Contraceptive efficacy and tolerability of ethinylestradiol 20 μg/drospirenone 3 mg in a flexible extended regimen: an open-label, multicentre, randomised, controlled study

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Abstract

Background The contraceptive efficacy and tolerability of a new flexible extended regimen of ethinylestradiol (EE) 20 μg/drospirenone (DRSP) 3 mg to extend the menstrual cycle and enable management of intracyclic (breakthrough) bleeding (flexibleMIB) was investigated and the bleeding pattern compared with a conventional 28-day regimen and a fixed extended 124-day regimen.

Study design This Phase III, 2-year, multicentre, open-label study randomly (4:1:1) allocated women (aged 18–35 years) to the following regimens: flexibleMIB (24–120 days’ active hormonal intake with 4-day tablet-free intervals); conventional (24 days’ active hormonal intake followed by a 4-day hormone-free interval); or fixed extended (120 days’ uninterrupted active hormonal intake followed by a 4-day tablet-free interval). Primary outcomes included the number of bleeding/spotting days during Year 1 (all regimens) and the number of observed unintended pregnancies over 2 years (flexibleMIB only).

Results Results were analysed in 1067 women (full analysis set). The mean number of bleeding/spotting days was lower with the flexibleMIB vs the conventional regimen (41.0±29.1 (95% CI 38.8–43.3) vs 65.8±27.0 (95% CI 62.2–69.4) days, p<0.0001; treatment difference −24.8 (95% CI −29.2 to −20.3) days). The corresponding value for the fixed extended regimen was 60.9±51.1 (95% CI 53.9–67.9) days. The Pearl Index for the flexibleMIB regimen was 0.64 (95% CI 0.28–1.26). All regimens had comparable tolerability profiles.

Conclusions EE 20 μg/DRSP 3 mg administered as a flexible extended regimen with MIB is effective, well tolerated and is associated with statistically significantly fewer bleeding/spotting days and fewer withdrawal bleeding episodes vs EE/DRSP in a conventional 28-day regimen. The flexibleMIB also provided statistically significantly fewer spotting days vs EE/DRSP in a fixed extended 124-day regimen (post hoc evaluation). The flexibleMIB regimen allows women to extend their menstrual cycle and manage their intracyclic (breakthrough) bleeding.

Introduction

Many modern-day combined oral contraceptives (COCs) have a 28-day cycle, usually comprising 21 days of active (i.e. hormonal) tablets followed by a 7-day hormone-free interval. Newer COCs with a shortened hormone-free interval (i.e. 24 days of active hormonal intake followed by a 4-day hormone-free interval), which are associated with more sustained ovarian suppression and reduced hormonal fluctuations,1 are available; such COCs still, however, follow the 28-day cycle paradigm. The 28-day cycle was originally designed to allow for monthly bleeding, even though this was not necessary, primarily to mimic the natural menstrual cycle and to reassure women that they were not pregnant.2

The long-term availability of COCs with a hormone-free interval has led many women to mistakenly believe that it is natural to have a withdrawal bleed during COC use or that missing a withdrawal bleed is associated with negative health effects.3–7 Despite this, given the choice, a substantial proportion of women would welcome a reduction in the frequency of their menstrual bleeding. Survey data indicate that as many as 59% of women aged 15–49 years would be interested in not menstruating every month.7,8 Furthermore, up to 46% of such women would rather not have a period at
FlexibleMIB
Fixed extended

Withdrawal bleeding
Started before or at the latest on the fourth day of the subsequent cycle
AND ended at the earliest 4 days before the first day of the tablet-free
interval of the current cycle or later

If more than one episode satisfied both of the above criteria, the first
episode to occur was considered to be the withdrawal bleeding episode
of that cycle

Intracyclic bleeding
Bleeding episodes (either spotting or
bleeding) shorter than 3 days

Scheduled bleeding
Any bleeding days that occurred during the tablet-free interval
or up to 4 days after the tablet-free interval

Unscheduled bleeding
Any bleeding days that occurred while taking active treatment,
unless they occurred (i) up to 4 days after the tablet-free interval
or (ii) during Days 1–7 of the first treatment cycle

*As tablet-free intervals were not documented with the conventional 28-day regimen, an analysis of scheduled and unscheduled bleeding was only
carried out for the two extended regimens.

