SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: ORTHO EVRA® NAME OF ACTIVE INGREDIENTS: 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.: CR003007

Title of Study: A Comparative Pharmacokinetic Study of EVRA® and CILEST® in Healthy Female Volunteers

Principal Investigator: Voncken D.S., M.D. - Farma Research B.V., Nijmegen; the Netherlands

Publication (Reference): Not Applicable

Studied Period (years): Clinical Conduct: 2 July 2002- 10 March 2003
Sample Analysis: 6 September 2002 – 25 March 2003

Phase of development: 1

Objectives: The primary objective was to compare the pharmacokinetics of norelgestromin (NGMN), norgestrel (NG), and ethinyl estradiol (EE) after 1 week of wear, and after once weekly wear of EVRA for 3 consecutive weeks of each cycle for 2 cycles, with the pharmacokinetics of NGMN, NG, and EE after daily administration of CILEST for the first 7 days of dosing, and after 21 consecutive days of dosing of each cycle for 2 cycles.

Methodology: This was a single center, randomized, open-label, 2-way crossover study, consisting of a pretreatment phase (a screening period up to 21 days), an open-label treatment phase (2 28-day cycles of 1 treatment, a washout period of 28 days, and cross-over to 2 28-day cycles of the other treatment), and a posttreatment phase (a follow-up or early withdrawal visit). Treatment Day 1 was the first day of menses or within 5 days after the first day of menses. Subjects wore an EVRA patch on the abdomen or buttock (based on the randomization schedule) applied once weekly for 3 consecutive weeks during each of 2 cycles in 1 treatment period. They received daily administration of CILEST tablets for 21 days of each cycle for 2 cycles in the other treatment period. No EVRA patch or CILEST tablets were used on Days 22 to 28 (the 4th week) of any cycle, during which subjects could experience withdrawal bleeding. The total open-label study duration was approximately 5 months.

Number of Subjects (planned and analyzed): 32 planned, 36 analyzed (34 randomized + 2 subjects with a positive pregnancy test before randomization)

Diagnosis and Main Criteria for Inclusion: Women aged between 18 and 48 years, inclusive; in good health; hematocrit of at least 36%; weight at least 121 pounds, body mass index (BMI) between 18.0 and 29.9 kg/m^2; not pregnant; not lactating; with regular menstrual cycles; no evidence of cervical dysplasia; tubal ligation or use of contraceptive methods during participation in the study; no use of any prescription or nonprescription medications; no use of alcohol beginning 3 days before Days 1 through Day 8 of Cycle 1, and Days 15 through 24 for CILEST or Day 25 for EVRA of Cycle 2; nonsmoker; tests negative for drugs of abuse; tests negative for HIV antibodies, hepatitis B surface antigen, and hepatitis C antibodies; informed consent signed.

Test Product, Dose and Mode of Administration, Batch No.: EVRA, 150 µg NGMN and 20 µg EE/24 hours, transdermal patch, 60L005

Reference Therapy, Dose and Mode of Administration, Batch No.: CILEST, 250 µg NGM and 35 µg EE/day, oral tablets, 02CS146 and 02ES053

Duration of Treatment: Treatment 1: 2x28 days, Treatment 2: 2x28 days (+ 28 days wash-out period)

Criteria for Evaluation:

Pharmacokinetics: Blood samples were drawn during Week 1 of Cycle 1, and Week 3 of Cycle 2 for analysis of plasma NGMN (total and anti- and syn-isomers), NG, and EE concentrations.

Pharmacokinetic parameters studied were C_{max}, t_{max}, C^{ss}, C_{avg}, AUC_{0-24}, AUC_{0-168}, AUC_{0-240}, $AUC_{0-\infty}$, AUC_{0-last} (EE), AUC ratios, λ_z, $t_{1/2}$ (EVRA); and C_{min}, C_{max}, t_{max}, C_{avg}, AUC_{0-24}, AUC_{0-168}, $AUC_{0-\infty}$, AUC_{0-last} (EE), AUC ratios, λ_z, $t_{1/2}$ (CILEST).

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: ORTHO EVRA® NAME OF ACTIVE INGREDIENTS: 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)

Pharmacodynamics: Blood samples for sex hormone-binding globulin (SHBG), corticosteroid binding globulin (CBG), and corticosteroid-binding globulin binding capacity (CBG-BC) were collected before treatment (between Days 21 and 28 of the prestudy menstrual cycle), and on Days 1, 7, and 22 of Cycle 1, Day 23 of the Washout Period, and Days 1 and 22 of Cycle 2, for each treatment. *(Protocol Amendment 1 and 2)*

Safety: was assessed by monitoring incidence and severity of adverse events, clinical laboratory tests, vital signs, physical and gynecological examination and ECG.

