Long-term tolerability of ethinylestradiol 20 µg/drospirenone 3 mg in a flexible extended regimen: results from a randomised, controlled, multicentre study

Christine Klipping,[1] Ingrid Duijkers,[2] Michel P Fortier,[3] Joachim Marr,[4] Dietmar Trummer,[5] Jörg Elliesen[6]

[1]President and Medical Director, Dinox BV, Groningen, The Netherlands
[2]Vice-President and Director Clinical Research, Dinox BV, Groningen, The Netherlands
[3]Researcher and Gynaecologist, Clinique de Recherche en Santé des Femmes, Québec, Canada
[4]Vice-President Clinical Development, Global Clinical Development, Bayer HealthCare Pharmaceuticals, Berlin, Germany
[5]Prinicipal Statistician, Global Biostatistics, Bayer HealthCare Pharmaceuticals, Berlin, Germany
[6]Global Clinical Leader, Bayer HealthCare Pharmaceuticals, Berlin, Germany

Correspondence to
Dr Jörg Elliesen, Bayer HealthCare Pharmaceuticals, Müllerstrasse 178, D-13353 Berlin, Germany;
joerg.elliesen@bayer.com

Received 5 September 2011
Accepted 10 February 2012

Abstract

Background This study was designed to assess the long-term safety and tolerability of a new flexible extended regimen of ethinylestradiol (EE) 20 µg/drospirenone (DRSP) 3 mg, which allows management of intracyclic (breakthrough) bleeding [flexible management of intracyclic (breakthrough) bleeding (MIB)], in comparison to conventional 28-day and fixed extended regimens.

Study design In this Phase III, multicentre, open-label study, women (aged 18–35 years) were randomised to EE/DRSP in the following regimens: flexible$_{MIB}$ (24–120 days' active hormonal intake followed by a 4-day tablet-free interval), conventional 28-day (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) during a 1-year comparative phase. Thereafter, women entered a 1-year safety extension phase in which the majority received the flexible$_{MIB}$ regimen. Safety/tolerability outcomes were measured over 2 years. A separate analysis of certain safety parameters (endometrial, hormonal, lipid, haemostatic and metabolic variables) was conducted at two of the study centres.

Results Results were analysed in 1067 and 783 women in the comparative and safety extension phases. Overall, 56.3% of women experienced ≥1 adverse event (AE) in the safety extension phase. Serious AEs occurred in 3.0%, 1.4% and 3.3% of women receiving the flexible$_{MIB}$, conventional and fixed extended regimens, respectively. No unexpected endometrial, hormonal, lipid, haemostatic or metabolic findings occurred with any of the three regimens.

Conclusions EE/DRSP in a flexible extended regimen with management of intracyclic (breakthrough) bleeding is well-tolerated and, when administered for up to 2 years, has a good safety profile comparable to other estrogen/progestogen oral contraceptives.

Key message points

- A flexible extended regimen of ethinylestradiol (EE) 20 µg/drospirenone (DRSP) 3 mg, which allows women to extend their menstrual cycle and manage intracyclic (breakthrough) bleeding, is well-tolerated.
- When administered for up to 2 years, a flexible extended regimen of EE/DRSP has a good safety profile comparable to other estrogen/progestogen combined oral contraceptives.

Introduction

Most combined oral contraceptives (COCs) follow a 28-day intake cycle, consisting of 21 days of active hormonal intake followed by a 7-day hormone-free interval. Some COCs are available in a 24/4-day regimen (24 days of active hormonal intake followed by a 4-day hormone-free interval); although 24/4-day regimen COCs have been shown to provide more sustained ovarian suppression and reduced hormonal fluctuations compared with 21/7-day regimens,[1] they still follow the traditional 28-day cycle paradigm. This cycle was adopted so that COC users would have a withdrawal bleed every 4 weeks (i.e. have a menstrual cycle that mimicked the natural menstrual cycle).[2]

Recently, fixed extended regimen COCs have become available. With such regimens, users do not experience a monthly withdrawal bleed because the active hormonal intake period is extended, resulting in fewer hormone-free intervals. Fixed extended regimen COCs may be appealing to the not insubstantial proportion of women who would welcome a reduction in the frequency of their menstrual bleeding.[3 4] Unfortunately, fixed extended regimen COCs are not currently available outside of the USA.

Given the interest that women have in reducing and also being able to control when they have their menstrual bleeding, it was considered that a regimen of ethinylestradiol (EE) 20 µg/drospirenone