**MIB, management of intracyclic (breakthrough) bleeding.

Methods

Study design
This was a Phase III, multicentre, randomised, open-label, parallel-group study conducted at 37 centres in Germany, Canada and The Netherlands between
December 2005 (first subject, first visit) and October 2008 (last subject, last visit). The study (protocol
number, 308683; ClinicalTrials.gov identifier, NCT00266032) was conducted in accordance with
the Declaration of Helsinki and the International
Conference on Harmonisation–Good Clinical Practice
guidelines. All participants received adequate informa-
tion about the study and signed an informed consent
form before entering the study.

The study consisted of two phases: a 1-year compara-
tive phase where women were randomly allo-
cated to receive EE 20 µg/DRSP 3 mg administered as a flexibleMIB, conventional 28-day or fixed extended
regimen and a 1-year safety extension phase during
which the majority of women received the flexibleMIB
regimen. For the most part, data from the 1-year compara-
tive phase are reported here, while data from the
safety extension phase are reported elsewhere.

Study population
Healthy females aged between 18 and 35 years who
requested contraceptive protection were eligible to
participate in the study. Women were required to
be in good general health with a normal cervical
smear test result at or in the 6-month period prior to
screening, and smokers could participate so long as
they were 30 years of age or younger at the time of
screening. The main exclusion criteria included: use
of other contraceptive methods, sterilisation, preg-
nancy or lactating, body mass index <18 and >30
kg/m², presence or history of any vascular diseases or coagulation disorders, known hypersensitivity to any of the study drug ingredients, and any disease or condition that could interfere with the study medication.

**Study regimens**

**Flexible extended regimen with management of intracyclic (breakthrough) bleeding**

With the flexible MIB regimen, women received EE/DRSP for a flexible number of cycles (minimum three, maximum 13 in 1 year), each of which was separated by a 4-day tablet-free interval. With this regimen, tablet taking was continuous for at least 24 days (‘mandatory phase’); in this manner, the minimum cycle length was 28 days and the design of the COC was based on the approved and marketed conventional 24/4-day regimen of EE 20 µg/DRSP 3 mg (YAZ®; Bayer HealthCare Pharmaceuticals). After the mandatory phase, the cycle could continue up to a maximum of 120 consecutive days (i.e. for a maximum cycle length of 124 days). A 4-day tablet-free interval had to be taken at the latest after 120 days of continuous tablet intake. Between Days 25 and 120 (‘flexible phase’) women were instructed to observe a 4-day tablet-free interval if they experienced three consecutive days of bleeding and/or spotting. After each 4-day tablet-free interval, women started a new cycle with a minimum of 24 days and a maximum of 120 days of tablet intake.

**Conventional 28-day regimen**

With the conventional 28-day regimen, women received EE/DRSP for 13 cycles. Each cycle comprised 24 days of active hormonal intake followed by a 4-day interval in which women took hormone-free (placebo) tablets to induce withdrawal bleeding.

**Fixed extended regimen**

With the fixed extended regimen, women received EE/DRSP for three cycles. Each cycle comprised 120 days of uninterrupted active hormonal intake followed by a 4-day tablet-free interval.

Study medication was to be commenced on the first day of menstrual bleeding (new COC starters) or scheduled withdrawal bleeding (COC switchers) following the baseline visit. During active hormonal intake, tablets could be taken in the morning or the evening, but the interval between two tablets had to remain as close as possible to 24 hours. If a woman missed a tablet she was to take it as soon as possible (even if this meant taking two tablets at the same time); thereafter, tablet intake was to continue as normal. With regard to the rules for the use of back-up contraception, a missed tablet was defined as tablet intake that was delayed by more than 24 hours.

**Study outcomes**

**Primary outcomes**

The main primary outcome was the total number of bleeding/spotting days during the 1-year comparative...
flexibleMIB regimen as the number of women in the Index was only calculated in women who received the multiplier by 100) and by life-table analysis. The Pearl pregnancies divided by the exposure in woman-years for a comparison of efficacy, calculated using the Pearl Index (number of tended pregnancies was used to measure contraceptive failure rate. A life-table analysis was performed for the time to administration of study medication. 

The full analysis set was defined as all women who received at least one dose of study medication and had at least one clinical observation after administration of study medication. BMI, body mass index; MIB, management of intracyclic (breakthrough) bleeding; COCs, combined oral contraceptives.

