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An open-label, multicentre trial to evaluate the vaginal bleeding pattern of the combined contraceptive vaginal ring NuvaRing®

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Abstract

Objective: The objective of this multicentre, non-controlled, open-label study is the evaluation of the bleeding patterns during the use of a vaginal combined contraceptive, its safety in relation to occurrence of adverse effects, its efficacy as a contraceptive method and user compliance.

Study design: Healthy female volunteers ($N = 165$), asking for contraception, were enrolled to participate in the study. Each subject was given seven vaginal rings, releasing an average amount of 120 μg etonogestrel (ENG) and 15 μg ethinylestradiol (EE) per day. Study period was 7 cycles. A total of 878 cycles was valid for statistical analysis. The primary parameter, (breakthrough bleeding and/or spotting), was recorded for each cycle. The subjects were asked to report any adverse effect experienced during the treatment period, general physical and gynaecological examinations were performed and haematological blood tests were taken.

Results: Breakthrough bleeding/spotting occurred in 5.01% cycles (44 out of 878 cycles, of whom 37 were breakthrough spotting only). Absence of withdrawal bleeding during the ring-free period was reported in 1.94% cycles (17 out of 878). Forty-one subjects (24.8%) reported 66 events that were potentially drug-related. The most frequently drug-related events were weight increase (10 cases), headache (9 cases), nausea (4 cases). No pregnancy was reported during the study period. Haematology and chemical chemistry tests showed no clinically significant abnormality.

Conclusions: In the present study, NuvaRing® has shown to be a valid contraceptive method to ensure optimal cycle control with low incidence of irregular bleeding and altered withdrawal bleeding. The low incidence of gastrointestinal side effects (nausea, vomiting) may be related the low hormonal dose and to the vaginal delivery of hormones which avoids the gastrointestinal tract.

Keywords: Contraception; Vaginal ring; NuvaRing®; Efficacy; Compliance

1. Introduction

Since oral contraceptives (OCs) first became available in the early 1960s, they represented the contraceptive method of choice for many women worldwide. OCs are highly effective, but rely on daily intake of tablets. New OCs containing ethinylestradiol (EE) doses less than 20 μg minimize steroid-related adverse events, but can compromise cycle control [1], an important factor in maintaining user compliance [2].

Contraceptive research has investigated other methods and formulations that may overcome the disadvantages discussed above. The potential higher bioavailability of non-oral routes of administration as well as the constant serum levels that can be obtained with controlled release formulations offers the possibility to achieve the same adequate contraceptive efficacy with a lower dosage. The contraceptive controlled release formulations that are on the market today mainly comprise progestagen-only products such as injectables and implants. A major disadvantage of progestagen-only treatment is the loss of cycle control [3].

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An alternative to the above-described routes of administration is vaginal delivery. With this route of administration it is possible to use a controlled release formulation that can be easily inserted and then removed by the woman herself only once a month with no need to remember daily administration. NuvaRing® is a flexible, soft vaginal ring with an outer diameter of 54 mm and a cross-section of 4 mm. Every day the ring releases 15 μg of the estrogen EE and 120 μg of the progestogen etonogestrel (ENG), the active metabolite of desogestrel [4–5].

NuvaRing® is associated with fast return to ovulation after discontinuation, furthermore, its convenient monthly formulation requiring one application per cycle (21-day use followed by a 7-day free period) maintains a cyclic bleeding pattern [5–6].

The objective of this phase III multicentre, uncontrolled, open-label study is the evaluation of the bleeding patterns during the use of NuvaRing®, its safety, and its efficacy as a contraceptive method and user compliance.

2. Materials and methods

2.1. Subjects

Subjects could be recruited if complying with the following criteria: healthy female volunteers asking for contraception, aged at least 18 years, with a cycle length between 24 and 35 days and an intra-individual variation of ±3 days; body mass index (kg/m^2) ≥18 and ≤29.

Exclusions criteria were: contraindications for contraceptive steroids, use of an injectable hormonal method of contraception within a period of 6 months before the start of the trial medication, medical contraindication for contraceptive steroids, status post-partum or post-abortion within the last 2 months, breastfeeding in the last 2 months, present use or use during 2 months before of drugs, an history of alcohol or drug abuse in the last 12 months, an abnormal cervical smear, clinically relevant abnormal laboratory results and pregnancy.

This study was conducted in compliance with the Declaration of Helsinki, revision of Edinburgh, Scotland, ICH guidelines for Good Clinical Practice and applicable local requirements. Informed consent was obtained in writing before the subject was included in the study.

2.2. Treatment

The duration of treatment was 7 cycles. Each ring is made up of ethylene vinylacetate copolymer (core 28% vinyl acetate; skin 9% vinyl acetate) and contains 11.7 mg ENG and 2.7 mg EE releasing an average amount of 120 μg ENG and 15 μg EE per day. Study visits were scheduled at screening, in the first week following cycle 3 and after ring-free period of cycle 7 or at premature discontinuation.

2.3. Assessments

Bleeding pattern was assessed daily by the subject by use of diary cards over the entire study period, including the ring-free period of cycle 7. Each subject was asked to report on a daily basis whether vaginal bleeding was present, and if a vaginal bleeding was present, to indicate whether it was considered to be spotting or bleeding. A urine home pregnancy test had to be done by the subjects themselves just before the first ring insertion. The possibility of women having conceived during treatment period was assessed by measuring serum β-hCG at the last assessment (visit after cycle 7) or at premature discontinuation. With respect to efficacy parameters analysed, vaginal bleeding was classified according to the definition of bleeding. The following variables were also monitored and recorded at screening or during the treatment period: gynaecological examination and cervical cytology. If abnormal screening results were reported, subjects were to be discontinued. Clinical adverse events, reported by the patients or observed by the physician, have been monitored all throughout the study and recorded, regardless of causal relationship with treatment. Vital signs, including systolic and diastolic blood pressure, heart rate and body weight, were recorded at each visit, scheduled as follows: at screening (baseline), after the third cycle and at the last assessment visit (i.e. after the seventh cycle). Haematology and blood chemistry were also scheduled at baseline and at the last assessment visit.

2.4. Compliance

In each subject the compliance was calculated from diary cards. A subject's cycle was defined compliant if the ring period length did not deviate more than 48 h from the scheduled 21 days × 24 h and the ring-free period length deviated no more than 24 h from the scheduled 7 days × 24 h. All non-compliant cycles have been excluded from the per protocol (PP) analysis.

3. Statistical analysis

Several study populations were defined in the study protocol: all-subjects-treated (AST) group consisted of all subjects who received at least one ring; the intent-to-treat (ITT) group was defined as all subjects from the AST group who returned the diary cards; the PP group was defined as all subjects from the ITT group without any major protocol violation. Data from the AST group were used for safety evaluation, whereas data from both the ITT and PP group were used to assess cycle control and contraceptive efficacy. Cycle control data were analysed using descriptive statistics and tested between groups using the two-sided Fisher exact test adjusting for country for the ITT population.