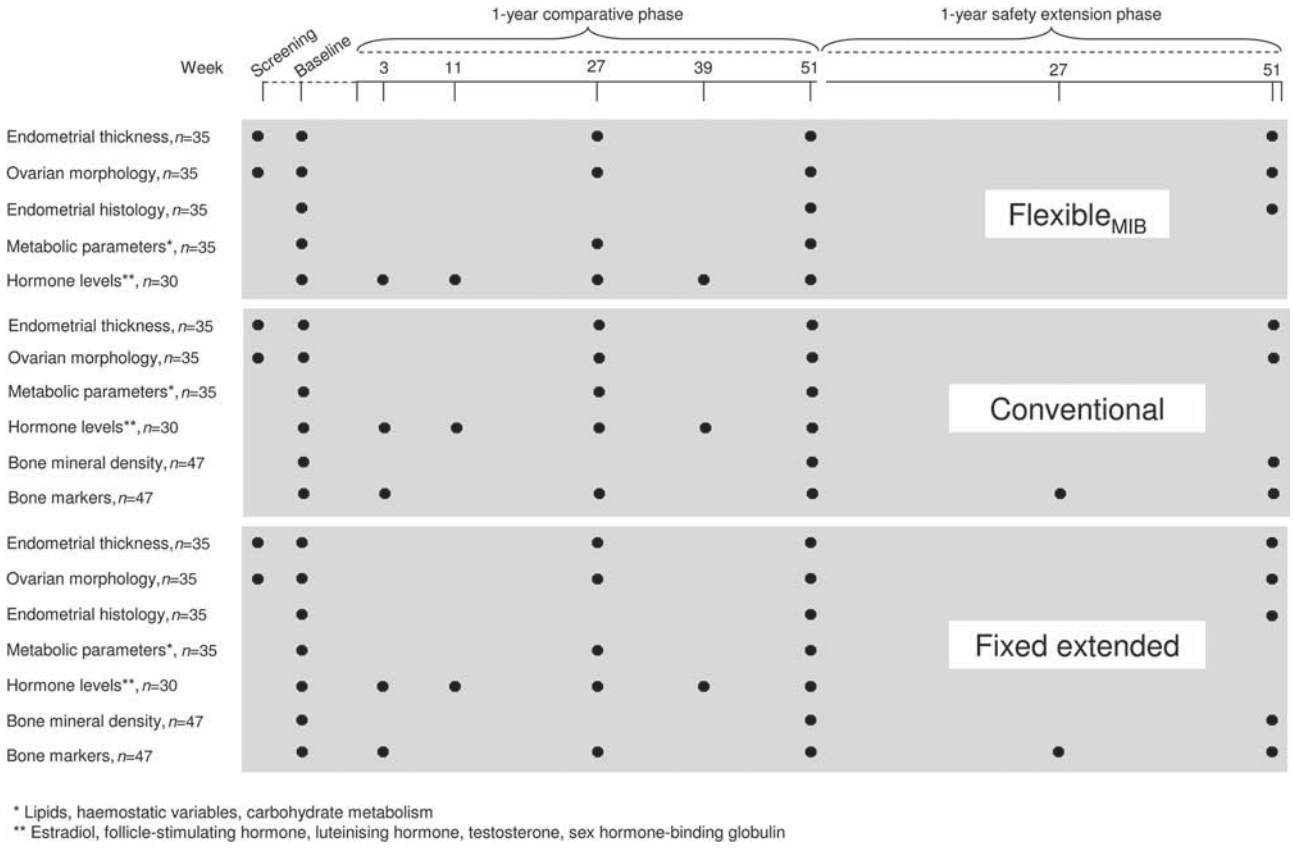

Figure 1 Overview of subgroup analyses undertaken during the 1-year comparative treatment phase and the 1-year safety extension phase. MIB, management of intracyclic (breakthrough) bleeding.

(DRSP) 3 mg that extended beyond the conventional 28 days and that enabled the management of intracyclic (breakthrough) bleeding (MIB), which can occur with fixed extended regimen COCs, would be appealing. The objective of this 2-year study was to compare the safety and tolerability of EE/DRSP in a flexible extended regimen with MIB ('flexible$_{MIB}$') with EE/DRSP in a conventional 28-day or a fixed extended regimen. The efficacy, bleeding data and 1-year safety of the three regimens has been reported elsewhere.[5] This paper focuses on the safety and tolerability over 2 years. In addition, a separate analysis was conducted to assess bone mineral density (BMD) and bone markers in women receiving the fixed extended regimen relative to the conventional regimen. This was because it has been reported that bone loss can occur during the use of depot contraceptives containing medroxyprogesterone acetate,[6] which has been speculated to be the result of prolonged ovarian suppression leading to reduced ovarian estradiol production.[7]

Methods

Study design

This was a Phase III, multicentre, randomised, open-label, parallel-group study conducted between December 2005 (first subject, first visit) and October 2008 (last subject, last visit) at 37 centres in Canada, Germany and The Netherlands (protocol number, 308683; ClinicalTrials.gov identifier, NCT00266032).

The study was conducted in two phases. In the comparative phase, women were randomly allocated to receive one of three different regimens of EE/DRSP for 1 year: a flexible$_{MIB}$ regimen, a conventional 28-day regimen or a fixed extended regimen. In order to provide long-term safety data for the flexible$_{MIB}$ regimen, all subjects who completed the comparative phase of the study were eligible to participate in a 1-year safety extension phase. During the safety extension phase, the majority of women received the flexible$_{MIB}$ regimen. There was, however, a small number of women (n=28) on the fixed extended and conventional regimens who remained on their respective first-year regimens in order to assess BMD and bone markers.

The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation–Good Clinical Practice guidelines. Participants could enter the study only if they had received adequate information about it, and had voluntarily signed an informed consent form.

Study population

The study population plus the inclusion and exclusion criteria have been described in detail elsewhere.[5] In

