SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: ORTHO EVRA® NAME OF ACTIVE INGREDIENT(S): Norelgestromin: 18,19-dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, 3-oxime, (17α) Ethinyl estradiol: 19-Norpregna-1, 3, 5 (10)-trien-20-yne-3, 17-diol (17α)	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: NRGEEP-P01-121 **Title of Study:** A Bioequivalence Study of a Low Cumulative Release Lot of Norelgestromin/Ethinyl Estradiol Transdermal Contraceptive Patches Compared With Currently Marketed ORTHO EVRA® in Healthy Female Volunteers		
Principal Investigator: Aziz Laurent, MD, PPD Development, Austin, Texas, USA		
Publication (Reference): None		
Studied Period (years): Clinical Conduct: From 08 April 2003 to 07 July 2003 Sample Analysis: For ethinyl estradiol: 8 May 2003 to 18 July 2003; For norelgestromin and norgestrel: 12 May 2003 to 03 July 2003		**Phase of development:** 1
Objectives: The primary objective of this study was to assess the bioequivalence of a norelgestromin/ethinyl estradiol (NGMN/EE) transdermal contraceptive system from a lot with a cumulative release profile below the lower limit of the specifications (LOW SPEC NGMN-EE) compared with a currently marketed ORTHO EVRA contraceptive system from a lot with a cumulative release profile well within the specification limits as the reference, after application to the buttock. Safety was also assessed.		
Methodology: This was a single center, randomized, double-blind, 2-way crossover study, with a screening period of ≤21 days, a double-blind treatment phase, and a posttreatment or early withdrawal visit. The double-blind treatment phase included two 7-day treatment periods separated by a 28-day washout period. Forty female subjects were randomly assigned to 1 of 2 treatment-sequence groups. A 20 cm^2 norelgestromin (NGMN)/ethinyl estradiol (EE) transdermal contraceptive patch (LOW SPEC NGMN-EE [test lot] or ORTHO EVRA [reference lot]) was applied to the buttock of each subject on Day 1 and was worn for 7 days. On Day 36, 28 days after removal of the first patch, the alternate treatment was applied. Subjects were admitted to the study unit on the evening before each treatment application. Negative serum pregnancy tests were required at both admissions for a subject to continue in the study. While wearing the patches, subjects were not to engage in physical exercise that promoted sweating; a 10-minute shower was allowed each day, but not bathing, swimming, or use of saunas or whirlpools. The first patch was applied on Day 1 and the second on Day 36. Both patches (LOW SPEC NGMN-EE and ORTHO EVRA) were placed on exactly the same location on the buttock. Before the patches were removed on Day 8 and Day 43, adhesion was evaluated. After removal of each patch, the application site was rated for erythema and site reaction. Blood samples were collected by direct venipuncture for determination of NGMN, norgestrel (NG), and EE serum concentrations at 0 hour (just before patch application) and at 6, 12, 24, 48, 72, 120, 144, 168, 171, 174, 180, 192, 204, 216, and 240 hours after. Subjects were confined for these collections (Days -1 to 2, 8 to 9, 35 to 37, and 43 to 44) and discharged after collection of the 240-hour blood sample. A posttreatment evaluation, including physical and gynecologic examinations, vital signs, laboratory evaluations, and a serum pregnancy test were performed on Day 46 or at early withdrawal. Adverse events, including erythema and application site reaction, were evaluated throughout confinements in the study unit and at each visit. Safety was assessed throughout the study.		
Number of Subjects (planned and analyzed): Planned: 40; Analyzed: 43 for Safety; 40 for pharmacokinetics.		
Diagnosis and Main Criteria for Inclusion: Women who were 18 to 45 years of age, inclusive; not pregnant or lactating; healthy as determined by physical and gynecologic examinations, clinical laboratory assessments, vital sign measurements, and a 12-lead electrocardiogram (ECG); and who met all other entry criteria were enrolled.		

