 for pharmacokinetics.

Diagnosis and Main Criteria for Inclusion: Subjects eligible for participation were between the ages of 18 and 45 years inclusive, were healthy, weighed at least 110 pounds with a body mass index (BMI) between 16 and 29.9 kg/m^2 and a hematocrit of at least 36% and ferritin levels above the lower limit of the normal range.

Test Product, Dose and Mode of Administration, Batch No.: ORTHO EVRA from a faster equilibrating lot: Lot number, 0325813; expiration date September 2004. Each patch contains 6.0 mg NGMN and 0.75 mg EE, which deliver to the system an average of 150 µg/day of NGMN and 20 µg/day of EE.

Reference Therapy, Dose and Mode of Administration, Batch No.: ORTHO EVRA from currently marketed lots: Lot number, 62M079; expiration date September 2005. Each patch contains and delivers the same amount of hormones as the test patch.

Duration of Treatment: Two 7-day patch-wear periods separated by a 21-day washout period.

Criteria for Evaluation:

Pharmacokinetics : The following pharmacokinetic parameters were estimated for NGMN, NG, and EE after each patch application: C_{max}, t_{max}, C_{ss} for NGMN and EE, C_{avg} for NG, AUC_{168}, AUC_{240}, and AUC_{∞} for NGMN, NG and EE as well as AUC_{last} for EE, and $t_{1/2}$ for all analytes. Patch adhesion was assessed and scores summarized.

Safety: Safety evaluations included treatment-emergent adverse event monitoring, 12-lead ECG, pregnancy testing, changes in pretreatment to posttreatment clinical laboratory evaluations (hematology, chemistry, urinalysis), vital sign measurements, and physical and gynecologic (including breast) examinations.

Statistical Methods:

Pharmacokinetics: The primary objective of this study was to compare the pharmacokinetics of ORTHO EVRA lots with different in vitro equilibration profiles. AUC_{168}, AUC_{240}, AUC_{∞}, and C_{ss} for NGMN and EE, AUC_{168}, AUC_{240}, AUC_{∞} and C_{avg} for NG were the primary pharmacokinetic parameters of interest. The statistical analyses were carried out for each analyte separately. The analyses were performed on log-transformed estimated pharmacokinetic parameters of interest. Analysis of variance models were fit to the data with one of the pharmacokinetic parameters of interest as the dependent variable and the effects due to treatment sequence group, period and treatment as fixed effects and subject as a random effect. The estimated least square means and intra-subject variability from the ANOVA model were used to construct 90% confidence intervals for the difference in means on the log scale between the 2 treatments.

SYNOPSIS (CONTINUED)

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Statistical Methods: (Continued)

Pharmacokinetics: (Continued) The limits of the confidence intervals were re-transformed using anti-logarithms to obtain 90% confidence intervals for the ratio of the mean pharmacokinetic parameters for test (ORTHO EVRA with faster equilibration) to reference (currently marketed ORTHO EVRA).

Safety: Treatment-emergent adverse events were summarized and individual data listings by subject were provided. Individual subject listings were provided for pre to posttreatment changes in physical and gynecologic examinations (including breast examinations), vital signs, 12-lead electrocardiograms, clinical laboratory test results, and laboratory values outside the normal ranges.

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS: The mean (SD) pharmacokinetic parameter estimates, geometric mean and 90% confidence intervals for EE, NGMN, and NG are presented below. The mean serum concentration-time profiles for EE, NGMN, and NG for the two treatments were similar.