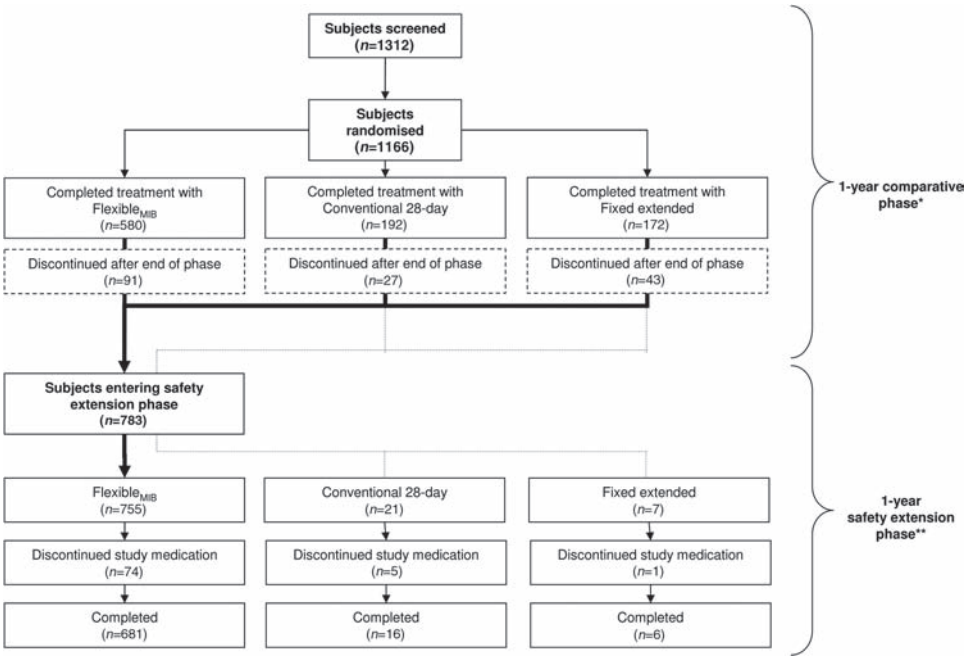

Figure 2 Disposition of women through the 1-year comparative phase and the 1-year safety extension phase. MIB, management of intracyclic (breakthrough) bleeding. *Additional information on the disposition of women through the comparative phase of the study is published separately.5 **All women who entered the safety extension phase received ethinylestradiol 20 µg/drospirenone 3 mg in the flexibleMIB regimen with the exception of 28 women participating in the bone mineral density analysis. Such women continued to receive either the conventional or the fixed extended, as shown in the figure.

brief, healthy females aged between 18 and 35 years who requested contraceptive protection were eligible for inclusion. Smokers over the age of 30 years were ineligible to participate.

Study treatments

During the comparative phase, women received one of three different regimens of EE 20 μg/DRSP 3 mg. With the flexible$_{MIB}$ regimen, women received EE/DRSP for a flexible number of cycles. Tablets were taken 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). During Days 25–120 ('flexible phase'), women were instructed to have a 4-day tablet-free interval if bleeding and/or spotting occurred for three consecutive days. The 4-day tablet-free interval was to be taken after no more than 120 days of continuous tablet intake. After a 4-day tablet-free interval, a new cycle with a minimum of 24 days and a maximum of 120 days of tablet intake was initiated.

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

For the fixed extended regimen, women received EE/DRSP for three cycles. Each cycle comprised 120 days of uninterrupted active hormonal intake, regardless of any bleeding/spotting, followed by a 4-day tablet-free interval to induce withdrawal bleeding.

All women who completed the comparative phase of the study were eligible to participate in the safety extension phase. Women who received the flexible$_{MIB}$ regimen in the comparative phase continued to do so in the safety extension phase. All women on the other two regimens, except those participating in the analysis investigating BMD and bone markers, were allowed to switch to the flexible$_{MIB}$ regimen for the safety extension phase.

Full details regarding how study medication was dispensed, when it was started and guidelines regarding study drug intake are reported elsewhere.[5]

Study variables

The primary and secondary efficacy variables are defined and reported elsewhere.[5] Safety was evaluated by assessing adverse events (AEs), general physical and gynaecological findings (including the outcomes of cervical smear tests), laboratory variables, vital signs and body weight. A separate safety analysis of the effects of treatment on endometrial characteristics (histology and thickness), ovarian morphology, metabolic parameters and hormone levels was conducted and assessed at two of the study centres (one in Germany and one in The Netherlands) (Figure 1). The effect of treatment

Table 1 Occurrence of adverse events (AEs) during the 1-year safety extension phase (full analysis set). (AEs are shown for all women who participated in the safety extension phase and according to the regimens received in the 1-year comparative phase)

		Regimen received in comparative phase†		
Adverse event [n (%)]	**All women (*n*=727)**	**Flexible$_{MIB}$ (*n*=453)**	**Conventional 28-day (*n*=155)**	**Fixed extended (*n*=119)**
Any AE	409 (56.3)	244 (53.9)	104 (67.1)	61 (51.3)
Most frequent AEs*				
Diarrhoea	39 (5.4)	25 (5.5)	7 (4.5)	7 (5.9)
Headache	53 (7.3)	25 (5.5)	20 (12.9)	8 (6.7)
Nasopharyngitis	81 (11.1)	51 (11.3)	19 (12.3)	11 (9.2)
Discontinued due to AE	9 (1.1)	5 (1.0)	4 (2.4)	0 (0)
Any SAEs	29 (2.7)	19 (3.0)	3 (1.4)	7 (3.3)

Data shown as mean (SD).
*AEs (shown in alphabetical order) are those that occurred in >5% of all women who participated in the 1-year safety extension phase.
†During the safety extension phase, all women received ethinylestradiol 20 µg/drospirenone 3 mg in the flexible$_{MIB}$ regimen with the exception of 28 women participating in the bone mineral density analysis. Such women continued to receive either the conventional 28-day or fixed extended regimens.
AE, adverse event; MIB, management of intracyclic (breakthrough) bleeding; SAE, serious adverse event.

on BMD and bone markers was also assessed in a small number of women participating in the study (Figure 1).

Endometrial biopsies were performed using a small curette, and endometrial material was obtained from the anterior and/or posterior wall in the area of the fundus. Biopsies were postponed if subjects had menstrual bleeding or spotting, had not taken tablets for at least 10 days or had an acute clinically relevant genital infection. Biopsies were analysed by a single reader. Endometrial thickness and ovarian morphology were assessed by transvaginal ultrasound.

Metabolic parameters were analysed using blood samples collected from women who had fasted for 12 hours. A total of 25 ml of blood was needed from each subject for all of the metabolic parameters, with the exception of the oral glucose tolerance test (OGTT), which was undertaken to assess carbohydrate metabolism. For the OGTT, subjects were instructed to consume a balanced diet (no alcohol and no excessive consumption of any food) on the day preceding each of the tests. The tests were performed after a 12-hour overnight fast. The 75 g standardised OGTT involved taking five blood samples (3 ml each) 30 minutes before and at 30, 60, 90 and 120 minutes after ingestion of a glucose load. Hormone levels were measured from blood samples. A total of 7.5 ml of blood was needed for each sample per subject.

For those women included in the analyses of endometrial characteristics, metabolic parameters and hormone levels who had received sex hormone prior to the study, a washout period of 2 months (i.e. two menstrual cycles) was required before study medication could be initiated.

