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Contraception

Contraception 71 (2005) 176–182

Original research article

Efficacy and safety of a contraceptive vaginal ring (NuvaRing) compared with a combined oral contraceptive: a 1-year randomized trial

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Received 4 August 2004; revised 8 September 2004; accepted 9 September 2004

Abstract

This open-label, randomized, Phase III study compared the efficacy and tolerability of and compliance with NuvaRing, a combined contraceptive vaginal ring releasing 15 μg of ethinylestradiol (EE) and 120 μg of etonogestrel daily, with those of and with a combined oral contraceptive (COC) containing 150 μg of levonorgestrel (LNG) and 30 μg of EE. Subjects received NuvaRing or a COC for 13 cycles (3 weeks of ring/pill treatment followed by a 1-week ring-/pill-free period). A total of 1030 subjects (NuvaRing, $n=512$; COC, $n=518$) was randomized and started treatment (intent-to-treat [ITT] population). The percentage of women in the ITT population who completed the trial was 70.9% for the NuvaRing group and 71.2% for the COC group. Five in-treatment pregnancies occurred in each group, giving Pearl indices of 1.23 for NuvaRing and 1.19 for the COC. Compliance with both treatments was excellent and both were well tolerated. In conclusion, NuvaRing has comparable efficacy and tolerability with a COC containing 150 μg of LNG and 30 μg of EE and does not require daily dosing.

Keywords: NuvaRing; Contraceptive; Pill; Efficacy; Compliance; Tolerability

1. Introduction

Combined oral contraceptives (COCs) provide effective and safe protection against pregnancy and are the method of choice for many women worldwide. However, COCs are associated with a number of disadvantages including exposure to hepatic first-pass metabolism, susceptibility to reduced uptake because of vomiting or food interactions and fluctuations in serum hormone levels resulting from daily pill administration [1–3]. Additionally, women regard the need for daily pill intake as a drawback to the use of oral contraceptives (OCs) [4].

These observations illustrated the need for alternative methods of hormonal contraception and led to the development of vaginal rings to administer contraceptive steroids. A combined contraceptive vaginal ring (NuvaRing, NV Organon, Oss, The Netherlands) that delivers 15 μg of ethinyl estradiol (EE) and 120 μg of etonogestrel (ENG) per day over 3 consecutive weeks has been developed.

NuvaRing has several advantages over OCs. It is the only self-administered contraceptive that can be taken once monthly and features a controlled-release design that results in more uniform contraceptive hormone concentrations throughout the day, thus avoiding the daily fluctuations associated with OCs. Also, the vaginal route of administration avoids hepatic first-pass metabolism and gastrointestinal interference, allowing lower doses of contraceptive hormones to be used [1]. Peak serum concentrations of EE and ENG are achieved approximately 1 week after insertion of the ring and are 60−70% lower than peak concentrations produced by a COC containing 150 μg of desogestrel and 30 μg of EE [1].

Tolerability is a major factor in determining the acceptability of a contraceptive method. The contraceptive efficacy, tolerability and safety of NuvaRing have been described in

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0010-7824/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.contraception.2004.09.001

large-scale studies conducted in Europe and North America [5,6], indicating that it is an effective and safe contraceptive method. NuvaRing is also perceived as a convenient contraceptive method with a high level of user and partner acceptability [4–6].

In small-scale studies over six treatment cycles, NuvaRing has been shown to produce superior cycle control and to have comparable tolerability with a COC delivering daily EE and levonorgestrel (LNG) at 30 and 150 μg, respectively [7]. To date, the efficacy and tolerability of NuvaRing have not been compared with those of a COC in a large, randomized study. With this in mind, we conducted a 1-year, randomized controlled trial to compare NuvaRing with a COC delivering 30 μg of EE and 150 μg of LNG daily by assessing cycle control, contraceptive efficacy, tolerability and treatment compliance. The primary objective of this trial was to compare the cycle control of NuvaRing with that of the COC; these data will be presented in full elsewhere. In this paper, we describe the contraceptive efficacy, tolerability and safety of and compliance with the two contraceptive regimens.

