SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: 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.: CR002212

Title of Study: An Open-Label, Randomized, Partially-Balanced, Incomplete Block Design Study to Evaluate the Hormone Exposure From Commercial EVRA® Manufactured by LOHMANN Therapie-Systeme and an Oral Contraceptive

Principal Investigator: Mathieu Peeters, M.D. – SGS Biopharma Research Unit Stuivenberg, Antwerp, Belgium

Publication (Reference): none

Studied Period (years): Clinical Conduct: 07 May 2004 to 08 October 2004
Sample Analysis: 18 June 2004 to 30 October 2004

Phase of development: 1

Objectives: The objectives of the study were to estimate ethinyl estradiol (EE), norgelstromin (NGMN), and norgestrel (NG) exposure across multiple commercial EVRA lots, and to compare these data to exposure data from lots of the commercially available oral contraceptive, CILEST, and to historical exposure data from 1 clinical lot used during the clinical development of ORTHO EVRA (Lot 01607. Safety was also evaluated.

Methodology: This single-center, open-label, randomized, partially-balanced, incomplete block design study was comprised of a pretreatment screening phase (lasting up to 21 days), an open-label treatment phase (three 7-day treatment periods separated by 21-day washouts), and a post-treatment phase (follow-up or early withdrawal visit). Six recently manufactured commercial lots of EVRA, manufactured by LOHMANN Therapie-Systeme AG (LTS) in Germany, and 3 recently manufactured CILEST lots were selected for the study. Eligible subjects were randomly assigned to 1 of 18 treatment-sequence groups. Subjects wore an EVRA patch or took CILEST tablets during each treatment period of 7 consecutive days. A minimum of 21 days after EVRA patch removal or last CILEST tablet, the subject began another treatment, until completing 3 open-label treatment periods. For comparison of the EVRA commercial lots to a clinical development lot, historical data obtained from Phase 1 ORTHO EVRA pharmacokinetic studies that used ORTHO EVRA clinical development Lot 01607 were used.

Number of Subjects (planned and analyzed): The planned total sample size was 54 subjects; subjects who did not complete the first 7-day treatment period and corresponding pharmacokinetic sampling were replaced. A total of 57 subjects were enrolled; 57 were analyzed for safety, 54 were analyzed for pharmacokinetics, and 51 completed all aspects of the study.

Diagnosis and Main Criteria for Inclusion: Eligible subjects included healthy women between the ages of 18 and 45 years, inclusive, who weighed at least 110 pounds, had a body mass index (BMI) between 16 and 29.9 kg/m^2, and had a hematocrit of at least 36% and a ferritin level above the lower limit of the normal range.

Test Products, Dose and Mode of Administration, Batch No.: EVRA 20 cm^2 transdermal contraceptive patches containing 6.0 mg of NGMN and 0.60 µg of EE; (product number: 01657; lot numbers: V04PE8828 through V04PE8833; supplier lot numbers 7/00869/4, 7/00870/4, 7/01053/4, 7/01054/4, 7/01055/4,and 7/01056/4)

Reference Therapy, Dose and Mode of Administration, Batch No.: CILEST commercially available tablets containing 250 µg of norgestimate (NGM) and 35 µg of EE per tablet. (product number: 01660; lot numbers: V04PE8834 through V04PE8836; supplier lot numbers: 03ls040, 04bs083, and 04bs154)

Duration of Treatment: Treatment was comprised of three 7-day open-label treatment periods separated by 21 day washouts, with an approximate total study duration of 67 days.

Criteria for Evaluation:

Pharmacokinetics: Following EVRA patch application, the following pharmacokinetic parameters were estimated for EE, NGMN, and NG: C_{max}, t_{max}, C_{ss} (mean steady-state concentration for EE and NGMN after patch application), C_{avg} (average concentration for NG), AUC_{24}, AUC_{168}, AUC_{240}, AUC_{∞}, AUC_{last}, and $t_{1/2}$

Following CILEST administration, the following pharmacokinetic parameters were estimated for EE, NGMN, and NG: C_{trough} (Days 2 through 6), C_{avg} (Day 1), C_{max} (Days 1 and 7), t_{max} (Days 1 and 7), $C_{avg,ss}$, AUC_{24}, AUC_{168} (EE and NGMN only), AUC_{∞} (Day 7 only), and $t_{1/2}$.

SYNOPSIS (CONTINUED)

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Criteria for Evaluation (Continued):

Patch Adhesion: Patch adhesion was evaluated and scored in each treatment period before patch removal.