Statistical Methods:

Pharmacokinetics: The primary parameters of interest were $AUC_{0\text{-}24h}$ for each analyte, ratio of anti-NGMN $AUC_{0\text{-}24h}$ to syn-NGMN $AUC_{0\text{-}24h}$ and ratio of total NG $AUC_{0\text{-}24h}$ to NGMN $AUC_{0\text{-}24h}$. Estimated parameters were log-transformed before analysis. Mixed-effects models were fit to the data with site (of application of EVRA), treatment, period, and site by treatment interaction as fixed effects, and subject as random effect. Poolability of the data from the 2 sites of application was concluded by the nonsignificance of the site by treatment interaction at a 10% level of significance.

Mixed effects models were fit to the data with treatment sequence group, treatment, and period as fixed effects and subject as random effect to estimate the least square means for each treatment and the intrasubject variability, which were used to construct 90% confidence intervals (CIs) for the ratio of the mean parameters from EVRA to CILEST.

Pharmacodynamics: Baseline adjusted SHBG, CBG, and CBG-BC measurements were used for the comparison of EVRA and CILEST. Mixed-effects models were fit to the data with site, cycle/day, treatment, period, and cycle/day by treatment, cycle/day by site, site by treatment, and cycle by site by treatment interaction terms as fixed effects, and subject as random effect. Poolability of the data from the 2 sites of application was concluded by the nonsignificance of site by treatment, and site by cycle/day by treatment interaction terms at 10% level of significance.

Mixed-effects models were fit to the data with treatment sequence group, cycle/day, treatment, period, and cycle/day by treatment as fixed effects and subject as random effect to estimate the least square means for each cycle/day and treatment combination and the pooled intrasubject variability. 90% CIs were constructed for the differences in the baseline adjusted SHBG, CBG, and CBG-BC between the 2 treatments for each cycle/day.

Safety: Adverse events and changes from baseline in laboratory test results, vital signs, physical and gynecological examination and ECG were summarized.

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®	Volume:	
NAME OF ACTIVE INGREDIENTS: 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)	Page:	

SUMMARY – CONCLUSIONS

DEMOGRAPHIC AND BASELINE CHARACTERISTICS:

Thirty-four adult women were randomized to this study. Two other subjects were not randomized because of a positive pregnancy test before randomization. The median (min-max) age of the intent-to-treat population (all randomized subjects who had at least 1 intake or application of the study drug) was 29.5 (18-48) years, and the majority (71%) were Caucasian. The differences between analysis groups with respect to the demographic parameters were small and were considered not clinically relevant.

PHARMACOKINETIC RESULTS:

Mean (SD) Pharmacokinetic Parameters Following Once Daily Oral Administration of CILEST and Weekly Application of EVRA in Healthy Female Volunteers

Parameter	CILEST		EVRA	
NGMN	Week 1 of Cycle 1	Day 22 of Cycle 2	Week 1 of Cycle 1	Week 3 of Cycle 2
t_{max} (h)		1.22 (0.49)	78.73 (22.17)	66.78 (41.89)
C_{max} (ng/mL)		2.16 (0.543)	0.928 (0.381)	1.12 (0.376)
$t_{1/2}$ (h)		21.2 (6.48)		23.4 (10.0)
AUC_{0-24h} (ng•h/mL)	11.7 (2.92)[a]	17.6 (5.31)	16.5 (6.44)[a]	20.8 (7.64)[a]
AUC_{0-168h} (ng•h/mL)	81.8 (20.5)	nc	115 (45.0)	145 (53.5)
C_{avg} (ng/mL)	0.487 (0.122)	0.732 (0.221)	0.766 (0.297)[b]	0.888 (0.325)[b]
NG				
t_{max} (h)		2.88 (2.80)	159.64 (19.83)	107.18 (57.14)
C_{max} (ng/mL)		3.01 (1.05)	1.09 (0.447)	2.70 (1.08)
$t_{1/2}$ (h)		49.0 (15.5)		61.7 (56.0)
AUC_{0-24h} (ng•h/mL)	13.1 (6.44)[a]	56.0 (23.2)	13.7 (5.52)[a]	52.4 (20.9)[a]
AUC_{0-168h} (ng•h/mL)	91.8 (45.1)	nc	95.7 (38.7)	367 (146)
C_{avg} (ng/mL)	0.546 (0.268)	2.33 (0.967)	0.648 (0.243)	2.18 (0.872)
EE				
t_{max} (h)		1.17 (0.37)	105.03 (32.56)	64.47 (49.32)
C_{max} (pg/mL)		133 (36.7)	76.3 (28.0)	97.4 (30.8)
$t_{1/2}$ (h)		16.9 (3.78)		17.8 (3.30)
AUC_{0-24h} (pg•h/mL)	843 (195) [a]	1183 (318)	1399 (507) [a]	1853 (614)[a]
AUC_{0-168h} (pg•h/mL)	5899 (1366)	nc	9793 (3547)	12974 (4295)
C_{avg} (pg/mL)	35.1 (8.13)	49.3 (13.2)	65.9 (23.6)[b]	80.0 (26.8)[b]
Anti-NGMN/ Syn-NGMN				
AUC_{0-24h} (ng•h/mL)	6.07 (1.69)	3.46 (0.52)	5.06 (1.14)	3.15 (0.48)
AUC_{0-168h} (ng•h/mL)	6.07 (1.69)	3.46 (0.52)		3.15 (0.48)

