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Original research article

Bleeding pattern and cycle control with estetrol-containing combined oral contraceptives: results from a phase II, randomised, dose-finding study (FIESTA)☆

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Abstract

Objectives: This study aims to assess vaginal bleeding patterns and cycle control of oral contraceptives containing estetrol (E4) combined with either drospirenone (DRSP) or levonorgestrel (LNG).
Study design: An open-label, multicentre, randomised, dose-finding study lasting six cycles in healthy women aged 18–35 years was used. Four treatments (15 mg or 20 mg E4, combined with either 3 mg DRSP or 150 mcg LNG) were administered in a 24/4-day regimen. A marketed dosing regimen of estradiol valerate with dienogest (E2V/DNG) served as reference since it contains (like E4) a natural oestrogen.
Results: A total of 396 women were randomised, of whom 389 received study medication, and 316 completed the study. By cycle 6, the frequencies of unscheduled bleeding and/or spotting and absence of withdrawal bleeding were the lowest in the 15 mg E4/DRSP group (33.8% and 3.5%, respectively). In the E2V/DNG reference group, these frequencies were 47.8% and 27.1%, respectively. By cycle 6, the frequency of women with absence of withdrawal bleeding was <20% for all E4 treatment groups: 3.5–3.8% combined with DRSP and 14.0–18.5% combined with LNG. By cycle 6, unscheduled intracyclic bleeding was reported by <20% of women in the 20 mg E4/LNG group (18.9%) and in the 15 mg E4/DRSP group (16.9%).
Conclusion: This study showed that, of the four treatment modalities investigated, the 15 mg E4/DRSP combination has the most favourable bleeding pattern and cycle control.
Implications: Due to its favourable bleeding pattern and cycle control, the 15 mg E4/DRSP combination is the preferred combination for further phase III clinical development.

Keywords: Estetrol; Estradiol valerate; Dienogest; Bleeding pattern; Cycle control

1. Introduction

The bleeding pattern of combined oral contraceptives (COCs) containing ethinyl estradiol (EE) is perceived as satisfactory by women, which may be due to the effective stabilisation of the endometrium, induced by its potent oestrogenic activity. However, EE causes subjective side effects [1], and it affects the synthesis of various liver proteins leading to an increased risk of cardiovascular complications [2–4]. Strategies have been developed to lower the EE dose or substitute EE with another oestrogen

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[5,6]. Original attempts at replacing EE by estradiol (E2) were associated with poor bleeding patterns, and therefore, the development was stopped [7]. Combinations of E2 with nomegestrol acetate (NOMAC/E2) or estradiol valerate with dienogest (E2V/DNG) were subsequently developed and led to acceptable cycle control [7–10] but were still suboptimal since absence of withdrawal bleeding was reported to be 31% and 20%, respectively [7,9].

The development of new oestrogens such as estetrol (E4) holds promise for the safety and tolerability of future COCs [2]. E4 is synthesised by the human foetal liver and is present only during human pregnancy [11]. In contrast to other oestrogens, E4 is an antagonist of the membrane oestrogen receptor alpha, it does not bind to the carrier protein sex-hormone binding globulin SHBG and it does not change the activity of relevant cytochrome P450 related liver enzymes [12,13]. The terminal half-life of E4 is 28 h versus 14 h for E2 [14], an important prerequisite for its development as a once daily oral drug [15].

Preclinical and phase I clinical research suggests that E4 inhibits ovulation and may be a suitable replacement for EE in COCs [16–18]. In a phase II, dose-finding study, 5 mg, 10 mg or 20 mg E4 in combination with drospirenone (DRSP) or levonorgestrel (LNG) completely inhibited ovulation and decreased ovarian activity dose-dependently [19]. These combinations also had a limited effect on liver function, lipid metabolism and bone and growth endocrine parameters [20].

The present phase II, randomised, dose-finding study was conducted with the aim of selecting an E4/progestin combination for phase III development. The primary objective was to investigate the effect of two dosages of E4 combined with either DRSP or LNG on vaginal bleeding patterns and cycle control, using a COC containing E2V/DNG as a reference.