BMD of the lumbar spine (L1 to L4) and hip (femoral neck and total hip) was assessed by dual energy X-ray absorptiometry. At each visit, two BMD measurements were taken at each anatomical site. Measurements of bone markers in serum [estradiol, plasma osteocalcin, bone-specific alkaline phosphatase and carboxy-terminal cross-linking telopeptide (CTx)] were assessed using blood samples taken in the morning after a 10-hour fast. Women were only eligible to participate in the analysis of BMD and bone markers if the mean of two pretreatment BMD T-scores was greater than –1 at the lumbar spine site.

Statistical analysis

Descriptive statistics were calculated for quantitative data, while frequencies were given for categorical data.

The randomisation scheme for the flexible$_{MIB}$, fixed extended and conventional regimens in the two study centres in which the additional safety analyses were conducted was 1:1:1, which used a separate randomisation list and schedule. Randomisation was conducted using blocks of three until the respective sample size defined for each specific investigation (Figure 1) was achieved. In those women recruited at all other centres, the randomisation ratio to the flexible$_{MIB}$, conventional and fixed extended regimens was 4:1:1. To prevent selection bias an interactive voice response system was used for randomisation. Further details regarding the randomisation of women to the different regimens are reported elsewhere.[5]

Analysis set

The full analysis set (FAS) was defined as all women who took at least one dose of study medication and for whom at least one clinical observation was available. Within the blind data review, 67 subjects from one study centre had to be excluded from the FAS because of suspected misconduct. The evaluation of safety data was based on the FAS.

Table 2 Lipid profile in women who received ethinylestradiol 20 µg/drospirenone 3 mg administered as a flexible$_{MIB}$, conventional 28-day or fixed extended regimen in the comparative phase (full analysis set)

	Flexible$_{MIB}$ (*n*=26)			Conventional 28-day (*n*=25)			Fixed extended (*n*=28)		
Lipid parameter	**Baseline**	**Week 27**	**Week 51**	**Baseline**	**Week 27**	**Week 51**	**Baseline**	**Week 27**	**Week 51**
Total cholesterol (mmol/l)	4.40 (0.70)	4.78 (0.76)	4.72 (0.78)	4.24 (0.65)	4.81 (0.75)	4.71 (0.79)	4.41 (0.64)	4.77 (0.65)	4.79 (0.65)
Triglycerides (mmol/l)	0.79 (0.23)	1.47 (0.45)	1.52 (0.49)	0.82 (0.35)	1.52 (0.95)	1.53 (0.71)	0.77 (0.28)	1.48 (0.59)	1.40 (0.37)
HDL cholesterol (mmol/l)	1.47 (0.30)	1.79 (0.29)	1.76 (0.34)	1.41 (0.24)	1.71 (0.33)	1.69 (0.34)	1.44 (0.24)	1.72 (0.30)	1.82 (0.35)
HDL_2 cholesterol (mmol/l)	0.32 (0.21)	0.26 (0.08)	0.36 (0.12)	0.25 (0.12)	0.29 (0.12)	0.32 (0.10)	0.31 (0.21)	0.28 (0.11)	0.42 (0.13)
LDL cholesterol (mmol/l)	2.56 (0.66)	2.71 (0.74)	2.65 (0.74)	2.48 (0.55)	2.83 (0.61)	2.69 (0.57)	2.62 (0.60)	2.78 (0.51)	2.69 (0.46)
VLDL cholesterol (mmol/l)	0.36 (0.11)	0.64 (0.20)	0.68 (0.23)	0.37 (0.16)	0.64 (0.23)	0.70 (0.32)	0.35 (0.12)	0.70 (0.28)	0.63 (0.17)
Lipoprotein(a) (g/l)	0.21 (0.18)	0.18 (0.15)	0.19 (0.13)	0.18 (0.16)	0.16 (0.13)	0.16 (0.13)	0.22 (0.19)	0.18 (0.13)	0.16 (0.12)

Data shown as mean (SD).
HDL, high-density lipoprotein; LDL, low-density lipoprotein; MIB, management of intracyclic (breakthrough) bleeding; VLDL, very low-density lipoprotein.

Sample size

For safety reasons, a treatment duration equivalent to 10 000 cycles of 28 days was to be achieved for the flexible$_{MIB}$ regimen. It was assumed that after the first year comparative phase, 50% of all subjects would voluntarily agree to receive the flexible$_{MIB}$ regimen in the safety extension phase. Assuming 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.

The sample size for BMD measurements was based on the assumption that the 95% confidence interval (CI) for the difference of mean BMD loss would exclude the value –2.3% [with an assumed standard deviation (SD) of 2.6%]. To achieve a power of at least 90%, 28 'completers' were needed per treatment arm. Assuming a dropout rate of 40%, 47 subjects were needed per treatment arm.

Results

Overall, 1312 women were screened for inclusion into the study and 1166 of these were randomly allocated to one of the three regimens. In total, 1067 women fulfilled the criteria for the FAS (flexible$_{MIB}$, *n*=642; conventional 28-day, *n*=216; fixed extended, *n*=209). The disposition of women through the comparative phase and the baseline demographic characteristics of the FAS are described elsewhere.[5] A total of 783 women proceeded to the safety extension phase; of these, 755 remained on or switched to the flexible$_{MIB}$ regimen. The remaining women, who were participating in the analysis assessing BMD and bone markers, remained on the conventional regimen (*n*=21) or the fixed extended regimen (*n*=7) (Figure 2). The FAS in the safety extension phase was 727 (originally received the flexible$_{MIB}$ regimen, *n*=453; originally received the conventional regimen, *n*=155; originally received the fixed extended regimen, *n*=119).