2. Materials and methods

This Phase III, open-label, randomized, group-comparative, multicenter trial was conducted in 11 countries in Europe and South America (Belgium, Brazil, Chile, Denmark, Finland, France, Germany, Italy, Norway, Spain and Sweden). The study was approved by the independent ethics committee/institutional review boards of the participating centers and was conducted in accordance with the Declaration of Helsinki and the ICH Guideline for Good Clinical Practice. All subjects provided written informed consent.

The primary objective of this trial was to demonstrate superiority of the vaginal bleeding characteristics of NuvaRing as compared with a standard COC containing 30 μg of EE and 150 μg of LNG (Microgynon, Schering, Berlin, Germany). These results will be published in full elsewhere. The secondary objective is to assess the efficacy and safety of and compliance with NuvaRing as compared with those of and with a COC, and these are the focus of this publication.

2.1. Subjects

It was planned to recruit 1000 healthy women, aged ≥18 years, who were at risk of pregnancy and seeking contraception. Important exclusion criteria included contraindications for contraceptive steroids, previous use of an injectable hormonal method of contraception within 6 months of the start of trial medication, postpartum or postabortion within 2 months of the start of trial medication, breast-feeding within 2 months of the start of trial medication, an abnormal cervical smear diagnosed during screening or use of drugs that interfere with the metabolism of contraceptive hormones.

2.2. Interventions

The treatment period for this study was 13 cycles of NuvaRing or COC use. Each 28-day cycle consisted of 3 weeks of ring or COC use followed by a 1-week ring-/pill-free period. Subjects were randomized to treatment using an interactive voice response system, which provided the treatment group and associated medication number to which the subjects were assigned.

2.2.1. Ring insertion

Upon study entry, women received verbal and written instructions on the use of the ring, including how and when they should insert and remove it. Subjects in the NuvaRing group received a new ring for each cycle. Women who were taking no hormonal contraception inserted the ring between Days 1 and 5 of the spontaneous onset of menses, according to instructions in the NuvaRing package insert. These women were advised to use a barrier method of contraception during the first 7 days of ring use. Women who were using hormonal contraception also followed the instructions in the NuvaRing package insert, according to the method they were using (women using COCs started using the ring following their usual pill-free interval).

2.2.2. Pill intake

Women who were taking no hormonal contraception took one COC tablet daily for 21 days, starting on the first day of spontaneous menses. Women who were using contraception followed the instructions on how to start the new treatment in the package insert of the study medication, according to the method they were using (women already using COCs started using the study COC following their usual pill-free interval). Pills were to be taken in the morning; however, if menstrual bleeding started in the afternoon or evening, the first COC pill was to be taken on the first morning after the start of bleeding.

2.3. Assessments

Study assessments were scheduled at the time of initial screening (within 1 month of starting treatment), within 1 week after the ring-/pill-free period of Cycles 3, 6 and 9 and after Cycle 13 or premature discontinuation.

2.3.1. Contraceptive efficacy

Contraceptive efficacy was assessed by determining the occurrence of pregnancy during the study. A home pregnancy test was performed just prior to starting study medication and at any point during the study if pregnancy was suspected. At the end of the last treatment cycle (Cycle 13 or at premature discontinuation), serum β-human chorionic gonadotrophin was measured to assess pregnancy status. Any pregnancy occurring during the study was fully documented.

2.3.2. Compliance

Subjects used diary cards to record ring/pill use, and these data were used to determine exposure and compliance. For NuvaRing, a cycle was considered compliant if the period of ring use did not deviate for more than 48 h from the scheduled 3 weeks (i.e., within a range of 19×24 h to 23×24 h) and if the ring-free period did not deviate by more than 24 h from the scheduled 1 week. In the COC group, full compliance was defined as a cycle in which all scheduled pills were taken.

2.3.3. Tolerability

At screening, all subjects provided a general medical and gynecological history and underwent general physical and gynecological examinations, including a cervical smear test. The physical and gynecological examinations were repeated at the last study visit. Height was measured at the screening visit only. At every study visit, blood pressure and body weight were measured and the use of concomitant medication and occurrence of adverse events were assessed and recorded. Any problem considered directly related to ring use such as vaginal discomfort and device-related events (i.e., coital problems, foreign body feeling and expulsion) was considered an adverse event. Subjects who withdrew from the study were asked to classify their reason for withdrawal as related to either an adverse event, a bleeding irregularity, pregnancy or "other" reasons (nonmedical- and nondevice-related reasons including no further requirement for contraception or being lost to follow-up).