2. Methods

2.1. Design and ethical approval

This was an open-label, multicentre, randomised, dose-finding study in healthy female volunteers of reproductive age. The study was conducted between September 2010 and 2011 in 10 centres in Finland (ClinicalTrials.gov identifier NCT01221831). Approval was obtained by the regional independent ethics committee of the Hospital District of Helsinki and Uusimaa and by the Finnish Medicines Agency. The study was conducted in accordance with the ethical principles established by the Declaration of Helsinki and the International Conference on Harmonisation — Good Clinical Practise Guidelines. Written informed consent was obtained from all participants before enrolment.

2.2. Participants

Healthy women, aged 18–35 years with a body mass index between 18 and 30 kg/m^2 and a regular menstrual cycle (24–35 days), were eligible for inclusion. Women who were already using hormonal contraceptives (switchers) and hormonal contraceptive-naïve women (starters) were able to participate. Switchers changed from a COC, vaginal ring or transdermal patch. Women were defined as starters when they had not used a hormonal contraceptive in the 3 months prior to randomisation. Women who used any hormonal contraceptive method within 3 months prior to randomisation, but not at screening (for starters), or women using a depot progestogen within 6 months prior to randomisation were excluded. Untreated chlamydia infection also led to exclusion. The other exclusion criteria were in line with the World Health Organisation's medical eligibility criteria for COC use [21] and included contraindications for contraceptive steroids (e.g., a history of, or existing thromboembolic, cardiovascular or cerebrovascular disorder or hypertension, defined as systolic and diastolic blood pressure > 140 and > 90 mmHg, respectively).

2.3. Treatment

There were five treatment groups: (1) 15 mg E4 plus 3 mg DRSP (15E4/DRSP), (2) 20 mg E4 plus 3 mg DRSP (20E4/DRSP), (3) 15 mg E4 plus 150 mcg LNG (15E4/LNG), (4) 20 mg E4 plus 150 mcg LNG (20E4/LNG) and (5) E2V plus DNG (E2V/DNG) (commercial packaging of 4-phasic Qlaira®, Bayer HealthCare, Germany). E2V/DNG was chosen as a reference because it is the only global COC containing a natural oestrogen (E2V), like E4.

To achieve equal distribution across the groups, randomisation was stratified by switchers, starters and sites. After randomisation, switchers completed their last pill blister (or completed the vaginal ring or patch treatment cycle) before starting study treatment. Starters took their first study medication on the first day of the first menstruation occurring after randomisation. Participants completed six treatment cycles of 28 days. For the E4 groups, one cycle comprised of 24-study medication days, followed by 4 placebo days. Women assigned to E2V/DNG took active study treatment for 26 days followed by 2 placebo days, according to the labelling of Qlaira®.

2.4. Assessments

Study visits were scheduled at randomisation, on days 1–14 of treatment cycles 2, 3, 4 and 5 and between days 25 and 28 of cycle 6 (final study visit). Women completed a daily diary to monitor vaginal bleeding. The intensity of vaginal bleeding was evaluated based on the number of sanitary protections needed (0, 1 or ≥ 2).

Safety was evaluated by recording treatment-emergent adverse events (TE-AEs), standard laboratory safety results, physical and gynaecological examination and vital signs. Of drug-related TE-AEs, headache/migraine and anxiety/depression were considered of special interest.

A pregnancy test (urinary β-hCG) was performed at randomisation and at monthly visits. Ovulation inhibition was assessed during cycles 1–4 by urinary pregnanediol glucuronide measurements [22].

2.5. Outcome variables

The primary aim of the study was to assess vaginal bleeding patterns and cycle control of 15 and 20 mg E4 combined with either DRSP or LNG, administered during six treatment cycles in a 24/4-day regimen.

The purpose of the study was to find a dosing combination with not more than 20% absence of withdrawal bleeding and not more than 20% unscheduled intracyclic bleeding in cycle 6. The optimal E4/progestin combination will be selected for further phase III clinical development.

Cycle control was evaluated on the basis of daily vaginal bleeding patterns. The primary bleeding parameters were unscheduled bleeding and spotting combined (referred to as bleeding/spotting) and absence of withdrawal bleeding. Secondary bleeding parameters comprised a bleeding/spotting cycle pattern by cycle day and early withdrawal bleeding (i.e., occurring between days 21 and 24). Bleeding or spotting reported during cycle days 5–24 was considered unscheduled. If bleeding or spotting did not occur on cycle days 1 and 2, but occurred on cycle day 3 or 4, it was also considered unscheduled (except for days 1–7 of cycle 1 [23]).