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: ORTHO EVRA® NAME OF ACTIVE INGREDIENT(S): Norelgestromin: 18,19-dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, 3-oxime, (17α) Ethinyl estradiol: 19-Norpregna-1, 3, 5 (10)-trien-20-yne-3, 17-diol (17α)	Volume: Page:	

Test Product, Dose and Mode of Administration, Batch No.: Transdermal contraceptive system applied to the skin containing 6.0 mg NGMN and 0.75 mg EE. LOW SPEC NGMN-EE (test): Lot Number 0307256 (expiration date February 2005).

Reference Therapy, Dose and Mode of Administration, Batch No.: Transdermal contraceptive system applied to the skin containing 6.0 mg NGMN and 0.75 mg EE. ORTHO EVRA (reference lot): Lot Number 62M079 (expiration date September 2004).

Duration of Treatment: Seven days with LOW SPEC NGMN-EE and 7 days with ORTHO EVRA.

Criteria for Evaluation:

Pharmacokinetics: The following pharmacokinetic parameters were estimated by model independent methods and summarized: C_{max}, C^{ss} (for NGMN and EE), C_{avg} (for NG), t_{max}, $t_{½}$, AUC_{168}, AUC_{240}, AUC_{last} (for EE), and AUC_{∞}.

Safety: Safety evaluations included adverse event monitoring, standard clinical laboratory evaluations (hematology, serum chemistry, and urinalysis), vital signs measurements, physical and gynecologic examinations (including breast examination), and pregnancy tests.

Statistical Methods:

Pharmacokinetics: For each subject, serum concentration-time profiles were plotted for both treatments. Plasma concentration data at each time point were summarized with mean, standard deviation and coefficient of variation for each treatment. All estimated pharmacokinetic parameters were summarized with mean, median, geometric mean, minimum, maximum, standard deviation, and coefficient of variation for each treatment.

The statistical analysis was carried out for each analyte separately. The primary pharmacokinetic parameters of interest for (1) NGMN and EE were AUC_{240} and C^{ss}, and for (2) NG were AUC_{240} and C_{avg}. The analysis was performed on log-transformed estimated pharmacokinetic parameters. Only the data from subjects who completed the study were included in the statistical analysis. Mixed effects models were fit to the data with 1 of the estimated pharmacokinetic parameters of interest (AUC_{240}, C^{ss}, or C_{avg}) as the dependent variable, treatment-sequence group, period, and treatment as fixed effects, and subject as a random effect. Testing for treatment sequence effect and period effect was carried out at 10% and 5% levels of significance, respectively, using the appropriate error terms. The estimated least square means and intrasubject variability from the mixed effects model was used to construct 90% confidence intervals for the difference in means on the logarithmic scale between the 2 treatments. The limits of the confidence intervals were re-transformed using anti-logarithms to obtain 90% confidence intervals for the ratio (LOW SPEC NGMN-EE to ORTHO EVRA) of the mean pharmacokinetic parameters. The 2 formulations were considered bioequivalent if the 90% confidence intervals for the ratios of mean parameters for analytes fell within the 80% to 125% limits.

Safety: The number of subjects with treatment-emergent adverse events was summarized for each treatment by body system and preferred term, severity, and relationship to study drug. Laboratory data were summarized by the type of laboratory test. The data collected at each scheduled time point and the changes in values from baseline in each treatment period were summarized using descriptive statistics. Vital signs data collected at each scheduled time point, and the changes from baseline for each treatment were summarized using descriptive statistics. Physical and gynecologic examination results were listed.

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: ORTHO EVRA® NAME OF ACTIVE INGREDIENT(S): Norelgestromin: 18,19-dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, 3-oxime, (17α) Ethinyl estradiol: 19-Norpregna-1, 3, 5 (10)-trien-20-yne-3, 17-diol (17α)	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS: Five subjects had predose EE concentrations ≥5% of C_{max} and were excluded from the pharmacokinetic and statistical analyses. The mean plasma concentration-time profiles for NGMN, NG, and EE for the 2 treatments were nearly superimposable. The mean (SD) pharmacokinetic parameters are presented below.