2.4. Statistical methods

Contraceptive efficacy was estimated by determination of the Pearl index (i.e., the expected number of pregnancies per 100 woman years of exposure) and its 95% confidence intervals (CIs). Homogeneity of Pearl indices between both treatment groups was tested by conditioning on the total number of pregnancies in both treatment arms (resulting in a binomial distribution) and rejecting for large and small relative numbers of pregnancies in one arm (two sided, $\alpha = 0.05$). The overall probability of in-treatment pregnancy was estimated using the Kaplan–Meier method.

Tolerability analysis was performed on the all-subjects-treated population and was performed via descriptive statistics.

3. Results

3.1. Subject disposition

A total of 1079 subjects was randomized for treatment. Of these, 49 women discontinued prior to treatment, 9 (NuvaRing, $n = 6$; COC, $n = 3$) withdrew as they were

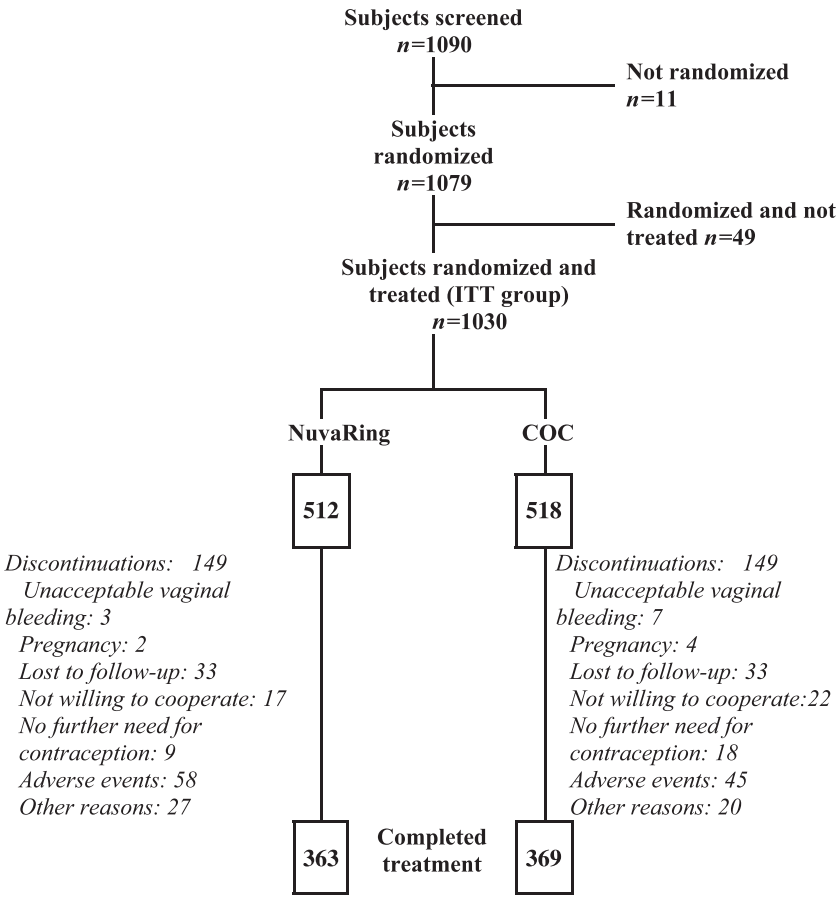

Fig. 1. Subject disposition. ITT = intent-to-treat; COC = combined oral contraceptive.

pregnant at baseline, 3 (NuvaRing, $n=3$) were lost to follow-up, 15 (NuvaRing, $n=7$; COC, $n=8$) were unwilling to cooperate with the study protocol and 22 (NuvaRing, $n=13$; COC, $n=9$) discontinued due to other reasons.