2.6. Statistical analyses

Data analyses were descriptive; 2-sided 95% confidence intervals (CIs) were calculated per treatment group and cycle for the primary and secondary bleeding endpoints versus the E2V/DNG reference group. The analyses were performed for both the intent-to-treat (ITT) and the per-protocol (PP) populations for cycles 2, 3 and 6. A *t* test was performed to determine whether there are significant differences in the mean number of unscheduled bleeding/spotting days between E4 treatment groups and the E2V/DNG group. The ITT population comprised all-subjects-treated (AST) with at least one evaluable cycle, and PP population comprised all ITT subjects without any major protocol violation. Since the aim of the present study was to select an E4/progestin combination for phase III development, the present paper focussed on the outcome of primary and secondary bleeding parameters in the PP population. The safety analysis was performed for the AST population, and only tabulations and frequencies are presented.

Since this was an exploratory study, the sample size was based on the precision of the estimates in the treatment groups. When the frequencies of absence of withdrawal bleeding and of unscheduled intracyclic bleeding are 15–20% in a group, a size of 80 evaluable subjects per group leads to standard errors of 4–4.5%.

3. Results

3.1. Study population

A total of 396 women were randomised (Fig. 1), of whom 389 (98.2%) received study medication, and 316 completed the study (79.8%). The number of completers was highest for 15E4/DRSP (72/79; 91.1%) and E2V/DNG (70/78; 89.7%) and was lowest for 20E4/LNG (54/77; 70.1%) (Fig. 1). TE-AEs were the most common reason for discontinuing the study (41/80; 51.3%). Seven women who had been randomised withdrew from the study before receiving treatment.

The proportion of switchers (66.8% overall) and starters (33.2% overall) was generally similar across treatment groups (Table 1). Of the 41 women who discontinued due to AEs, 27 (65.9%) were switchers and 14 (34.1%) were starters. The completion rate was similar among starters, but among switchers, it was highest for E2V/DNG and 15E4/DRSP (97.4% and 96.2%, respectively) (data not shown).

Demographic and baseline characteristics were similar across the treatment groups, with the exception of the proportion of smokers, which varied between 10.7% for 20E4/DRSP and 24.7% for 20E4/LNG (Table 1).

3.2. Primary bleeding parameters

The frequency of unscheduled bleeding/spotting was lower in the E4/DRSP groups across treatment cycles 2, 3 and 6, compared to the other treatment groups. By cycle 6, the frequency varied between 33.8% in the 15E4/DRSP group and 47.8% in the E2V/DNG group (Table 2 and Fig. 2). The maximum intensity of unscheduled bleeding ($\geq$2 sanitary protections needed) per cycle increased over time in the E2V/DNG group (up to 60%) and stayed the same with minor fluctuations in the 15 mg E4/LNG and 15 mg E4/DRSP groups (25–35%) (data not shown).

For both switchers and starters, the incidence of unscheduled bleeding/spotting generally decreased with time in all groups. By cycle 6, the frequency of unscheduled bleeding/spotting varied in switchers between 29.3% for 15E4/DRSP and 48.7% for 20E4/DRSP, and in starters, it varied between 38.5% for 20E4/LNG and 66.7% for E2V/DNG (Fig. 2).

The frequency of women with absence of withdrawal bleeding was <20% for all E4 treatment groups throughout the study. For E4/DRSP, it was absent for 1.3–1.5% in cycle 2, 1.5–2.8% in cycle 3 and 3.5–3.8% in cycle 6. In the E4/LNG groups, these frequencies were 2.9–9.9%, 10.8–13.6% and 14.0–18.5%, respectively, and for E2V/DNG, these were 12.1%, 16.4% and 27.1%, respectively. By cycle 6, this resulted in a difference of 23.6% fewer subjects with an absence of withdrawal bleeding in the 15E4/DRSP group than in the E2V/DNG group (95% CI: −35.9, −11.3) (Table 2 and Fig. 3).

In starters, none or only one single subject in any treatment group had an absence of withdrawal bleeding in cycle 2 or 3. By cycle 6, this remained the same in the E4 treatment groups but increased to 22.2% for E2V/DNG. For switchers, the pattern was similar to the overall population, showing that the lowest incidence of absence of withdrawal bleeding was observed in the E4/DRSP groups in any cycle (data not shown).