Adverse events

Details pertaining to tolerability and safety outcomes during the comparative phase of the study are reported separately.[5]

In the safety extension phase, at least one AE was experienced by 409 (56.3%) of all the women who participated. The occurrence of AEs and serious adverse events (SAEs) (including all non-drug-related events), the most frequent AEs and discontinuations due to AEs, overall and according to the regimen received in the comparative phase, are shown in Table 1.

Overall, 9.8% of subjects who participated in the safety extension phase had an AE that was deemed to be possibly, probably or definitely related to study medication. There were no deaths reported in the study. Four women who received the flexible$_{MIB}$ regimen had SAEs that were considered to be possibly related to study medication [focal nodular hyperplasia (*n*=1; diagnosed in the safety extension phase), uterine

Table 3 Bone mineral density in women who received ethinylestradiol 20 µg/drospirenone 3 mg administered as a fixed extended or conventional 28-day regimen in the comparative and safety extension phases (full analysis set)

BMD (g/cm²)	Fixed extended			Conventional 28-day			Treatment difference (95% CI)		
	Baseline (*n*=38)	Week 51 (comparative) (*n*=23)	Week 51 (safety) (*n*=6)	Baseline (*n*=42)	Week 51 (comparative) (*n*=37)	Week 51 (safety) (*n*=16)	Baseline	Week 51 (comparative)	Week 51 (safety)
Lumbar spine	1.08 (0.08)	1.09 (0.08)	1.07 (0.07)	1.09 (0.08)	1.09 (0.09)	1.08 (0.08)	−0.02 (−0.04–0.01)	0 (−0.03–0.03)	−0.01 (−0.06–0.03)
Femoral neck (left hip)	0.90 (0.09)	0.91 (0.08)	0.96 (0.06)	0.90 (0.10)	0.90 (0.10)	0.91 (0.11)	−0.01 (−0.03–0.01)	0.01 (−0.02–0.04)	0.04 (−0.01–0.10)
Total hip (left hip)	1.00 (0.08)	1.02 (0.08)	1.03 (0.07)	1.02 (0.09)	1.03 (0.09)	1.03 (0.08)	−0.02 (−0.04–0.03)	−0.01 (−0.03–0.02)	0.01 (−0.03–0.05)

Data shown as mean (SD) unless otherwise stated. Data represent the average of two corrected measurements.
BMD, bone mineral density; CI, confidence interval.

leiomyoma (*n*=1; diagnosed in the comparative phase) and deep vein thrombosis (DVT) (*n*=2; diagnosed in the comparative phase)].

SAEs of special interest occurred in four patients who received the flexible$_{MIB}$ regimen: three cases of DVT, including one case of a postoperative thrombosis, and one case of focal nodular hyperplasia of the liver. One case of DVT occurred in the left calf of a 22-year-old Caucasian non-smoker. The subject had received study medication for approximately 7 months, and before that had received other COCs for approximately 14 months. The subject had no personal or family history of thrombosis and an assessment of clotting status showed normal values; however, diagnostic examination revealed a heterozygous prothrombin gene mutation (factor II) and a heterozygous factor V Leiden mutation. The woman was treated accordingly without the need for hospitalisation, and recovered approximately 4 months after diagnosis. The event was considered to be possibly related to the study medication. The second case of DVT (of the right lower leg) occurred in a 25-year-old Caucasian non-smoker approximately 1 month after study medication was initiated. The subject had used a COC for 8 months before enrolling in the study. An assessment of clotting status showed normal values, and laboratory results excluded factor V and prothrombin gene mutations; however, the woman was found to have a family history of thrombosis and varices. The woman received treatment for 5 months. The event was considered to be possibly related to the study medication. The case of postoperative thrombosis (of the crural vein) occurred in a 29-year-old Caucasian non-smoker 1 day after knee surgery that took place approximately 2 months after starting study medication. The subject had used a COC for almost 1 year before starting the study. The event was considered to be most likely related to the knee surgery and postoperative immobilisation and unlikely to be related to the study medication.

The case of focal nodular hyperplasia of the liver occurred in a 20-year-old Caucasian smoker (10 cigarettes daily) who had a 26-month history of COC use prior to study entry. Study medication was received for almost 19 months before being discontinued because of high alkaline phosphatase levels; prior to medication being discontinued, increasing values of alkaline phosphatase and γ-GT were found. Three months afterwards the subject was diagnosed with benign focal nodular hyperplasia in the right lobe of the liver. Neither the focal nodular hyperplasia nor the increased liver enzymes were treated with specific drugs or procedures. The relationship of the event to the study medication was defined as possible.

Safety laboratory evaluations

In general, changes in safety laboratory values were minimal with all three regimens over time. Only a small proportion of subjects had high or low levels of laboratory

values. During the course of the study, there was a transient increase in the proportion of subjects with laboratory values for potassium that were above normal (peak proportion of 2.0% at Week 27 of the safety extension phase). That said, absolute changes from baseline were minimal, levels remained stable in all treatment groups and the proportion of subjects with levels above the normal range was similar to baseline at the end of the treatment (Week 51 of the safety extension phase).

Endometrial and ovarian characteristics

The endometrium was characterised at the end of the comparative phase in 23 women who received the flexible$_{MIB}$ regimen and in 17 women who received the fixed extended regimen. Most women who received the flexible$_{MIB}$ and fixed extended regimens had an inactive endometrium (7/23 and 3/17 women), an atrophic endometrium (6/23 and 5/17 women) or a secretory endometrium of the progestational type (5/23 and 4/17 women), respectively. A weakly proliferative endometrium occurred in 4/23 and 3/17 women. The endometrium was characterised at the end of the safety extension phase in seven women who had originally received the flexible$_{MIB}$ regimen and in nine women who had originally received the fixed extended regimen. Most of these women had insufficient material for diagnosis; in those that did, an atrophic endometrium (4/7 women who originally received the flexible$_{MIB}$ regimen and 0/9 women who originally received the fixed extended regimen) or secretory endometrium of the progestational type (1/7 and 4/9 women, respectively) was the most common. No abnormal findings were identified, including no hyperplasia, carcinomas, sarcomas, carcinomatous or other types of metaplasia or cervical carcinomas.

