SYNOPSIS

NAME OF SPONSOR/COMPANY: The R.W. Johnson Pharmaceutical Research Institute [and Janssen-Cilag] NAME OF FINISHED PRODUCT: 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.: CR005503 **Title of Study:** An Open Label Study to Evaluate Contraceptive Efficacy and Safety of the Transdermal Contraceptive System of 17-Deacetylnorgestimate and Ethinyl Estradiol with the Oral Contraceptive Mercilon®		
Investigators: Multicenter study (65 investigators)		
Study Centre(s): Multicenter study conducted at 65 centers including two in Switzerland; four in Austria, Belgium, and Hungary; six in Poland; eight in Finland and Germany; nine in France and the Netherlands; and 11 in South Africa.		
Publication (Reference): None		
Studied Period (years): October 1997 to April 1999		**Phase of development:** 3
Objectives: The objective of this study was to compare the contraceptive efficacy, cycle control, safety, compliance, and subject satisfaction of a transdermal contraceptive system containing 17-deacetylnorgestimate (17d-NGM) and ethinyl estradiol (EE) with that of orally administered Mercilon.		
Methodology: This was a randomized, open label, multicenter study; the ratio of subjects randomized to the EVRA™ group versus the Mercilon group was 4:3. Subjects were treated with either EVRA (a 20 cm^2 transdermal contraceptive system estimated to deliver 250 µg 17d-NGM and 25 µg EE daily) or Mercilon (containing 150 µg desogestrel and 20 µg EE). One third of subjects were to be treated for 13 cycles, the remainder were to be treated for 6 cycles. Following enrollment into the study, all subjects returned on Day 28 of Cycles 1, 3, and 6; those subjects enrolled for 13 cycles also returned on Day 28 of Cycles 9 and 13. Diary cards and empty medication packages were collected at each visit. Adverse events also were assessed at each visit. Other safety evaluations, physical examination, gynecologic examination, blood chemistries, and hematology were conducted at pre- and poststudy visits or at early withdrawal.		
Number of Subjects (planned and analyzed): One thousand four hundred (800 in the EVRA group and 600 in the Mercilon group) healthy female volunteers of child bearing potential were to be enrolled. A total of 861 subjects were randomized to the EVRA group. One subject randomized to the Mercilon group received EVRA; this subject was included in the EVRA group. A total of 656 subjects were randomized to the Mercilon group. Two subjects randomized to the EVRA group received Mercilon; these subjects were included in the Mercilon group.		
Diagnosis and Main Criteria for Inclusion: For inclusion in the study, subjects were required to be healthy, ovulatory women, 18 to 45 years old, with regular menstrual cycles, sexually active and at risk of pregnancy, with no disorders that would preclude oral contraceptive use. Subjects also gave written informed consent to participate in the study.		
Test Product, Dose and Mode of Administration, Batch No.: Subjects in the EVRA group applied one 20 cm^2 patch (Batch R6378) weekly during Weeks 1, 2, and 3 of each cycle, wore each patch for the full week (seven days), and did not wear a patch during Week 4 of each cycle. Each patch was estimated to deliver 250 µg 17d-NGM and 25 µg EE daily; total drug content was 6.0 mg 17d-NGM and 0.75 mg EE per patch.		

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Duration of Treatment: One third of subjects were to be treated for thirteen 28-day cycles; the remainder were to be treated for six 28-day cycles.

Reference Therapy, Dose and Mode of Administration, Batch No.: Mercilon (Batch D99LB0035). One tablet containing 150 μg desogestrel and 20 μg ethinyl estradiol taken orally once-daily for 21 days, followed by seven drug-free days.

Criteria for Evaluation:

Efficacy: Contraceptive efficacy was assessed by determination of pregnancy rates. Pregnancy screening was conducted by the quantitative measurement of β-hCG by radioimmunoassay at the prestudy visit, as needed during the study, and at the poststudy visit. Ultrasonography was performed to confirm gestational age and to estimate the probable date of conception. Overall and method failure pregnancy rates were evaluated by the Pearl Indices and life table analysis.

To assess cycle control and compliance, diary cards were used to record compliance and bleeding information. The primary endpoint for evaluation of cycle control was the incidence of breakthrough bleeding and/or spotting at Cycle 3. The following bleeding parameters were used to evaluate cycle control for each subject for every cycle: breakthrough bleeding and/or spotting; breakthrough bleeding; breakthrough spotting; early withdrawal flow; breakthrough bleeding/spotting and/or early withdrawal flow; duration of menses; duration of latent period.

A subject questionnaire assessed the extent to which satisfaction with each contraceptive treatment was achieved. All questions were administered during the visits at the completion of on-therapy Cycles 6 and 13, or early withdrawal if applicable. Assessment of emotional and physical well-being also occurred at the end of on-therapy Cycles 1 and 3.

Safety: Safety was assessed from summaries of data on treatment-emergent adverse events; changes in clinical laboratory parameters, blood pressure, body weight, and physical and gynecologic examination findings from pretreatment to the end of treatment.