	Arithmetic Mean (SD)		Geometric Mean			
Analyte/Parameter	Faster Equilibrating ORTHO EVRA (N=40)	Currently Marketed ORTHO EVRA (N=40)	Faster Equilibrating ORTHO EVRA (N=40)	Currently Marketed ORTHO EVRA (N=40)	% Ratio Test/Reference	90 % CI
EE						
C_{max} (pg/mL)	65.8 (32.4)	74.4 (44.8)	-	-	-	-
t_{max} (h)	108.14 (45.31)	94.70 (41.37)	-	-	-	-
C_{ss} (pg/mL)	54.1 (23.8)	55.6 (21.9)	49.80	52.48	94.91	87.86 – 102.52
$t_{1/2}$ (h)	18.2 (5.13)[d]	18.0 (4.36)[e]	-	-	-	-
AUC_{168} (pg.h/mL)	7797 (3445)	8024 (3284)	7198.14	7537.65	95.50	88.44 – 103.11
AUC_{240} (pg.h/mL)	8837 (3845)	9197 (3776)	8156.02	8625.36	94.56	87.91 – 101.71
AUC_{∞} (pg.h/mL)	9084 (3814)[d]	9090 (3569)[e]	8411.26[f]	8546.41[f]	98.42	93.08 – 104.06
NGMN						
C_{max} (ng/mL)	0.878 (0.236)	0.873 (0.260)	-	-	-	-
t_{max} (h)	93.14 (34.65)	84.08 (32.35)	-	-	-	-
C_{ss} (ng/mL)	0.738 (0.195)	0.703 (0.195)	0.71	0.68	105.39	98.45 – 112.82
$t_{1/2}$ (h)	28.1 (7.4)[a]	29.4 (10.3)[a]	-	-	-	-
AUC_{168} (ng.h/mL)	110 (30.1)	105 (30.7)	106.44	100.68	105.72	99.12 – 112.76
AUC_{240} (ng.h/mL)	130 (35.5)	123 (33.8)	124.99	118.55	105.44	98.93 – 112.38
AUC_{∞} (ng.h/mL)	137 (38.3)[a]	128 (35.8)[a]	131.31[g]	123.59[g]	106.24	98.38 – 114.73
NG						
C_{max} (ng/mL)	1.26 (0.476)	1.23 (0.553)	-	-	-	-
t_{max} (h)	168.68 (12.79)	168.45 (17.09)	-	-	-	-
C_{avg} (ng/mL)	0.576 (0.242)	0.559 (0.304)	0.53	0.50	106.79	97.44 – 117.03
$t_{1/2}$ (h)	62.9 (35.1)[b]	54.3 (18.2)[c]	-	-	-	-
AUC_{168} (ng.h/mL)	96.7 (40.7)	94.0 (51.1)	89.10	83.44	106.79	97.44 – 117.03
AUC_{240} (ng.h/mL)	161 (61.2)	157 (74.3)	150.01	142.83	105.03	95.60 – 115.38
AUC_{∞} (ng.h/mL)	231 (76.8)[b]	219 (76.4)[c]	225.57[h]	211.56[h]	106.62	95.99 – 118.43

[a] n=34, [b] n=22, [c] n=26, [d] n=39, [e] n=37, [f] n=36, [g] n=30, [h] n=18

SYNOPSIS (CONTINUED)

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PHARMACOKINETIC RESULTS: (Continued) The 90% confidence intervals for geometric mean ratios of all pharmacokinetic parameters (C_{ss}, [or C_{avg}] and AUCs [AUC_{168}, AUC_{240} and AUC_{∞}]) tested for EE, NGMN, and NG fell within the bio-equivalence range of 80% to 125%. For all 3 analytes drug exposure based on AUCs (AUC_{168}, AUC_{240} and AUC_{∞}) and C_{max} was similar for both treatments, as was the half-life ($t_{1/2}$).

SAFETY RESULTS: A total of 26 (62%) subjects reported at least one adverse event during the course of the study. The most common events were headache (12 subjects; 29%), nausea (9 subjects; 21%), and application site reactions (10 subjects; 24%). The majority of all adverse events were mild in severity and possibly or probably related to study drug.

No deaths or serious adverse events occurred during the study. One subject from each treatment sequence group withdrew consent after the 24-hour pharmacokinetic blood sampling; both subjects were withdrawn from the study on Day 4.

No clinically significant changes from screening to final visit occurred in clinical laboratory values, vital signs, physical, gynecologic, and breast examinations, or ECG results.

CONCLUSION:

- The faster equilibrating ORTHO EVRA was bioequivalent to currently marketed ORTHO EVRA based on the pharmacokinetic parameters C_{ss} (or C_{avg}) and AUCs (AUC_{168}, AUC_{240} and AUC_{∞}) for NGMN, NG, and EE.
- Both treatments were safe and well tolerated. No deaths or serious treatment-emergent adverse events were reported.

Date of the report: 18 May 2005

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