Endometrial thickness was assessed at Weeks 27 and 51 of the comparative phase in 32 and 34 women who received the flexible$_{MIB}$ regimen, 27 and 25 women who received the conventional regimen, and 28 and 30 women who received the fixed extended regimen. At Week 27, mean endometrial thickness was 3.99 mm with the flexible$_{MIB}$ regimen (vs 7.61 mm at baseline), 3.99 mm with the conventional regimen (vs 7.08 mm at baseline) and 3.97 mm with the fixed extended regimen (vs 7.71 mm at baseline). Mean thickness at Week 51 was 4.27 mm, 3.94 mm and 4.48 mm, respectively. Endometrial thickness was assessed at Week 51 of the safety extension phase in nine women who had originally received the flexible$_{MIB}$ regimen, 13 women who had originally received the conventional regimen and 10 women who had originally received the fixed extended regimen. Mean endometrial thickness was 3.69 mm, 3.37 mm and 4.10 mm, respectively.

Ovarian morphology was assessed at Weeks 27 and 51 in the comparative phase in 32 and 34 women who received the flexible$_{MIB}$ regimen, 27 and 26 women who received the conventional regimen, and 28 and 30 women who received the fixed extended regimen. One woman who received the conventional regimen was pregnant at Week 51 of the comparative phase. One woman who received the fixed extended regimen had suspected chocolate cysts on both ovaries at Week 27; this was confirmed by Week 51 following laparoscopic enucleation of the cysts. The woman prematurely discontinued study medication. Ovarian morphology was assessed at Week 51 of the safety extension phase in nine women who had originally received the flexible$_{MIB}$ regimen, 13 women who had originally received the conventional regimen and 10 women who had originally received the fixed extended regimen. There were no abnormal findings in the safety extension phase.

Metabolic parameters

Changes in the serum lipid profile over time are shown in Table 2. Total cholesterol increased from baseline to a similar extent with all three regimens; a similar pattern was observed for triglycerides. Low-density lipoprotein cholesterol remained relatively unchanged in all three regimens, while high-density lipoprotein (HDL) cholesterol increased slightly to a similar extent in all three regimens.

Haemostatic parameters

Haemostatic variables were assessed at Weeks 27 and 51 of the comparative phase in 22 and 20 women who received the flexible$_{MIB}$ regimen, 22 and 22 women who received the conventional regimen and 25 and 16 women who received the fixed extended regimen. A 2-month washout period from any treatment with sex hormones prior to the intake of study medication was a participation criterion. Increases in prothrombin fragment 1+2, D-dimer, fibrinogen, factor VII activity and protein C activity, relative to baseline levels, were observed at Weeks 27 and 51. Activated protein C resistance and protein S activity were decreased versus baseline at Weeks 27 and 51. Factor VIII activity was increased versus baseline at Week 27, but was decreased versus baseline at Week 51. In contrast, antithrombin III was decreased versus baseline at Week 27, but was increased versus baseline at Week 51. Similar trends were observed in all three treatment groups with no between-treatment differences observed in changes in haemostatic variables.

Carbohydrate metabolism

An OGTT was performed at Weeks 27 and 51 of the comparative phase in 22 and 19 women who received the flexible$_{MIB}$ regimen, 22 and 22 women who received the conventional regimen and 24 and 16 women who received the fixed extended regimen. Results of the OGTT showed that there was no evidence of impaired glucose tolerance during treatment with any of the three regimens. C-peptide measurements reflected changes in glucose levels during the OGTT and the insulin response following the OGTT, both of which were normal.

Hormone levels

Hormone levels were assessed in 20–26 women who received the flexible$_{MIB}$ regimen, 22–24 women who

received the conventional regimen and 17–28 women who received the fixed extended regimen during treatment. Study participation required a minimum of 2 months without the use of sex steroids prior to intake of medication. There were decreases from baseline in all three treatment groups in the levels of estradiol, follicle-stimulating hormone (FSH), luteinising hormone (LH) and testosterone. Changes in the levels of these hormones were rapid and were similar with all three regimens. Marked increases from baseline in the levels of sex hormone-binding globulin (SHBG) were observed with all three regimens; SHBG levels had increased by a factor of 3–4 at Week 3 of treatment, and by a factor of 4–5 at Week 51 of treatment.

Vital signs, serum chemistry and body weight

Mean heart rate, systolic blood pressure and diastolic blood pressure were stable throughout the course of the study in all three regimens. None of the regimens adversely affected blood pressure, and mean blood pressure recordings generally remained within normal limits. Overall changes in safety laboratory values (haematology, serum chemistry) were small in all three regimens, and the proportion of subjects with high or low levels of laboratory values was small. From baseline to the end of the comparative phase, body weight remained stable in all three regimens. In the safety extension phase, there was a mean weight gain of approximately 1 kg; this was observed in all women, regardless of their regimen in the comparative phase.

Gynaecological examination

An abnormal cervical smear test at the end of the comparative phase was found in 13 (2.1%), 4 (1.9%) and 5 (2.5%) women who received the flexible$_{MIB}$, conventional and fixed extended regimens, respectively. At the end of the safety extension phase, an abnormal smear was observed in 13 (2.9%), 3 (2.0%) and 2 (1.8%) women who originally received the flexible$_{MIB}$, conventional and fixed extended regimens, respectively. The most frequently reported abnormal findings from cervical smears were atypical squamous cells of undetermined significance and Papanicolaou (Pap) IIID. In one woman, Stage 0 cervical carcinoma was diagnosed less than 1 month after study medication (conventional 28-day regimen) was initiated. The diagnosis was deemed unrelated to study medication.

Bone mineral density and bone markers

At the end of both phases of the study, there were no appreciable changes in lumbar spine or hip BMD in the small number of women who received the fixed extended or conventional regimens for 2 years (Table 3). Similar decreases in the levels of osteocalcin, bone alkaline phosphatase and CTx were observed with the fixed extended and conventional regimens.