[a] calculated as $AUC_{0-168}/7$
[b] C^{ss}
nc = not calculated

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: ORTHO EVRA® NAME OF ACTIVE INGREDIENTS: 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)

Ratio of Means and 90% Confidence Intervals of the Ratio of Means for AUC_{0-24h} of EVRA (Test) to CILEST (Reference) for Week 1 of Cycle 1

Analyte	Geometric Mean				90% confidence limits			
	EVRA		CILEST		Ratio (%)		Lower limit (%)	Upper limit (%)
	Abdomen	Buttock	Abdomen	Buttock	Abdomen	Buttock		
Total NGMN	14.74	16.35	11.97	10.64	123.09	153.71	120.01	154.49
	15.45		11.34		136.16			
NG	11.06	14.31	11.07	12.17	99.92	117.60	93.53	123.19
	12.52		11.66		107.34			
EE	1261.15	1353.38	822.06	826.55	153.41	163.74	141.45	174.45
	1300.65		827.98		157.09			
Ratio of anti-NGMN AUC_{0-24h} to syn-NGMN	3.32	3.49	5.35	6.11	62.14	57.18	53.68	66.33
	3.41		5.71		59.67			
Ratio of NG to total NGMN	0.75	0.87	0.93	1.14	81.13	76.52	72.09	86.16
	0.81		1.03		78.81			

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: ORTHO EVRA® NAME OF ACTIVE INGREDIENTS: 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)

Ratio of Means and 90% Confidence Intervals of the Ratio of Means for AUC_{24} of EVRA (Test) to CILEST (Reference) for Week 3 of Cycle 2

	Geometric Mean						90% confidence limits	
	EVRA		CILEST		Ratio (%)		Lower limit	Upper limit
Analyte	Abdomen	Buttock	Abdomen	Buttock	Abdomen	Buttock	(%)	(%)
Total NGMN	19.49	19.65	18.35	15.06	106.19	130.42		
	19.49		16.69		116.75		102.39	133.11
NG	47.64	48.34	51.08	51.64	93.26	93.59		
	47.73		51.64		92.43		80.89	105.60
EE	1709.24	1825.05	1115.25	1183.94	153.26	154.15		
	1759.81		1153.25		152.59		137.04	169.92
Ratio of anti NGMN AUC_{24} to syn NGMN	3.00	3.25	4.64	5.32	64.60	61.11		
	3.12		4.95		62.74		58.85	66.88
Anti-NGMN	14.60	15.05	15.12	12.79	96.59	117.65		
	14.76		13.97		105.71		92.52	120.77

Ratio of Means and 90% Confidence Intervals of the Ratio of Means for AUC_{24} of EVRA (Test) to CILEST (Reference) for Week 3 of Cycle 2

		Geometric Mean		90% confidence limits		
Site	Analyte	EVRA	CILEST	Ratio (%)	Lower limit (%)	Upper limit (%)
Abdomen	Syn-NGMN	4.87	3.26	149.54	125.30	178.47
	Ratio of NG to total NGMN	2.45	2.78	87.90	79.01	97.79
Buttock	Syn-NGMN	4.63	2.41	192.39	159.96	231.38
	Ratio of NG to total NGMN	2.46	3.43	71.62	63.30	81.03

PHARMACODYNAMIC RESULTS:

Baseline-adjusted SHBG following EVRA vs CILEST was slightly higher on Day 22 of Cycle 1 and Days 1 and 22 of Cycle 2. Conversely, overall CBG and CBG-BC values for EVRA and CILEST were very similar, and CBG-BC values for EVRA applied to the abdomen were even slightly less compared to CILEST. Thus, the somewhat higher observed EE exposure for EVRA vs CILEST is not reflected consistently in the pharmacodynamic data.