A self-reported, non-validated, menstrual bleeding questionnaire was used to assess the impact of the three regimens on subjects’ menstrual bleeding and the problems associated with it; data were collected retrospectively for the 12 weeks prior to inclusion into the study and at four time points during the study. Subjects in each of the three groups also completed the 22-item validated Psychological General Well-Being Index (PGWBI) at baseline and at two time points during the study. A third questionnaire was used to assess satisfaction with the regimen in women who received the two extended regimens; this was completed at the end of the first year of the study.

### Safety outcomes

The following safety outcomes were evaluated: adverse events (AEs); laboratory variables; bone markers and bone mineral density; general physical and gynecological findings (including the outcomes of cervical smear tests); endometrial biopsies; and vital signs and body weight. AEs for the first year of the study are reported here; data pertaining to long-term safety outcomes are reported separately.18

Table 2  Demographic and baseline characteristics of women who received ethinylestradiol 20 μg/drospirenone 3 mg administered as a flexibleMIB, conventional 28-day or fixed extended regimen (full analysis set)

| Characteristic                             | FlexibleMIB (n=642) | Conventional 28-day (n=216) | Fixed extended (n=209) |
|--------------------------------------------|---------------------|----------------------------|-----------------------|
| Age (years)                                | 24.8 (4.4)          | 24.3 (4.3)                 | 24.8 (4.5)            |
| Height (cm)                                | 167.2 (6.3)         | 167.8 (5.8)                | 168.0 (6.2)           |
| BMI (kg/m²)                                | 22.5 (2.7)          | 22.6 (2.8)                 | 22.5 (2.6)            |
| Caucasian ethnicity (n [%])                | 636 (99.1)          | 212 (98.1)                 | 202 (96.7)            |
| Current smokers (n [%])                    | 205 (31.9)          | 67 (31.0)                  | 67 (32.1)             |
| Contraceptive method at screening (n [%])  | COCs 538 (83.8)     | 158 (73.1)                 | 148 (70.8)            |
|                                            | Condoms 77 (12.0)   | 48 (22.2)                  | 52 (24.9)             |
|                                            | None 17 (2.6)       | 7 (3.2)                    | 5 (2.4)               |
|                                            | Other 10 (1.6)      | 3 (1.4)                    | 4 (1.9)               |

Data are presented as mean (SD) unless otherwise stated.

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Secondary outcomes

Secondary outcomes included bleeding pattern and cycle control outcomes over the first year. Bleeding pattern parameters included the number and length of bleeding/spotting episodes and spotting-only episodes (days with bleeding/spotting or spotting only preceded and followed by at least two bleed-free days); these parameters were determined for each subject for 90-day reference periods. The first reference period started on the first day of study medication intake. Cycle control parameters included withdrawal bleeding, intracyclic bleeding, scheduled bleeding and unscheduled bleeding defined according to the different regimens (Table 1). Cycle control parameters were determined for each subject at every cycle.

Bleeding data were recorded by every subject using diary cards that were to be completed on a daily basis. Each day, subjects rated their bleeding as none, spotting, light, normal or heavy. Diary records were to start with the onset of the first menstrual or withdrawal bleeding episode following the baseline visit (i.e. the bleeding episode that prompted the initiation of study medication), and were to continue until the end of the last bleeding episode within the study. The daily diary cards were also used to monitor compliance with study medication.

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Data are presented as mean (SD) unless otherwise stated.

The full analysis set was defined as all women who received at least one dose of study medication and had at least one clinical observation after administration of study medication.

BMI, body mass index; MIB, management of intracyclic (breakthrough) bleeding; COCs, combined oral contraceptives.
Statistical analysis
Descriptive statistics [number, mean, standard deviation (SD)] were calculated for each quantitative variable, while frequencies were given for categorical data. Regarding the primary outcome of the number of bleeding/spotting days, the main evaluation was a comparison of the flexible\textsubscript{MIB} regimen versus the conventional regimen using Student’s $t$-test assuming a normal distribution. A statistical comparison between the flexible\textsubscript{MIB} and the fixed extended regimen was not planned, although a post hoc analysis was conducted.