Discussion

This two-phase study indicates that EE/DRSP administered in a flexible$_{MIB}$ regimen is well-tolerated and has an acceptable safety profile when administered for a period of up to 2 years. A low number of treatment-related SAEs were reported and no deaths occurred during the study. The flexible$_{MIB}$ regimen has also been shown to have reliable contraceptive efficacy.[5]

Only four SAEs were considered to be possibly related to study medication: focal nodular hyperplasia, uterine leiomyoma and two cases of DVT. DVT and pulmonary embolism, collectively referred to as venous thromboembolism (VTE), are rare events in users of hormonal contraceptives. Nonetheless, the use of estrogen-progestogen combination products, including COCs, is a known risk factor for VTE, with the risk being highest during the initial months of use.[8 9] Additional risk factors include increasing age, increasing body mass index, genetic mutations that affect coagulation, and a family history of VTE.[9 10] One DVT case that was deemed to be possibly related to study medication occurred in a woman 1 month after the study medication was initiated. Contrary to initial information, the woman had a family history of thrombosis, which was an exclusion criterion of the study. The other case occurred in a woman approximately 7 months after treatment was initiated; diagnostic examination revealed that this woman had a heterozygous prothrombin gene mutation (factor II) and a heterozygous factor V Leiden mutation. A third VTE was considered to be most likely related to knee surgery and the postoperative immobilisation. It is not possible to evaluate the risk of rare events such as VTE using the results of clinical trials such as this one that have limited treatment exposure. That said, this topic needs to be investigated in robust postmarketing epidemiological studies. The risk of thrombotic events has been associated with estrogen, although controversy remains as to whether or not there may be an increased risk of VTE associated with specific progestogens. Recent database studies have suggested that the risk of VTE is lower in women using levonorgestrel-containing COCs relative to women using so-called 'third-generation' COCs, and women using COCs containing DRSP.[11–14] These findings are in contrast to those of the European Active Surveillance Study (EURAS)[9] and the Ingenix database study,[15] which show that the risk of VTE is comparable for low-dose COCs, regardless of the type of progestogen included.

The use of COCs is associated with distinct changes in endometrial histology, including the inhibition of glandular growth and differentiation, often resulting in an inactive or atrophic endometrium.[16] These changes contribute to the contraceptive efficacy of COCs. In this study, endometrial biopsies showed that the use of the flexible$_{MIB}$ or fixed extended regimens resulted in an inactive, atrophic or secretory endometrium in most women. These findings are similar to those reported for low-dose COCs administered in a 28-day regimen[16–18] or as fixed extended regimens.[19 20] Endometrial hyperplasia or malignancy was not observed in any endometrial biopsy sample in the current study, comparable to other

studies that have investigated the endometrial effects of fixed extended regimen COCs.[19 20] In this study, for all three regimens, endometrial thickness was reduced to an extent that was comparable to other COCs.[18 21]

Hormone levels were measured to assess possible differences in ovarian suppression. For all three regimens, levels of estradiol, FSH, LH and testosterone decreased compared with baseline; these changes were similar with all three regimens and were typical of those that occur during COC use.[22–24] An increase in the levels of SHBG was observed, which is typical in users of EE-containing COCs.

The results of the BMD analysis suggest that neither the fixed extended nor the conventional regimen had a negative impact. This agrees with studies that have shown that low-dose COCs containing EE 20 μg have no negative effects on BMD in young women.[25 26] In the current study, decreases in osteocalcin, bone alkaline phosphatase and CTx were observed with both regimens, which suggests a low bone turnover rate and confirms a constant BMD. These BMD and bone marker findings should be interpreted with caution because of the small number of women assessed.

COCs are known to be associated with various metabolic and haemostatic effects, and it is possible that such changes may impact upon their overall safety and tolerability profile. In this study, alterations in lipid parameters, haemostatic variables and carbohydrate metabolism with the flexible$_{MIB}$ regimen were comparable to those with the conventional and fixed extended regimens. These results are consistent with those of a study that showed no statistically significant differences in lipid, carbohydrate and coagulation parameters with EE 30 μg/DRSP 3 mg when administered continuously for 168 days, or as six 28-day cycles comprising 21 days of active tablets followed by a 7-day tablet-free interval.[27] The changes in certain lipid parameters [HDL cholesterol, triglycerides, HDL$_2$ cholesterol, very-low-density lipoprotein cholesterol and lipoprotein(a)] observed in this study are comparable to those reported in a study of 59 women who received a 24/4 regimen of EE 20 μg/DRSP 3 mg or a 21/7 regimen of EE 20 μg/desogestrel 150 μg for seven cycles.[23] Extension of the intake cycle with the flexible extended or fixed extended regimens has no impact on the known effect of COCs on the haemostatic system. The findings suggested that the balance between factors influencing haemostasis were maintained on an up-regulated level with all three regimens, including the conventional regimen. This agrees with a previous study that showed that the effect of conventional and extended regimen COCs on haemostasis variables did not substantially differ.[28]

Conclusions

The results of this study show that EE/DRSP administered using a flexible$_{MIB}$ regimen is well-tolerated and, when administered for up to 2 years, has a good safety profile that is comparable to other estrogen/progestogen COCs.

Acknowledgements The authors would like to thank Lyndal Staples and Clare Wheatcroft of *in*Science Communications for medical writing support. This work was funded by Bayer HealthCare Pharmaceuticals, Berlin, Germany. The authors would like to thank Martina Bongartz of Bayer HealthCare Pharmaceuticals for preparation of the clinical study report.

Funding This study was funded by Bayer HealthCare Pharmaceuticals, Berlin, Germany, the manufacturer of ethinylestradiol 20 μg/drospirenone 3 mg.

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.

Provenance and peer review Not commissioned; externally peer reviewed.