Of the randomized subjects, 1030 received treatment (NuvaRing, $n=512$; COC, $n=518$) and comprised the intent-to-treat (ITT) population. The per protocol (PP) population comprised 899 subjects (NuvaRing, $n=440$; COC, $n=459$). A total of 298 randomized subjects (NuvaRing, $n=149$; COC, $n=149$) discontinued treatment prematurely (Fig. 1) primarily because of adverse events (NuvaRing, $n=58$; COC, $n=45$) and being lost to follow-up (NuvaRing, $n=33$; COC, $n=33$). Cumulative rates of discontinuation are shown in Fig. 2. During the first few months of the study, discontinuation rates were higher in the NuvaRing group than in the COC group, but in the second half of the study, the discontinuation rate in the NuvaRing group was lower and became similar to that in the COC group. The percentage of women in the ITT population who completed the trial was 70.9% for the NuvaRing group and 71.2% for the COC group.

Subject baseline demographic and clinical characteristics are shown in Table 1. There were no notable differences between the two treatment groups.

3.2. Contraceptive efficacy

In the NuvaRing group, the ITT population was exposed to 5321.7 treatment cycles, equivalent to 408.0 woman years. In the COC group, treatment exposure was similar at 5461.4 treatment cycles, equivalent to 418.7 woman years (Table 2).

Table 1
Baseline characteristics for the NuvaRing and COC treatment groups (ITT population)

	NuvaRing ($n=512$)	COC ($n=518$)
Age (years)	27.0±6.2	27.2±6.3
Race [n (%)]		
Caucasian	463 (90.4)	471 (90.9)
Weight (kg)	61.7±9.2	62.0±9.0
Height (cm)	164.9±7.1	165.0±(6.6)
Body mass index (kg/m^2)	22.7±2.8	22.7±2.8
Nulligravid [n (%)]	291 (56.8)	273 (52.7)
Nulliparous [n (%)]	324 (63.3)	305 (58.9)
Last used contraceptive method [n (%)][a]		
Oral contraceptive	335 (65.4)	343 (66.2)
Foam, condom, suppositories or diaphragm	99 (19.3)	104 (20.1)
None	46 (9.0)	40 (7.7)

All continuous data are presented as means±SD.
[a] Combinations of contraceptive methods could have been used.

A total of 10 pregnancies occurred during treatment in the ITT population (NuvaRing, $n=5$; COC, $n=5$ [Table 2]). Of these, 3 subjects in the NuvaRing group and 2 subjects in the COC group had no protocol variations or only minor protocol variations that occurred after the estimated date of conception. Following exclusion of the subjects with protocol violations, the number of in-treatment pregnancies was reduced from 10 to 5 (NuvaRing, $n=3$; COC, $n=2$); there was no significant difference between treatment groups in the PP population (Table 2). The Pearl indices for the ITT populations were 1.23 (95% CI: 0.40, 2.86) and 1.19 (95% CI: 0.39, 2.79) for the ring and COC groups,