For the 1-year comparative phase, subjects were randomly allocated in a 4:1:1 ratio to the flexible\textsubscript{MIB}, conventional and fixed extended regimens. The randomisation sequence was generated by the responsible biometrician and performed by the central randomisation group at Bayer HealthCare Pharmaceuticals using the software package SAS (Release 9.1 or higher; SAS Institute, Cary, NC, USA). Randomisation blocks of 12 were used. Eligible subjects were assigned their randomisation numbers via an interactive voice response system to avoid any assignment bias in this open-label study. With this system, neither the subject nor the investigator knew the identity of the study regimen before the assignment of the randomisation number.

Analysis set
The full analysis set (FAS) was defined as all women who received at least one dose of study medication and for whom at least one clinical observation following administration of study medication was available. The evaluation of the primary outcomes was based on the FAS, as was the evaluation of safety data. It should be noted that 67 subjects were excluded from the FAS because of invalid data owing to suspected misconduct at one study centre.

Sample size
In order to undertake a reasonable assessment of safety, it was considered that a treatment duration equivalent to 10 000 cycles of 28 days should be achieved for the flexible\textsubscript{MIB} regimen. Based on previous experience with cycle control studies using conventional regimens, it
was considered that at least 200 subjects per treatment arm would be sufficient to reliably describe the bleeding data.

Given that the flexible_MiB is the preferred regimen and assuming a difference of 10 days and a SD of 28 days plus an annual dropout rate of 40%, approximately 660 subjects were needed for the flexible_MiB regimen, and 225 subjects were needed for each of the other two regimens. This resulted in a proposed total sample size of 1110 subjects, which would result in a power of at least 94% to show superiority of the flexible_MiB regimen over the conventional regimen in terms of the primary bleeding variable.

The proposed sample size for the flexible_MiB group was also expected to provide sufficient statistical power to reliably determine contraceptive efficacy, as per the guidelines of the European Medicines Agency.

**Results**

Overall, 1312 women were screened, and 1166 of these were subsequently randomised to one of the three regimens. Reasons for non-randomisation are shown in Figure 1. Study medication was administered to 1134 subjects in the three groups. After excluding the 67 subjects from a study centre with suspected study misconduct, 1067 women took at least one dose of study medication and had at least one clinical observation after administration of study medication; these women comprised the FAS (flexible_MiB, n = 642; conventional, n = 216; fixed extended, n = 209; Figure 1). The demographic and baseline characteristics of women included in the FAS were generally similar in the three groups (Table 2). Study medication was completed by 88.5% of all subjects in the FAS. Overall, 83.9%, 80.3% and 72.9% of all women randomised to the flexible_MiB, conventional and fixed extended regimens, respectively, completed treatment. The mean treatment exposure times were 339 days for the flexible_MiB regimen, 340 days for the conventional regimen and 318 days for the fixed extended regimen.

**Primary outcomes**

The mean number of bleeding/spotting days within the comparative phase was significantly lower with the flexible_MiB regimen than with the conventional regimen [41.0±29.1 (95% CI 38.8–43.3; n=640) vs 65.8±27.0 (95% CI 62.2–69.4; n=215) days, p<0.0001; treatment difference −24.8 (95% CI −29.2 to −20.3) days; Figure 2]. The mean number of bleeding/spotting days with the fixed extended regimen was 60.9±51.1 (95% CI 53.9–67.9) days (n=209). No statistical testing was preplanned for this comparison; however, the between-treatment difference was in the same order of magnitude as that

### Table 3  Bleeding pattern outcomes by 90-day reference period in women who received ethinylestradiol 20 μg/drospirenone 3 mg administered as a flexible_MiB, conventional 28-day or fixed extended regimen (full analysis set)

| Reference period | Flexible_MiB | Conventional 28-day | Fixed extended |
|------------------|-------------|---------------------|----------------|
| Bleeding/spotting days |
| 1                | 13.7 (n=605) | 22.6 (n=203) | 21.7 (n=182) |
| 2                | 10.7 (n=575) | 15.3 (n=198) | 16.0 (n=174) |
| 3                | 9.4 (n=554)  | 14.8 (n=189) | 14.1 (n=161) |
| 4                | 8.2 (n=522)  | 14.2 (n=171) | 9.4 (n=146)  |
| Spotting-only days |
| 1                | 6.5         | 8.0               | 12.7          |
| 2                | 5.4         | 5.0               | 9.8           |
| 3                | 4.7         | 4.9               | 9.0           |
| 4                | 4.3         | 4.7               | 6.8           |
| Bleeding-only days |
| 1                | 7.2         | 14.6              | 9.0           |
| 2                | 5.3         | 10.2              | 6.3           |
| 3                | 4.6         | 9.8               | 5.1           |
| 4                | 3.9         | 9.5               | 2.6           |