Safety: Safety evaluations included adverse event monitoring, clinical laboratory evaluations (hematology, serum chemistry, and urinalysis), vital sign measurements (including pulse, blood pressure, respiratory rate, and body temperature), physical and gynecological examinations (including body weight and breast exam), and 12-lead electrocardiograms (ECGs).

Statistical Methods:

Pharmacokinetics: The objectives of the study were to estimate EE, NGMN, and NG exposure across 6 commercial EVRA lots and to compare these data to exposure data from 3 lots of the commercially available oral contraceptive, CILEST, and to historical exposure data from 1 ORTHO EVRA clinical development lot (Lot 01607). Plasma concentration-versus-time profiles were plotted for each subject and for each lot of study drug. Mean profiles were plotted and descriptive statistics for plasma concentrations at each point were generated for each lot. The pharmacokinetic parameters were summarized for each lot of study drug using descriptive statistics.

For NGMN and EE, the pharmacokinetic parameters AUC_{168} and C_{avg} were log-transformed before analysis. Mixed effects models were fit to the log-transformed parameter data with drug (EVRA or CILEST) and lot as fixed effects and subject as a random effect. The least square means for each lot and each drug, 95% confidence intervals for the least square means, and the variance components were estimated. Ninety percent confidence intervals for the difference in mean pharmacokinetic parameters (on log scale) between EVRA and CILEST were constructed using the estimated mean and variance components. The limits of the 90% confidence intervals were re-transformed using anti-logarithms to obtain 90% confidence intervals for the ratio of mean pharmacokinetic parameters between EVRA and CILEST. The least square means and 95% confidence interval limits were re-transformed using anti-logarithm to obtain least square geometric means and 95% confidence interval limits for each lot.

For NG, only log-transformed AUC_{168} data from the 6 commercial EVRA lots was included in the analysis. Mixed effects model was fitted with lot as a fixed effect and subject as a random effect and the least square means for each lot, 95% confidence intervals for the least square means, and the variance components were estimated. The least square means and 95% confidence interval limits were re-transformed using anti-logarithm to obtain least square geometric means and 95% confidence interval limits for each lot.

The historical data from 7 studies using clinical development Lot 01607 were used for the evaluation of commercial lot to clinical lot. Analysis of variance (ANOVA) models were fit to the log-transformed pharmacokinetic parameter (AUC_{168} and C_{ss}) data for single patch application from 7 studies using the clinical development lot, with study as a fixed effect. Using the least square means and variance components estimated from this model, 90% confidence intervals for the mean pharmacokinetic parameters of the clinical development lot were calculated both within a single study and across all studies. The comparability of commercial lots to the clinical development lot was evaluated by the overlap of confidence intervals for mean EVRA pharmacokinetic parameters from this study and 7 previous studies using the clinical development lot (01607).

Patch Adhesion: Patch adhesion scores were summarized.

Safety: Treatment-emergent adverse events were categorized and summarized using World Health Organization Adverse Reaction Terminology (WHOART) by body system and preferred term. Adverse events were also categorized by severity and by relationship to study drug. Individual listings of laboratory data, including a listing of normal reference ranges and a listing of subjects with any laboratory results outside the reference ranges, were provided. Results of the physical (including body weight) and gynecologic examinations (including breast examination), vital signs, and ECGs were listed by individual subject.

SYNOPSIS (CONTINUED)

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SUMMARY – CONCLUSIONS

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

	Arithmetic Mean		Commercial Lots (NRGEEP- P01-1025)		Clinical Development Lot 01607	
	Commercial Lots (N=104)	Clinical Lot 01607 (N=209)	Estimated Geometric Mean	95% Confidence Intervals	Estimated Geometric Mean	95% Confidence Intervals
EE						
C_{ss} (pg/mL)	49.9 (17.4)	52.9 (18.6)	47.77	44.17 – 51.67	49.58	46.86 - 52.46
Range	22.1-129	11-113				
AUC_{168} (pg•h/mL)	7289 (2611)	7899 (2931)	6960	6415 - 7552	7367	6945 – 7815
Range	3054-18141	1429-17819				
NGMN						
C_{ss} (ng/mL)	0.768 (0.261)	0.798 (0.273)	0.73	0.68 – 0.79	0.76	0.72-0.80
Range	0.282-1.71	0.17-1.98				
AUC_{168} (ng•h/mL)	118 (43.5)	123 (44.4)	111.30	102.4 – 120.97	116.21	109.98-122.79
Range	41.7-276	31.7-312				
NG						
AUC_{168} (ng•h/mL)	118 (62.7)	114 (85.0)	101.89	87.38 – 118.80	92.79	84.27 – 102.17
Range	17.2-337	6.1-793				

Arithmetic and geometric means and 95% confidence intervals for C_{ss}, C_{avg}, and AUC_{168} for NGMN, NG, and EE following EVRA patch application and administration of CILEST tablets are presented below. The pharmacokinetic parameters for EVRA and CILEST were similar.