Statistical Methods:

Efficacy: Contraceptive efficacy was determined by pregnancy results estimated from the Pearl Indices and life table analysis. Pregnancy rates included subjects who took study drug for at least one day and excluded those who had pre-therapy pregnancies. The endpoints of interest for the life table analysis were the 6-cycle and 13-cycle gross cumulative probabilities of pregnancy. Two-sided, 95% confidence limits for each treatment group were calculated.

The proportion of subjects in both treatment groups who experienced each bleeding variable was summarized by cycle. The mean duration of menses and the mean duration of the latent period were summarized for each treatment group by cycle; differences between the treatment groups were evaluated by 95% confidence intervals. The incidence of cycles with no withdrawal flow and cycles with no bleeding or spotting were summarized by cycle and treatment group. Finally, the incidence of amenorrhea was given by treatment group. Bleeding summaries and analyses included only data from valid cycles.

For subjects in both treatment groups, assessments used as indicators of compliance included the percentage of subjects with compliance at each cycle, and the number and percentage of subjects with missing days of drug taking. Patch wearability was summarized from the number of patches that fell off and the number of subjects with patches that fell off.

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Safety: Only TEAEs were included in the assessment of adverse events. The incidence of each TEAE for both treatment groups was summarized by body system and WHOART term. A listing of SAEs was compiled. All clinical laboratory evaluations and vital signs were presented for each group by planned duration of treatment. PAP smears at baseline and the end-of-study visit were summarized.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS: A total of 1517 healthy, ovulatory women were enrolled in the study at 65 centers in 10 countries. The randomization ratio was 4:3. For the EVRA group, 861 subjects were enrolled; 846 subjects took study drug. For the Mercilon group, 656 subjects were enrolled; 643 subjects took study drug.

Only 2.0% (17/861) of subjects in the EVRA group and 2.4% (16/656) of subjects in the Mercilon group had data that were not included in the efficacy analysis. The most common reason subjects in both treatment groups were randomized and not included in the efficacy analysis was pretherapy pregnancy. The demographics of the subjects who took study drug were similar for the treatment groups with respect to age, race, body mass index, and previous oral contraceptive use. A slightly lower percentage of subjects completed EVRA treatment compared to Mercilon treatment (80% and 86%, respectively). Protocol deviations other than pre-therapy pregnancy occurred infrequently (six subjects treated with EVRA; three subjects treated with Mercilon) and data from these subjects were included in the efficacy and safety analyses.

Compliance was better in subjects using EVRA compared with those using Mercilon. The percentage of subjects who exhibited compliance at each cycle ranged from 90% to 97% in the EVRA group and from 85% to 92% in the Mercilon group. There were no dosing errors in 97% of cycles in the EVRA group, compared with 91% of cycles in the Mercilon group.

Four subjects (0.5%) in the EVRA group had on-therapy pregnancies, compared with two subjects (0.3%) in the Mercilon group. The method failure and overall Pearl Indices with the 95% CI were 0.66 (0.00, 1.40) and 0.88 (0.02, 1.74) in the EVRA group, respectively; and 0.28 (0.00, 0.83) and 0.56 (0.00, 1.33) in the Mercilon group, respectively. The life table analyses indicated that the probability of pregnancy through 13 cycles was similar for both treatment groups (overall probability for EVRA was 0.5%, compared with 0.3% for Mercilon); and there was no difference in the relative risk of pregnancy using EVRA as compared with Mercilon (overall relative risk was 1.550; p=0.613).

The primary efficacy endpoint for the evaluation of cycle control was the incidence of breakthrough bleeding and/or spotting (BBS) at Cycle 3. The percentage of subjects with BBS was similar between the treatment groups: 14% of subjects in the EVRA group compared with 15% of subjects in the Mercilon group. The incidence of early withdrawal flow for all cycles combined was lower in the EVRA group (15%) as compared with the Mercilon group (31%). For all cycles combined, the percentage of subjects in the EVRA group (47%) who experienced BBS and/or early withdrawal flow was lower than that of the Mercilon group (58%). Despite numerical differences between the treatment groups in cycle control parameters, there were no statistically significant differences between EVRA and Mercilon for any of the bleeding parameters (except for duration of menses and duration of the latent period) at any time during the study.

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Only 2% of all patches applied during the study fell off. For individual cycles, the percentage of subjects with at least one patch that fell off ranged from 1% to 7%. It is important to note that subjects learned to use EVRA more efficiently as the study progressed; more subjects had patches fall off at the start of the study (7% of subjects had at least one patch fall off during Cycle 1) than at the end of the study (2% of subjects had at least one patch fall off during Cycle 13).

SAFETY RESULTS: In this 6 cycle/13-cycle study of combination hormonal contraception, 72% of subjects in the EVRA group, and 66% of subjects in the Mercilon group reported at least one adverse event during the study. However, there were no unexpected adverse events associated with the use of either treatment. The percentage of subjects reporting each adverse event was similar for EVRA and Mercilon. For eight of 11 of the most frequently reported adverse events (≥5% of subjects in any treatment group), the difference between the groups was not more than 5%.