All data refer to mean values. The full analysis set was defined as all subjects who received at least one dose of study medication and had at least one clinical observation after administration of study medication. Subject numbers shown for bleeding/spotting days apply to the data for spotting-only days and bleeding-only days. Reference periods 1, 2, 3 and 4 refer to Days 1–90, 91–180, 181–270 and 271–360, respectively. NB. The greatest number of bleeding/spotting days, spotting-only days and bleeding-only days was reported in the first reference period, which was not unexpected. For all three groups, subjects initiated intake of study medication on the first day of menstrual or withdrawal bleeding after baseline. Therefore, the first reference period contained additional bleeding days (associated with the menstrual cycle prior to the start of study medication) compared with the subsequent reference periods.

MIB, management of intracyclic (breakthrough) bleeding.
between the flexible\textsuperscript{MIB} regimen and the conventional regimen, and a post hoc analysis indicated that the flexible\textsuperscript{MIB} regimen significantly reduced the mean number of bleeding/spotting days versus the fixed extended regimen \((p<0.0001)\). The variation in the overall number of days of bleeding in the first year in women who received the flexible\textsuperscript{MIB} regimen was similar to that in women who received the conventional regimen (Figure 3). The fixed extended regimen showed more variability (Figure 3).

Over the full 2 years of the study, the Pearl Index for the flexible\textsuperscript{MIB} regimen was 0.64 (95% CI 0.28–1.26) based on eight pregnancies and 1253 woman-years of exposure. One of these pregnancies was deemed to be a subject failure; the others were reported without information supporting subject failure, and were therefore classified as method failures. The cumulative pregnancy rate for up to 2 years of treatment (determined using the Kaplan–Meier life-table analysis) was 1.28% (95% CI 0.62–2.66). This corresponds to 99% contraceptive protection.

**Secondary outcomes**

**Bleeding pattern**

The flexible\textsuperscript{MIB} regimen was associated with the lowest mean number of bleeding/spotting days (analysed by 90-day reference periods). The mean number of bleeding/spotting days was generally higher with the conventional regimen at all time points (Table 3). During the 1-year comparative phase, the proportion of bleeding/spotting days was lowest in women treated with the flexible\textsuperscript{MIB} regimen (13.3±11.1%); corresponding proportions in recipients of the conventional and fixed extended regimens were 20.4±9.8% and 23.1±20.7%, respectively.

**Cycle control**

The mean number of cycles in women who received the flexible\textsuperscript{MIB}, conventional and fixed extended regimens...
was 4.5±2.1 (median 4.0), 11.9±2.9 (median 13.0) and 2.8±0.9 (median 3.0), respectively. Values for mean cycle length were 78.2±39.8 (median 72.0), 27.9±1.8 (median 28.0) and 121.6±27.9 (median 124.0) days, respectively. The cycle length observed with the flexibleMIB regimen is shown in Figure 4. In women who received the flexibleMIB regimen, approximately 20% of all cycles were of the maximum length of 124 days.

Withdrawal bleeding episodes occurred approximately every 8–10 weeks in recipients of the flexibleMIB regimen and, as expected, every 4 weeks in recipients of the conventional regimen and every 124 days in recipients of the fixed extended regimen. The mean length of withdrawal bleeding episodes appeared to be shorter with the conventional 28-day regimen (4.4–5.2 days) than with the flexibleMIB regimen (7.5–14.2 days) and fixed extended regimen (2.0–10.5 days). For the majority of withdrawal bleeding episodes, the maximum intensity was reported as light to normal with all three regimens.

The mean number of intracyclic bleeding/spotting days during the comparative phase appeared similar in recipients of the flexibleMIB and conventional regimens, and lower than that in recipients of the fixed extended regimen (Table 4). A similar result was observed for the number of days with intracyclic bleeding only, and the mean number and maximum length of intracyclic bleeding episodes (Table 4). The maximum intensity of intracyclic bleeding was deemed spotting or bleeding with light intensity with all three regimens (Table 4).