	Norelgestromin		Norgestrel		Ethinyl Estradiol	
Parameter	LOW SPEC NGMN-EE	ORTHO EVRA	LOW SPEC NGMN-EE	ORTHO EVRA	LOW SPEC NGMN-EE	ORTHO EVRA
N	40	40	40	40	35	35
t_{max} (h)	72.49 (35.05)	74.48 (32.91)	163.4 (25.55)	159.4 (29.59)	98.7 (48.0)	100.1 (45.6)
C_{max} (ng/mL)	1.02 (0.287)	1.06 (0.301)	1.26 (0.430)	1.29 (0.492)	81.9 (34.7)[b]	79.2 (28.0)[b]
C^{ss} (ng/mL)	0.793 (0.241)	0.840 (0.284)	0.652 (0.275)[a]	0.650 (0.264)[a]	62.7 (17.4)[b]	65.0 (20.1)[b]
AUC_{168} (ng•h/mL)	124 (37.5)	130 (44.0)	110 (46.2)	109 (44.4)	9409 (2836)[c]	9648 (3121)[c]
AUC_{240} (ng•h/mL)	141 (42.2)	148 (50.7)	172 (64.1)	172 (68.6)	10477 (3097)[c]	10727 (3406)[c]
AUC_{last} (pg•h/mL)	--	--	--	--	10440 (3109)[c]	10709 (3407)[c]
AUC_{∞} (ng•h/mL)	148 (48.5)	161 (50.1)	203 (75.3)	215 (85.8)	10553 (3128)[c]	10804 (3429)[c]
$t_{1/2}$ (h)	32.6 (35.9)	27.8 (8.48)	46.7 (17.9)	44.9 (20.1)	16.4 (3.75)	16.9 (3.65)

[a] C_{avg}; [b] pg/mL; [c] pg•h/mL.

The 90% confidence intervals for the ratios of the geometric means comparing the LOW SPEC NGMN-EE patch with the ORTHO EVRA patch fell within the 80% to 125% limits of bioequivalence for the AUC_{240} and C^{ss} of NGMN and EE and for the AUC_{240} and C_{avg} of NG.

	Geometric Mean			90% Confidence Limits	
Analyte Parameter	LOW SPEC NGMN-EE (Test)	ORTHO EVRA (Reference)	Ratio (%)	Lower Limit (%)	Upper Limit (%)
Norelgestromin					
AUC_{240} (ng•h/mL)	134.07	138.44	96.84	93.01	100.83
C^{ss} (ng/mL)	0.74	0.77	96.55	92.50	100.79
Norgestrel					
AUC_{240} (ng•h/mL)	161.66	158.75	101.84	96.22	107.78
C_{avg} (ng/mL)	0.61	0.60	101.31	95.86	107.07
Ethinyl estradiol					
AUC_{240} (pg•h/mL)	10179.17	10146.41	100.32	94.67	106.32
C^{ss} (pg/mL)	61.20	61.57	99.39	93.45	105.71

SAFETY RESULTS: Twenty-three subjects (53%) reported adverse events while wearing the ORTHO EVRA patch and 18 (45%) while wearing the LOW SPEC NGMN-EE patch. Erythematous rash was the most frequently reported event (11 subjects, 26%), followed by nausea (10 subjects, 23%), headache (8 subjects, 19%), and menstrual disorder (7 subjects, 16%). Sixty of the 65 adverse events reported by body system were considered to be mild in severity and 5 moderately severe. Eighteen of these adverse events were considered very likely related to study drug, 23 as probably related, 15 as possibly related, 8 as doubtfully related, and 1 as not related. No deaths or other serious adverse events were reported, and all reported events were followed to resolution. No change in vital signs measurements was reported as an adverse event or noted to be clinically significant. One subject had hematuria at her end-of-study examination, which was reported as a mild adverse event that was unlikely to be related to study medication. No other clinically significant findings in clinical laboratory data were reported. No clinically significant trends in changes in clinical laboratory results, vital signs measurements, or physical examinations were seen, and all pregnancy tests were negative.

CONCLUSION: The LOW SPEC NGMN-EE contraceptive system patch was bioequivalent to the ORTHO EVRA marketed contraceptive system patch. Both patches were well-tolerated by the healthy adult subjects in this study.

Date of the report: 2 February 2004

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.