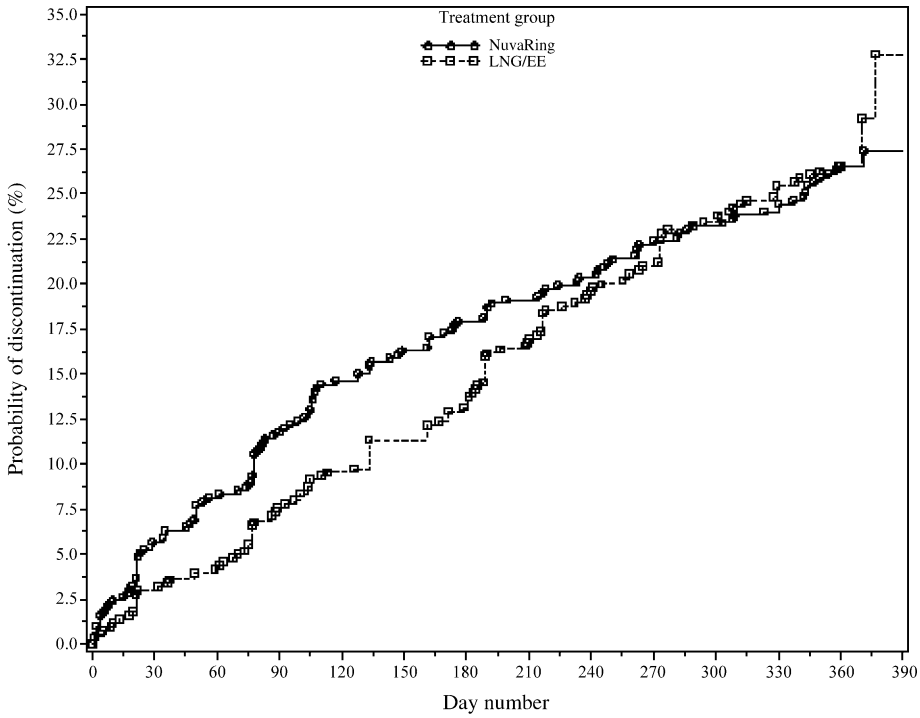

Fig. 2. The cumulative probability of discontinuation due to any reason in subjects receiving NuvaRing or a COC. LNG=levonorgestrel; EE=ethinylestradiol.

Table 2
Contraceptive efficacy: estimated Pearl indices for NuvaRing and COC recipients

	Population	Number of subjects	Total exposure		In-treatment pregnancies	Pearl index estimate (95% CIs)
			Cycles	Years		
NuvaRing	ITT	512	5321.7	408.0	5	1.23 (0.40, 2.86)
	PP	440	4062.8	311.5	3	0.96 (0.20, 2.82)
COC	ITT	518	5461.4	418.7	5	1.19 (0.39, 2.79)
	PP	459	4950.5	379.5	2	0.53 (0.06, 1.90)

ITT = intent-to-treat; PP = per protocol; CIs = confidence intervals.

respectively. No significant difference was found between the two treatment groups. The estimated cumulative probabilities of in-treatment ITT pregnancy after Cycle 13 were 1.20% (95% CI: 0.14, 2.26%) for the ring group and 1.07% (95% CI: 0.13, 2.00%) for the COC group. For the PP population, the estimated probabilities were 0.71% (95% CI: 0.00, 1.52%) and 0.43% (CI: 0.00, 1.01%) for the ring and COC groups, respectively.

3.3. Compliance with treatment

Compliance with the prescribed regimen was high in both groups. In the NuvaRing group, 87.4% of ITT cycles were fully compliant compared with 86.6% of ITT cycles in the COC group.

In the NuvaRing group, the ring-free period was prolonged in 6.6% of the cycles. Approximately 90% of all subjects never temporarily removed the ring (e.g., for sex) during any of the ring periods of Cycles 1–13. In the COC group, the pill-free period was longer than the scheduled 7 days in 2.9% of cycles.

3.4. Tolerability

The tolerability of both contraceptives was good. Throughout the study period, 57.6% of NuvaRing recipients and 54.3% of COC recipients reported an adverse event, of which 28.9% and 22.1%, respectively, were considered by the investigator to be at least possibly related to study treatment.

Headache was the most commonly reported adverse event in both groups (Table 3). Vaginitis and leukorrhea were reported by more subjects in the NuvaRing group than in the COC group (Table 3). Most cases of vaginitis were caused by candidal infection (data not shown). By definition, ring-related problems (comprising expulsion, foreign body sensation and coital problems) were reported only by subjects in the NuvaRing group (5.9%). The incidence of nausea, breast pain and abdominal pain was low in both the NuvaRing and COC groups (Table 3).

Eight subjects in the COC group and four in the NuvaRing group experienced hypertension. Six subjects (NuvaRing, $n=2$; COC, $n=4$) had varicose veins and one subject in the NuvaRing group had a deep vein thrombosis.

Eighteen serious adverse events (NuvaRing, $n=11$; COC, $n=7$) were reported during the study, but only 2 (the subject with deep venous thrombosis in the NuvaRing group and one subject with hypertension in the COC group) were considered to be related to study medication.