The flexibleMIB regimen appeared to have a higher mean number of scheduled bleeding days (23.3±14.3 days) than the fixed extended regimen (14.0±5.9 days). In contrast, the opposite was observed for the number of unscheduled bleeding days, which was lower with the flexibleMIB regimen than with the fixed extended regimen (17.1±17.4 vs 46.6±48.4 days).

**Subject questionnaires**

Improvements in various items of the menstrual bleeding questionnaire were observed, compared with the 12 weeks prior to inclusion into the study. Between-treatment differences in symptoms were found, primarily as a result of extended cycles resulting in an absence of menstrual bleeding-related events. Aspects related to the PGWBI, user satisfaction and menstruation-related symptoms with the three regimens is shown in Table 5. Of those women who had painful menstruation before the start of the study, 52.5% treated with the flexibleMIB regimen and 58.1% treated with the fixed extended regimen reported feeling better having received treatment. In addition, 86.0% and 79.1% of women, respectively, would recommend their regimen to a friend.

**Safety**

The occurrence of AEs during the comparative phase is reported in Table 6. The vast majority (93.1%) of AEs that occurred were mild or moderate in intensity; there was no difference in AE intensity between the three groups.

There were four serious AEs (SAEs) that were considered to be possibly related to study medication: focal nodular hyperplasia of the liver, uterine leiomyoma and two cases of deep vein thrombosis (DVT). More detailed data pertaining to long-term safety outcomes during the 2-year study are reported separately.18

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**Table 5** User satisfaction, Psychological General Well-Being Index score and menstruation-related symptoms in women who received ethinylestradiol 20 μg/drospirenone 3 mg administered as a flexibleMIB, conventional 28-day or fixed extended regimen (full analysis set)

| Parameter | FlexibleMIB (n=179) | Conventional 28-day (n=18) | Fixed extended (n=43) |
|-----------|---------------------|-----------------------------|----------------------|
| **Regimen satisfaction** [n (\%)] | | | |
| Very satisfied | 111 (62.0) | -- | 25 (58.1) |
| Quite satisfied | 60 (33.5) | -- | 14 (32.6) |
| Improved frequency of painful menstruations [n (\%)] | 138 (77.1) | 14 (77.8) | 35 (81.4) |
| Improved intensity of painful menstruations [n (\%)] | 133 (74.3) | 16 (88.9) | 38 (88.4) |
| PGWBI (change in total score from baseline to Week 51) | +0.35 | −1.02 | +0.26 |

| Menstruation-related symptoms [n (\%)] | | | |
| Baseline (n=642) | Week 51 (n=554) | Baseline (n=216) | Week 51 (n=196) | Baseline (n=209) | Week 51 (n=165) |
| Mild abdominal/pelvic pain | 296 (46.1) | 132 (23.8) | 90 (41.7) | 54 (29.0) | 84 (40.2) | 25 (15.2) |
| Mild backache | 158 (24.6) | 94 (17.0) | 57 (26.4) | 30 (16.1) | 57 (27.3) | 19 (11.5) |
| Daily activities slightly impaired | 38 (5.9) | 12 (2.2) | 8 (3.7) | 11 (5.9) | 7 (3.3) | 0 (0) |
| Confined to bed for part of a single day | 14 (2.2) | 7 (1.3) | 3 (1.4) | 0 (0) | 10 (4.8) | 1 (0.6) |
| Leisure activities slightly affected | 72 (11.2) | 19 (3.5) | 18 (8.3) | 9 (4.8) | 19 (13.9) | 6 (3.7) |

*Assessed in women who reported painful menstruation before the start of study medication (32.3% of women who received the flexibleMIB regimen, 14.4% of women who received the conventional regimen and 26.1% of women who received the fixed extended regimen).

MIB, management of intracyclic (breakthrough) bleeding; PGWBI, Psychological General Well-Being Index.
Discussion

The results of this trial show that EE 20 µg/DRSP 3 mg administered in a flexibleMIB regimen was associated with significantly fewer bleeding/spotting days over a period of 1 year compared with the conventional regimen. It was also associated with a similarly significant reduction in the number of days of bleeding/spotting than the fixed extended regimen. In addition, the flexibleMIB regimen showed good contraceptive efficacy similar to other COCs and was well tolerated.