References

1 **Klipping C**, Duijkers I, Trummer D, *et al*. Suppression of ovarian activity with a drospirenone-containing oral contraceptive in a 24/4 regimen. *Contraception* 2008;**78**:16–25.
2 **Szarewski A**. Sisters doing it for themselves. *J Fam Plann Reprod Health Care* 2009;**35**:71–72.
3 **Wiegratz I**, Hommel HH, Zimmermann T, *et al*. Attitude of German women and gynecologists towards long-cycle treatment with oral contraceptives. *Contraception* 2004;**69**:37–42.
4 **Andrist LC**, Arias RD, Nucatola D, *et al*. Women's and providers' attitudes toward menstrual suppression with extended use of oral contraceptives. *Contraception* 2004;**70**:359–363.
5 **Klipping C**, Duijkers I, Fortier MP, *et al*. Contraceptive efficacy and tolerability of ethinylestradiol 20 μg/drospirenone 3 mg in a flexible extended regimen: an open-label, multicentre, randomised, controlled study. *J Fam Plann Reprod Health Care* 2012;**38**:73–83.
6 **Westhoff C**. Bone mineral density and DMPA. *J Reprod Med* 2002;**47**:795–799.
7 **Kaunitz AM**. Injectable depot medroxyprogesterone acetate contraception: an update for U.S. clinicians. *Int J Fertil Womens Med* 1998;**43**:73–83.
8 **Dinger J**, Do Minh T, Moehner S. The risk of venous thromboembolism in OC users: time patterns after initiation of treatment. *Pharmacoepidemiol Drug Saf* 2010;**19**: S214–S215.
9 **Dinger JC**, Heinemann LA, Kühl-Habich D. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142 475 women-years of observation. *Contraception* 2007;**75**:344–354.
10 **Anderson FA** Jr, Spencer FA. Risk factors for venous thromboembolism. *Circulation* 2003;**107**:19–16.
11 **Lidegaard Ø**, Løkkegaard E, Svendsen AL, *et al*. Hormonal contraception and risk of venous thromboembolism: national follow-up study. *BMJ* 2009;**339**:b2890.

12 **van Hylckama Vlieg A**, Helmerhorst FM, Vandenbroucke JP, *et al.* The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. *BMJ* 2009;**339**:b2921.
13 **Jick SS**, Hernandez RK. Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. *BMJ* 2011;**342**:d2151.
14 **Parkin L**, Sharples K, Hernandez RK, *et al.* Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database. *BMJ* 2011;**342**:d2139.
15 **Seeger JD**, Loughlin J, Eng PM, *et al.* Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. *Obstet Gynecol* 2007;**110**:587–593.
16 **Bitzer J**, Parke S, Roemer T, *et al.* Endometrial safety of an oral contraceptive containing estradiol valerate and dienogest. *Int J Womens Health* 2011;**3**:127–132.
17 **Coenen CM**, Hollanders JM, Rolland R, *et al.* The effects of a low-dose gestodene-containing oral contraceptive on endometrial histology in healthy women. *Eur J Contracept Reprod Health Care* 1996;**1**:325–329.
18 **Rabe T**, Hartschuh E, Wahlstrom T, *et al.* Endometrial safety of a novel monophasic combined oral contraceptive containing 0.02 mg ethinylestradiol and 2 mg chlormadinone acetate administered in a 24/4-day regimen over six cycles. *Contraception* 2010;**82**:358–365.
19 **Anderson FD**, Feldman R, Reape KZ. Endometrial effects of a 91-day extended-regimen oral contraceptive with low-dose estrogen in place of placebo. *Contraception* 2008;**77**:91–96.
20 **Johnson JV**, Grubb GS, Constantine GD. Endometrial histology following 1 year of a continuous daily regimen of levonorgestrel 90 micro g/ethinyl estradiol 20 micro g. *Contraception* 2007;**75**:23–26.
21 **Lüdicke F**, Johannisson E, Helmerhorst FM, *et al.* Effect of a combined oral contraceptive containing 3 mg of drospirenone and 30 microg of ethinyl estradiol on the human endometrium. *Fertil Steril* 2001;**76**:102–107.
22 **Duijkers IJ**, Klipping C, Verhoeven CH, *et al.* Ovarian function with the contraceptive vaginal ring or an oral contraceptive: a randomized study. *Hum Reprod* 2004;**19**:2668–2673.
23 **Klipping C**, Marr J. Effects of two combined oral contraceptives containing ethinyl estradiol 20 microg combined with either drospirenone or desogestrel on lipids, hemostatic parameters and carbohydrate metabolism. *Contraception* 2005;**71**:409–416.
24 **Spona J**, Feichtinger W, Kindermann C, *et al.* Inhibition of ovulation by an oral contraceptive containing 100 micrograms levonorgestrel in combination with 20 micrograms ethinylestradiol. *Contraception* 1996;**54**:299–304.
25 **Gargano V**, Massaro M, Morra I, *et al.* Effects of two low-dose combined oral contraceptives containing drospirenone on bone turnover and bone mineral density in young fertile women: a prospective controlled randomized study. *Contraception* 2008;**78**:10–15.
26 **Nappi C**, Di Spiezio Sardo A, Acunzo G, *et al.* Effects of a low-dose and ultra-low-dose combined oral contraceptive use on bone turnover and bone mineral density in young fertile women: a prospective controlled randomized study. *Contraception* 2003;**67**:355–359.
27 **Machado RB**, de Melo NR, Maia H Jr, *et al.* Effect of a continuous regimen of contraceptive combination of ethinylestradiol and drospirenone on lipid, carbohydrate and coagulation profiles. *Contraception* 2010;**81**:102–106.
28 **Wiegratz I**, Stahlberg S, Manthey T, *et al.* Effects of conventional or extended-cycle regimen of an oral contraceptive containing 30 mcg ethinylestradiol and 2 mg dienogest on various hemostasis parameters. *Contraception* 2008;**78**:384–391.