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.: CR005506

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 Triphasil®

Investigators: Multicenter study (45 investigators).

Study Center(s): Multicenter study conducted at 45 centers including six in Canada and 39 in the United States.

Publication (Reference): None

Studied Period (years): October 1997 to June 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 Triphasil.

Methodology: This was a randomized, open label, multicenter study; the ratio of subjects randomized to the EVRA™ group versus the Triphasil® 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 Triphasil (containing 50 µg levonorgestrel/30 µg EE [Days 1-6], 75 µg levonorgestrel/40 µg EE [Days 7-11], and 125 µg levonorgestrel/30µg EE [Days 12-21]. 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 Triphasil group) healthy female volunteers of child bearing potential were to be enrolled.

The total number of subjects randomized was 1495; 856 to receive EVRA and 639 to receive Triphasil. Of these, a total of 1417 subjects took study drug and were evaluable for safety: 812 in the EVRA group and 605 in the Triphasil 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 (lot number: R6973, R7033, and R7175) 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.

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.

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Reference Therapy, Dose and Mode of Administration, Batch No.: Triphasil (lot number: R6912, R6993, and R7167). One tablet containing 50 μg levonorgestrel/30 μg EE on Days 1 to 6, one tablet containing 75 μg levonorgestrel/40 μg EE on Days 7 to 11, and one tablet containing 125 μg levonorgestrel/30 μg EE on Days 12 to 21, followed by seven placebo tablets. Each tablet was taken orally, once daily.

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 post-study 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 was administered 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 numver and percentage of subjects with compliance, 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: The demographics of 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 Triphasil treatment (70% and 76%, respectively). Protocol deviations other than pre-therapy pregnancy occurred infrequently (six subjects treated with EVRA; five subjects treated with Triphasil) and data from these subjects was included in the safety and efficacy analyses.

Compliance was better for subjects using EVRA than for those using Triphasil. The percentage of subjects who exhibited compliance at each cycle ranged from 86% to 95% in the EVRA group and from 76% to 86% in the Triphasil group. At Cycles 1-6 and 10-13, the between-group difference was statistically significant. There were no dosing errors in 95% of cycles in the EVRA group, compared with 81% of cycles in the Triphasil group.

Five (0.6%) subjects in the EVRA group and seven (1.2%) in the Triphasil group had on-therapy pregnancies. The method failure and overall Pearl Indices (with 95% confidence intervals) were 0.99 (0.02, 1.96) and 1.24 (0.15, 2.33), respectively, for the EVRA group and 1.25 (0.02, 2.47) and 2.18 (0.57, 3.80), respectively, for the Triphasil group. The life table analyses indicated that the probability of pregnancy through 13 cycles was similar for the two treatment groups (overall probability of 1.3% for the EVRA group and 1.8% for the Triphasil group). The overall relative risk of pregnancy for the EVRA group as compared with the Triphasil group was 0.57 ($p=0.332$, not statistically significant).

The primary efficacy endpoint for the evaluation of cycle control was the incidence of breakthrough bleeding and/or spotting at Cycle 3. The percentage of subjects with BBS at Cycle 3 was similar for the treatment groups: 10% of subjects in the EVRA group compared with 9% of subjects in the Triphasil group.

Only 2% of patches applied during the study fell off. For individual cycles, the percentage of subjects with at least one patch that fell off ranged from 2% to 8%. 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 (5% of subjects had at least one patch fall off during Cycle 1) than at the end of the study (3% of subjects had at least one patch fall off).

SAFETY RESULTS: With the exception of two adverse events, the percentage of subjects reporting each of the adverse events was similar for EVRA and Triphasil. The two adverse events for which the observed difference between the treatment groups was ≥5% were application site reaction (EVRA 20.2%; Triphasil 0%) and breast discomfort (EVRA 18.7%; Triphasil 5.8%).

One death occurred during this study. The subject was a 23-year old female in the Triphasil group who committed suicide by taking an overdose of sleeping pills. The investigator considered the event to be possibly related to study drug.

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Twenty-six subjects experienced nonfatal serious adverse events: 16 (2.0%) in the EVRA group and 10 (1.7%) in the Triphasil group. One of the subjects in the EVRA group reported severe right hemiparesthesia that was considered to be very likely related to study drug. One subject in the Triphasil group reported increased intracranial pressure considered to be possibly related to study drug.

Overall, 13% of subjects in the EVRA group and 6% of subjects in the Triphasil group discontinued treatment for one or more adverse event. In the EVRA group, adverse events leading to discontinuation of study drug included application site reaction (2.6%), nausea (1.8%), headache (1.5%), dysmenorrhea (1.5%), breast discomfort (1.0%), and menorrhagia (1.0%). All other adverse events associated with discontinuation of either EVRA or Triphasil occurred at a frequency of less than 1%.

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

CONCLUSION: EVRA, a 20 cm^2 transdermal contraceptive system, has excellent contraceptive efficacy that is comparable to Triphasil. The overall Pearl Index rates and associated 95% confidence intervals for EVRA and Triphasil in this study were 1.24 (0.15, 2.33) and 2.18 (0.57, 3.80), respectively. Life table analysis of on-therapy pregnancies confirms comparable efficacy between EVRA and Triphasil.

Compliance with the contraceptive regimen was better with EVRA compared with Triphasil. There were no dosing errors in 95% of cycles in the EVRA group, compared with 81% of cycles in the Triphasil group.

Cycle control associated with the use of EVRA is comparable to that associated with the use of Triphasil.

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 Triphasil. The most frequently reported adverse events in the EVRA group were headache (22%), nausea (20%), application site reactions (20%), breast discomfort (19%) breast discomfort (19%), dysmenorrhea (13%) and upper respiratory infection (13%).

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Date of the report: 22 December 1999

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