	Arithmetic Mean		Geometric Mean (95% confidence intervals)		Ratio (%) of EVRA to OC (90% confidence intervals)
	EVRA (N=104)	CILEST (N=54)	EVRA	CILEST	
EE					
C_{ss} (pg/mL)	49.9 (17.4)	45.2 (12.6)[a]	47.77	42.23[a]	113.14 %
Range	22.1-129	20.4-75.1	(44.17 –51.67)	(38.63 – 46.16)	(106.28 – 120.43)
AUC_{168} (pg•h/mL)	7289 (2611)	7226 (2046)	6960	6681	104.18 %
Range	3054-18141	3296-12305	(6415 – 7552)	(6088 – 7332)	(97.73 – 111.06)
NGMN					
C_{ss} (ng/mL)	0.768 (0.261)	0.663 (0.167)[a]	0.73	0.63[a]	115.21 %
Range	0.282 – 1.71	0.348 – 1.29	(0.68 – 0.79)	(0.58 – 0.69)	(108.16 – 122.72)
AUC_{168} (ng•h/mL)	118 (43.5)	108 (23.2)	111.30	103.35	107.69 %
Range	41.7-276	54.1-191	(102.40 – 120.97)	(93.66 – 114.04)	(100.58 – 115.31)

[a] $C_{avg,ss}$

SYNOPSIS (CONTINUED)

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SUMMARY – CONCLUSIONS (Continued)

PATCH ADHESION RESULTS: None of the commercial EVRA patches became completely detached. Adhesion throughout the 3 treatment periods was greater than or equal to 90% for the majority of study subjects wearing any of the 6 commercial EVRA patches.

SAFETY RESULTS: All treatments and lots were safe and well tolerated. No deaths or serious adverse events occurred during the study. Two subjects discontinued due to adverse events (severe phlebitis of the left leg, which occurred during treatment with CILEST in Period 3 and resolved, and moderate vaginitis, which persisted, respectively). A total of 52 (91%) subjects reported at least 1 adverse event during the course of the study; 45 (83%) subjects reported events while wearing the EVRA patch compared with 36 (80%) subjects taking CILEST. All treatment assignments appeared to have a comparable incidence of adverse events. There was a higher incidence of application site reactions in the EVRA treatment groups overall compared with CILEST treatment (17% versus 0%, respectively), which was not unexpected. Other than slightly higher incidences of headache (57% versus 47%), dizziness (11% versus 2%), menstrual disorder (11% versus 2%), rhinitis (17% versus 2%), and fatigue (17% versus 9%) in the EVRA treatment groups overall compared to CILEST treatment, respectively, there were no clinically noteworthy differences in the incidences of adverse events for the EVRA patches compared with CILEST treatment. The most common events reported by subjects in all treatment groups overall were: headache (39 [68%]), nausea (27 [47%]), abdominal pain (20 [35%]), fatigue (13 [23%]), breast pain (11 [19%]) subjects, vaginal hemorrhage (10 [18%]) subjects, application site reaction (9 [16%]) subjects, rhinitis (9 [16%]), dermatitis (9 [16%]), dizziness (7 [12%]), vomiting (7 [12%]), menstrual disorder (7 [12%]), pharyngitis (7 [12%]), and back pain (6 [11%]). The majority of adverse events resolved spontaneously and were considered mild in severity and not related or of doubtful relationship to study treatment.

CONCLUSIONS:

- There were no statistically significant differences in the pharmacokinetic parameters among the 6 commercial lots of EVRA for EE, NGMN, and NG based on the ANOVA model.
- The mean AUC_{168} and C_{ss} for EE and NGMN from the commercial lots of EVRA were within the range of mean AUC_{168} and C_{ss} observed in the clinical development studies (Lot 01607).
- For EE and NGMN, the 90% confidence intervals for the ratio of mean pharmacokinetic parameters (AUC_{168} and C_{ss} or $C_{avg,ss}$) of EVRA to CILEST fell within 80% and 125%, indicating comparable systemic exposure.
- All treatments and lots were safe and well tolerated. No serious adverse events or deaths were reported.

Date of the report: 21 April 2005

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