The flexibleMIB regimen had a more favourable effect on various aspects of menstrual bleeding than the two other regimens, including fewer bleeding/spotting days overall and fewer days with unscheduled bleeding. The reduction in bleeding/spotting days with the flexibleMIB regimen compared with the conventional regimen was mainly related to 50% fewer days of menstruation-like bleeding. The reduction in bleeding/spotting days with the flexibleMIB regimen compared with fixed extended regimen could be related to one-half the number of days with spotting only (Figure 2). Overall, the flexibleMIB regimen was associated with a reduced proportion of bleeding days of any intensity; by one-third compared with the conventional regimen and potentially by one-third compared with the fixed extended regimen. In addition, the flexibleMIB regimen appeared to be associated with less variation in the overall number of days of bleeding/spotting than the fixed extended regimen. On average, women taking the flexibleMIB regimen can expect to have approximately 40 days of bleeding per year in comparison to approximately 65 days with the conventional regimen (corresponding to 5 days of bleeding per cycle).

The mean number of intracyclic bleeding/spotting days in recipients of the flexibleMIB regimen seemed to be markedly lower than that in recipients of the fixed extended regimen. This may be because women who received the latter regimen were instructed to take 120 days of uninterrupted active hormonal intake irrespective of any bleeding/spotting. In contrast, women who received the flexibleMIB regimen who experienced three consecutive days of bleeding/spotting during Days 25–120 were instructed to observe a 4-day tablet-free interval; in this manner, the 3 days of bleeding/spotting that preceded the tablet-free interval became part of the bleeding episode of the withdrawal bleed. As such, the length of the whole bleeding episode in the flexibleMIB group was prolonged by 3 days because of the stipulated ‘wait and see’ period of three consecutive days of bleeding/spotting. Ultimately, this may translate into fewer bleeding days overall and better cycle control with fewer episodes of intracyclical bleeding, which could improve the acceptability of the flexibleMIB regimen compared with the fixed extended regimen.

The acceptability of the flexibleMIB regimen may also be influenced by the fact that the onset of bleeding could be managed, within the limitations of the regimen. With the flexibleMIB regimen women could take treatment for 24 days, 120 days, or for an amount of time between 25 and 120 days, depending on the occurrence of bleeding/spotting. Although this study did not allow the flexibleMIB regimen group to observe a 4-day tablet-free interval at any time between Days
bleeding/spotting days in women who received the fixed extended regimen (median 35 days) versus the conventional 28-day regimen (median 53 days), similar to the findings reported here. The proportion of women on the EE/LNG fixed extended regimen who prematurely discontinued medication because of any AE or bleeding irregularities was 14.9% and 7.7%, respectively. In the current study these values were lower: 6.4% and 1.2% with the flexibleMIB regimen, respectively. In a second study, women received EE 20 µg/LNG 100 µg (n=16) administered for 168 days without a pill-free interval or as six 28-day cycles (n=16) on an open-label basis. Over the course of the study, women on the fixed extended regimen had a mean of 25.9±29.2 days of bleeding/spotting. In a similarly designed, double-blind study, in which 31 women received EE 20 µg/norethindrone acetate 1 mg for 168 days, 31.5±21.8 days of vaginal bleeding were reported. It should be noted that the latter two studies were conducted over 168 days, whereas bleeding outcomes in the current study are reported for a full year.

Conclusions
The results of this study show that EE/DRSP administered as a flexibleMIB regimen is associated with fewer days of bleeding/spotting and fewer withdrawal bleeding episodes over 1 year compared with the same hormonal combination in a conventional 28-day regimen. It also appeared to provide fewer spotting days compared with the same combination in a fixed extended 124-day regimen. The flexibleMIB regimen provides reliable contraceptive efficacy, and has a comparable tolerability profile to the conventional and fixed extended regimens. The flexibleMIB regimen is unique in that it extends the menstrual cycle and provides women with the flexibility to manage their intracyclic (breakthrough) bleeding.

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Competing interests
Christine Klipping and Ingrid Duijkers are employees of Dinox BV, one of the centres in which the study was conducted. Michael P. Fortier is a physician collaborating with the Clinique de Recherche en Santé des Femmes, one of the centres in which the study was conducted. Joachim Marr, Dietmar Trummer and Jörg Elliesen are employees of Bayer HealthCare Pharmaceuticals.
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