A total of 103 women in the ITT population (NuvaRing, $n=58$; COC, $n=45$) discontinued treatment because of an adverse event/serious adverse event. Most of the adverse events leading to discontinuation were considered by the investigator to be at least possibly related to study medication. In the NuvaRing group, the most frequently reported adverse events that resulted in discontinuation were ring-related problems ($n=11$), leukorrhea ($n=7$), headache ($n=4$), depression ($n=4$), vaginal discomfort ($n=3$) and nausea ($n=3$). In the COC group, the most frequently reported adverse events resulting in discontinuation were headache ($n=8$), weight increase ($n=6$), decreased libido ($n=5$), hypertension ($n=4$), nausea ($n=4$), acne ($n=4$) and depression ($n=3$).

Physical and gynecological examinations revealed very few clinically relevant abnormalities. A total of 94 subjects (NuvaRing, $n=43$; COC, $n=51$) had a clinically significant increase ($\geq 7\%$) in body weight from baseline. In addition,

Table 3
Number (%) of subjects who reported adverse events that were considered by the investigator to be at least possibly related to study treatment (occurring in $\geq 2\%$ of subjects in either treatment arm)

	NuvaRing		COC	
	Related to study medication[a]	Total	Related to study medication[a]	Total
Headache	37 (7.2)	97 (18.9)	30 (5.8)	77 (14.8)
Ring-related problems	24 (4.7)	30 (5.9)	0 (0.0)	0 (0.0)
Vaginitis	20 (3.9)	54 (10.5)	5 (1.0)	24 (4.6)
Leukorrhea	18 (3.5)	26 (5.1)	1 (0.2)	12 (2.3)
Breast pain	16 (3.1)	17 (3.3)	7 (1.3)	11 (2.1)
Nausea	14 (2.7)	20 (3.9)	21 (4.0)	25 (4.8)
Dysmenorrhea	13 (2.5)	23 (4.5)	7 (1.3)	15 (2.9)
Weight increase	9 (1.8)	13 (2.5)	12 (2.3)	15 (2.9)
Abdominal pain	8 (1.6)	17 (3.3)	5 (1.0)	13 (2.5)
Libido decrease	8 (1.6)	8 (1.6)	10 (1.9)	11 (2.1)
Leg pain	7 (1.4)	10 (2.0)	3 (0.6)	3 (0.6)
Genital pruritus	7 (1.4)	13 (2.5)	1 (0.2)	5 (1.0)
Urinary tract infection	3 (0.6)	15 (2.9)	0 (0.0)	15 (2.9)
Acne	2 (0.4)	4 (0.8)	13 (2.5)	15 (2.9)
Sinusitis	1 (0.2)	15 (2.9)	0 (0)	9 (1.7)

COC = combined oral contraceptive.

[a] Considered by the investigator to be definitely, probably or possibly related to study drug.

more subjects in the NuvaRing group had a clinically significant decrease in body weight (≤7%) from baseline (35 vs. 26 subjects) than in the COC group. Abnormal blood pressure was observed in ≤4% of subjects in each treatment group. Clinically relevant changes in blood chemistry or hematology occurred infrequently. There was no significant difference between groups in these parameters at study end.

4. Discussion

This Phase III, open-label, randomized, group-comparative, multicenter trial demonstrated that NuvaRing is as effective and well tolerated as a commonly used COC.

The efficacy, tolerability and acceptability of NuvaRing have been well established [5,6] and its cycle control and tolerability have been shown to be comparable with those of a COC over six contraceptive cycles [7]. Our study is the first 1-year, open-label, randomized controlled trial to directly compare the efficacy and safety of NuvaRing with those of a COC containing 150 μg of LNG and 30 μg of EE daily.

Five pregnancies occurred in both the NuvaRing and COC groups, and the Pearl indices for the two groups were similar (1.23 and 1.19, respectively). The Pearl index for the NuvaRing group is similar to that previously demonstrated in a large-scale trial (1.18) [5] and demonstrates that NuvaRing provides reproducible and robust contraceptive protection.

Compliance with a contraceptive method is necessary to maintain contraceptive reliability. This is illustrated by the proportion of pregnancies in subjects with protocol violations (50% of all pregnancies) described above. Most of the women in this study were compliant with ring and pill regimens.