With the exception of application site reactions occurring in subjects in the EVRA group, the adverse events reported in this study are typical of hormonal contraceptives. The most frequently reported adverse events in the EVRA group were headache (20%), breast discomfort (19%), nausea (12%), and abdominal pain (11%). The most frequently reported adverse events in the Mercilon group were headache (24%), abdominal pain (11%), and influenza-like symptoms (10%). The frequency of adverse events was similar for both treatment groups except that more subjects in the EVRA group reported application site reactions, breast discomfort, and vomiting. Most adverse events were mild or moderate in severity, not serious, and not treatment-limiting.

The occurrence of application site reactions with a topically applied product is not unexpected. Although 13.8% of subjects reported application site reactions, these reactions were associated with discontinuation of treatment in only 1.2% of subjects who used EVRA. Breast discomfort and nausea are adverse events known to be associated with estrogenic compounds. From the literature, the frequency of breast symptoms and of nausea is dose-related, and the breast discomfort and nausea experienced by subjects in this study are consistent with an estrogen dose response. The circulating level of EE based on AUC for EVRA is similar to oral contraceptives delivering 35 μg EE. The oral product of Mercilon is a 20 μg EE tablet. Therefore, it is not surprising that more subjects using EVRA reported breast discomfort and nausea than those using orally administered Mercilon.

No deaths occurred during this study and the number of nonfatal SAEs was similar between the treatment groups; 15 subjects in the EVRA group, and 13 subjects in the Mercilon group, experienced SAEs. One subject in both treatment groups had SAEs that were possibly related to study drug.

Overall, 10% of subjects in the EVRA group and 5% of subjects in the Mercilon group discontinued treatment for one or more adverse event. In the EVRA group, adverse events led to discontinuation of study drug with a frequency of 1% to 2% and included breast discomfort (1.9%), nausea (1.5%), application site reaction (1.2%), breast pain (0.9%), and headache (0.9%). All other adverse events associated with discontinuation of either EVRA or Mercilon occurred at a frequency of less than 1%.

The safety profile based on changes in laboratory parameters, PAP screening results, blood pressure, and weight change is similar for EVRA and Mercilon. The frequency of markedly abnormal laboratory values was low and similar for EVRA treatment compared to Mercilon treatment.

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The number of subjects with nonfatal SAEs was similar for both treatment groups. One subject in each treatment group had an SAE that was possibly related to study drug. Subject 1181 in the EVRA group had a chest X-ray performed approximately seven months after the start of treatment that revealed pleuritis. One month later, she was hospitalized with a blood clot in the lung and treated with warfarin and enoxaparin; study drug was permanently discontinued at this time. She recovered without sequelae. Subject 2035 in the Mercilon group had a medical history of ovarian cyst. She was diagnosed with a tumor in the left breast approximately five months after treatment was initiated. An adenocarcinoma was surgically removed; she also underwent chemotherapy and radiotherapy. The adverse event was unresolved.

No subjects died during this study.

Application site reactions were reported by 14% of subjects in the EVRA group and 10 subjects discontinued treatment for this reason. While 9% of subjects experienced skin irritation, the incidence of skin irritation decreased over the course of the study. There were no reports of skin irritation during the last two cycles of treatment.

In general, only small, clinically unimportant changes in most laboratory analytes, systolic and diastolic blood pressures, and body weight occurred during study drug administration. The incidence of laboratory and vital sign abnormalities and weight gain were similar for both treatment groups.

CONCLUSION: EVRA, a 20 cm^2 transdermal contraceptive system, has excellent contraceptive efficacy that is comparable to Mercilon. The Pearl Index rates and associated 95% confidence intervals for EVRA and Mercilon in this study were 0.88 (0.02, 1.74) and 0.56 (0.00, 1.33) respectively. Life table analysis of on-therapy pregnancies confirms comparable efficacy between EVRA and Mercilon.

Compliance with the contraceptive regimen was significantly better with EVRA compared with Mercilon. There were no dosing errors in 97% of cycles in the EVRA group, compared with 91% of cycles in the Mercilon group.

Cycle control associated with the use of EVRA is comparable to Mercilon. The incidence of breakthrough bleeding and/or spotting and early withdrawal flow was numerically lower for EVRA than for Mercilon, but there were no statistically significant differences between EVRA and Mercilon for any of the bleeding parameters at any time during the study.

Patch wearability, as defined by the number of patches that were replaced due to lack of adhesion, was excellent. Only 2% of all patches used in this study were replaced because of loss of adhesion.

EVRA has an excellent safety profile that is comparable to Mercilon. The most frequently reported adverse events in the EVRA group were headache (20%), breast discomfort (19%), application site reaction (14%), nausea (12%), and abdominal pain (11%).

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Date of the report: 16 December 1999

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