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/ethinyl estradiol	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: CR002215 **Title of Study:** An Open-Label, Randomized, Partially Balanced, Incomplete Block Design Study to Evaluate the Hormone Exposure From Commercial ORTHO EVRA®		
Coordinating Principal Investigator: Maria Gutierrez, M.D., Comprehensive Phase 1, Fort Lauderdale, FL, USA		
Publication (Reference): none		
Studied Period (years): Clinical Conduct: 19 May 2004 to 2 September 2004 Sample Analysis: NGMN and NG: 03 June 2004 to 21 September 2004 EE: 15 June 2004 to 05 October 2004		**Phase of development:** 1
Objectives: The objectives of this study were to estimate NGMN, NG, and EE exposure across multiple commercial lots of ORTHO EVRA and to compare these data with historic exposure data from 1 clinical development Lot of ORTHO EVRA. Safety was also evaluated.		
Number of Subjects (planned and analyzed): The planned total sample size was 52 subjects; patches from each of 13 lots were worn by 12 subjects during 3 study periods. A total of 53 subjects were included in the safety analysis, and 52 subjects were included in the pharmacokinetic analysis.		
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 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 20 cm^2 transdermal contraceptive patches containing 6.0 mg NGMN and 0.75 mg EE; commercial batch numbers: 0307246, 0307251, 0307256, 0307280, 0308563, 0308582, 0309487, 0310022, 0311258, 0311780, 0311785, 0314947, and 0316948.		
Reference Therapy, Dose and Mode of Administration, Batch No.: Historic data from ORTHO EVRA 20 cm^2 transdermal contraceptive patches containing 6.0 mg NGMN and 0.75 mg EE; clinical batch number, 01607.		
Duration of Treatment: The open-label treatment phase consisted of three 7-day treatment periods separated by 21-day washouts. Total duration of the study was approximately 67 days.		
Criteria for Evaluation: Pharmacokinetics: The following PK parameters were estimated for NGMN, NG, and EE following ORTHO EVRA patch application: C_{max}, t_{max}, C^{ss} (for NGMN and EE), C_{avg} (for NG), AUC_{168}, AUC_{240}, AUC_{∞}, AUC_{last}; (for EE), and $t_{1/2}$. Patch adhesion was evaluated at time of removal and the results tabulated. Safety: Safety assessment was based on reported adverse events and changes in physical and gynecologic examinations (including breast examinations), vital signs, 12-lead ECGs, and clinical laboratory test results. Serum pregnancy testing and urine drug screening were also performed.		
Statistical Methods: Pharmacokinetics: Serum concentration-versus-time profiles were plotted for each subject and lot. Mean profiles were plotted for each lot. Descriptive statistics for serum concentrations at each point were generated for each lot. The PK parameters were summarized for each lot using descriptive statistics. The PK parameters AUC_{168} and C^{ss} were log-transformed before analysis. Random effect models were fit to the log-transformed parameters with lot as a fixed effect and subject as a random effect, and least square means and the variance components were estimated. Using the least square means and variance components, 90% confidence intervals for the mean PK parameters were calculated both within a single lot and across all lots.		

SYNOPSIS (CONTINUED)

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Statistical Methods: (Continued)

Pharmacokinetics: (Continued) For the comparison or for evaluation of the comparability of commercial lots to the clinical lot, historic data were obtained from PK studies (NRGEEP-PHI-013, 014, 016, 018, 020, 022, 021) using Lot 01607 with buttock application. Lot 01607 was also used in Phase 2 and 3 ORTHO EVRA studies. ANOVA models were fitted to the log-transformed PK parameter (AUC_{168} and C^{ss}) data for single patch application from the previous 7 studies using the clinical lot. The models included study as a fixed effect. Using the least square means and variance components from the model, 90% confidence intervals for the mean PK parameters of the clinical development lot were calculated both within a single study and across all studies.

The comparability of commercial lots to clinical Lot 01607 was evaluated by the overlap of confidence intervals from this study and previous PK studies using that clinical lot.

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 ECGs, clinical laboratory test results, and markedly abnormal laboratory test results.

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS: Arithmetic and geometric means and 95% confidence intervals for C^{ss}, C_{avg}, and AUC_{168} for NGMN, NG, and EE are presented below. The pharmacokinetic parameters for the commercial lots and clinical development Lot 01607 were similar.

	Arithmetic Mean		Commercial Lots (NRGEEP- P01-1024)		Clinical Lot 01607	
	Commercial Lots (N=151)	Clinical Lot 01607 (N=209)	Estimated Geometric Mean	95% Confidence interval	Estimated Geometric Mean	95% Confidence intervals
NGMN						
C^{ss} (ng/mL)	0.697 (0.278)	0.798 (0.273)	0.66	0.61 – 0.71	0.76	0.72-0.80
Range	0.260-2.48	0.17-1.98				
AUC_{168} (ng.h/mL)	105 (42.9)	123 (44.4)	99.14	91.35 – 107.60	116.21	109.98-122.79
Range	42.8-367	31.7-312				
NG						
C_{avg} (ng/mL)	0.632 (0.522)	nc				
Range	0.096-3.82					
AUC_{168} (ng.h/mL)	106 (87.7)	114 (85.0)	86.81	74.76 – 100.80	92.79	84.27 – 102.17
Range	16.1-641	6.1-793				
EE						
C^{ss} (pg/mL)	59.9 (21.6)	52.9 (18.6)	56.29	51.45 – 61.58	49.58	46.86 - 52.46
Range	16.3-142	11-113				
AUC_{168} (pg.h/mL)	8720 (3299)	7899 (2931)	8133	7380 – 8941	7367	6945 - 7815
Range	2460-21280	1429-17819				

nc = not comparable due to different calculation methods

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SUMMARY – CONCLUSIONS (Continued)

SAFETY RESULTS: A total of 41 (77%) of the 53 subjects reported 1 or more treatment-emergent adverse events. The most common events were headache (22 subjects, 42%), nausea (21 subjects, 40%), and vomiting (15 subjects, 28%). The majority of events were considered mild in severity and possibly or probably related to study drug. When adverse events were evaluated across the 13 treatment groups, no single treatment appeared to have a significantly higher incidence of events.

No deaths or serious adverse events occurred during the study. One subject discontinued after completing Period 2 because of recurrent headache, which resolved.

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:

- There were no statistically significant differences in the pharmacokinetic parameters between the 13 commercial lots for NGMN, NG, and EE based on the Analysis of Variance Model (p value ≥ 0.156 for all analytes).
- The mean AUC_{168} for NGMN, NG, and EE, and the mean C^{ss} for NGMN and EE from the commercial lots were within the range of mean AUC_{168} and C^{ss} observed in the clinical development studies (Lot 01607).
- All treatments (lots) were safe and well tolerated. No deaths or serious adverse events were reported.

Date of the report: 03 FEBRUARY 2005

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