In addition to contraceptive efficacy and cycle control, the occurrence of adverse events is a major determinant of the overall acceptability of a contraceptive method [8]. In our study, both NuvaRing and the COC were well tolerated, with no unexpected adverse events experienced during the study, and the incidence of study medication-related events was generally low. The main difference between the treatment groups was that local events such as vaginitis, device-related problems and leukorrhea were more frequently reported in the NuvaRing group. This finding is consistent with previously published data comparing the tolerability of NuvaRing with the same COC as used in this study [7] and with other studies on NuvaRing's efficacy and tolerability [5,6].

Hormone-related adverse events such as headache, breast tenderness and nausea are commonly associated with combined contraceptive use and often cause women to stop taking COCs [9–12]. The incidence of treatment-related adverse events was low for both groups in this study, as seen in a previous study with the same preparations [7]. Hormonal contraception is also associated with medical and cosmetic concerns relating to body weight. NuvaRing has previously been shown to have a neutral effect on body weight [5]. In the current study, fewer NuvaRing users experienced a clinically significant increase in body weight and more experienced a clinically significant decrease in body weight as compared with COC users. Although there were no significant differences between the groups in terms of change from baseline in body weight, increased body weight was more commonly reported as a reason for discontinuation for COC users ($n=6$) as compared with NuvaRing users ($n=2$). The low frequency with which clinically relevant changes were observed in physical or gynecological examinations or in hematology or biochemistry values indicates that NuvaRing has a good safety profile that is comparable with that of a commonly used COC.

Equal numbers of subjects discontinued in both the NuvaRing and COC groups, with the occurrence of adverse events being the main reason for discontinuation in each group. Interestingly, the discontinuation rate in the COC group tended to be fairly uniform throughout the study. In contrast, the discontinuation rate in the NuvaRing group tended to be higher in the first half of the study. This is similar to the findings of previous NuvaRing studies [5] and appears to be related to users deciding on the suitability of the NuvaRing method during the first few months of use. This explanation is supported by the observation that the main reason for discontinuation due to adverse events in the NuvaRing group was ring-related events (e.g., foreign body sensation) and local events such as leukorrhea, whereas, in the COC group, the main reason for discontinuation was predominantly hormone-related events.

In conclusion, the results of this study have shown that the NuvaRing has comparable contraceptive efficacy with a COC delivering 150 μg of LNG and 30 μg of EE daily. NuvaRing also exhibits tolerability and safety equivalent to that of an OC, but in a formulation that does not require daily dosing.

Acknowledgments

This study was supported by NV Organon, Oss, The Netherlands. T. Dieben and C. Verhoeven are employees of NV Organon.

The authors would like to thank and acknowledge the participation of the following investigators during this trial: A. Saey, U. Gaspard, M. Renier (**Belgium**); N.R. de Melo, M. Poli, E. Coutinho, E.A.J. Pellini, R. Pereira de Andrade, L. Bahamondes, M.E.H.D. Yazzle, M.A. Albernaz, J. Sabino Pinho Neto, C.E. Fernandes (**Brazil**); J.C. Montero (**Chile**); P. Hein, F. Ahlstrøm, K. Rubeck Petersen, L. Skive (**Denmark**); A. Kivelä, M. Vartiainen, U. Ågren, S. Korhonen, P. Taipale, A. Kiilavuori (**Finland**); D. Wiel-Masson, M.-L. Bollengier, J. Levy-Frebault, A. Mallet, A. Malvy, J. Sentenac, C. Matuchansky (**France**); B. Leifels-Fischer, W. Harlfinger, H.-P. Zahradnik, K. Muschel, F. Starflinger (**Germany**); C. Benedetto, G.B. Melis, A. Volpe, A. Genazzani (**Italy**); K. Oddsson, B. Eriksen, P. Lossius, K.A. Trosterud, T. Nygaard, M. Blakstad, N. Farnes (**Norway**); F. Martínez, C. Coll, R. Sánchez, A. Albert (**Spain**); and B.-M. Landgren, M. van Rooijen, I. Östlund, T. Bäckström, O Tydén (**Sweden**).

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