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: ORTHO EVRA® NAME OF ACTIVE INGREDIENTS: 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)

SAFETY RESULTS:

After 1 week of wear, 69% of the patches were still completely on, in 29% the edges had lifted off, in 2% the patches were half off, and none of the patches was just hanging or had fallen off. There was no clear difference in adhesion between the buttock versus abdomen application-site group.

Overall, all 34 randomized subjects reported at least 1 adverse event (31 subjects during both CILEST and EVRA treatment). Application-site reaction was the most frequently reported adverse event, noted in 94% subjects in the EVRA group (100% subjects in the buttock application-site group and 88% in the abdomen application-site group) and in no subjects in the CILEST group. The severity was mild in all but 1 subject, and the investigator considered the adverse event probably or possibly related to the study medication. The adverse event resolved without sequelae by the end of the study in all but 2 subjects. Other adverse events occurring in at least 10% of the subjects and for which the incidence was comparable between EVRA and CILEST treatment were rhinitis (41%), vaginal hemorrhage (32%), pharyngitis, and influenzalike symptoms (each noted in 26%), fever, and diarrhea (each noted in 18%), dizziness (15%), and leukorrhea, fatigue, and increased appetite (each noted in 12%). Adverse events reported in 10% more subjects in 1 treatment group versus the other were breast pain (41%) and abdominal pain (35%), which were reported more frequently under EVRA treatment, and headache (56%), nausea (50%), and vomiting (21%), which were reported more often under CILEST treatment. Three adverse events were considered of marked severity by the investigator: headache (noted in 1 subject); influenzalike symptoms (2 subjects) and unintended pregnancy (1 subject). Apart from most application-site reactions, the investigator considered none of the adverse events very likely or probably related to the study medication. No subjects died during the study, and serious adverse events were not reported in the 34 subjects randomized to treatment. Next to these, between screening and randomization, unintended pregnancy (WHO preferred term) was reported in 2 subjects (verbatim terms: pregnancy [unwanted], and positive serum pregnancy test after spontaneous abortion). These subjects were not randomized to treatment. None of the subjects had a dose reduction, temporary or permanent stop of the study medication because of adverse events.

There were 63 shifts in laboratory test results from within the laboratory normal limits at screening to outside the laboratory normal limits at any time point thereafter: 40 were noted in the EVRA/CILEST group, 21 in the CILEST/EVRA group, and 2 in the subjects who were not randomized. In almost all cases, the lab values changed to only just above or below the laboratory normal ranges. In 3 subjects, the laboratory test results were reported as adverse events: anemia (2 subjects) and abnormal WBC count in the urine (1 subject). The adverse events were of mild intensity and considered doubtfully related to the study medication. In a follow-up sample, values were no longer considered clinically significant or had returned to normal.

For vital signs, no individual abnormal changes were noted except for 5 low pulses, 4 at the end of the study, and 1 during CILEST, on Day 21 predose. The lowest value observed was 42 beats per minute, a decrease of 16 beats per minute as compared with screening. For physical and gynecological examination, none of the changes versus screening was considered clinically significant by the investigator, except for sensitive mammae (in 5 subjects, all in the CILEST/EVRA sequence) and Candida infection of the vagina (in 1 subject).

No clinically significant ECG abnormalities were recorded according to the investigator.

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: ORTHO EVRA® NAME OF ACTIVE INGREDIENTS: 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)

CONCLUSION:

EVRA delivered relatively constant plasma levels of hormones, characteristic of transdermal delivery, compared to pronounced peaks and troughs of CILEST, characteristic of oral delivery. However, maintenance of lower plasma concentrations for a longer period of time with EVRA, compared with higher plasma concentrations for shorter periods of time for CILEST resulted in somewhat higher estimated extent of exposure comparisons to NGMN and EE for EVRA vs CILEST. The extent of exposure to NG for EVRA and CILEST appeared to be similar. The extent of exposure to the anti isomer of NGMN was higher than for the syn isomer for both EVRA and CILEST but this observation does not appear to be clinically relevant as they are are equally active and equally potent progestogens.

The estrogenic effect of EVRA was similar to CILEST based on stimulation of the hepatic synthesis of CBG, but was slightly greater than CILEST based on stimulation of hepatic synthesis of SHBG.

The application of the transdermal contraceptive patch on the abdomen or buttock for 2 cycles was safe and well tolerated by healthy adult women.

Date of the report: 28 October 2003

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.