3.3. Secondary bleeding parameters

Throughout the study, the frequency of unscheduled intracyclic bleeding was highest for E2V/DNG (35.8–45.5%)

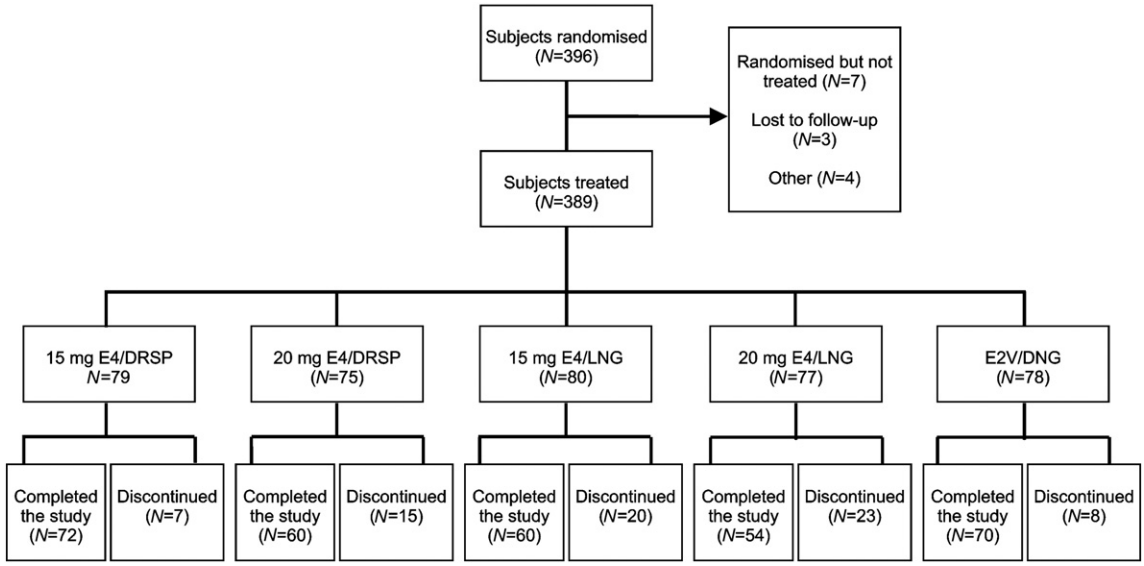

Fig. 1. Subject disposition by treatment group (all-subjects-randomised population). Subject disposition in a study evaluating the bleeding pattern and cycle control of four contraceptive combinations containing E4 (15 and 20 mg E4 combined with either 3 mg DRSP or 150 mcg LNG) and a marketed quadriphasic combination containing E2V/DNG. The E4 combinations were administrated in a 24/4-day regimen while the E2V/DNG combination was administered in a 26/2-day regimen. More women receiving the 15 mg E4/DRSP combination or the E2V/DNG combination completed the study in comparison to the other groups. DNG: dienogest; DRSP: drospirenone; E4: estetrol; E2V: estradiol valerate; LNG: levonorgestrel.

and lowest in the 15E4/DRSP group (16.9–30.6%). By cycle 6, the reported frequency of unscheduled bleeding was < 20% for 20E4/LNG (18.9%) and 15E4/DRSP (16.9%) (Table 2 and Fig. 3).

Unscheduled bleeding/spotting on individual days during cycle 1 was reported by 12–34% of women in the E4/DRSP groups and by 16–46% of women in the other groups. The daily frequency of unscheduled bleeding/spotting decreased notably by cycle 2 and remained lower in subsequent cycles in all groups. By cycle 6, the occurrence of unscheduled bleeding/spotting on any cycle day was 3–8% for 15E4/DRSP, 9–19% for the other E4 groups and 10–27% for E2V/DNG (Fig. 4). As shown in Fig. 5, the mean number of days with unscheduled bleeding/spotting was statistically significantly lower in the 15 mg E4/DRSP group in comparison to the E2V/DNG group at cycles 2, 3 and 6 (at cycle 1, there was no statistical difference between the five groups — data not shown). By cycle 6, the mean number of days with unscheduled bleeding/spotting varied between 1.3 in the 15E4/DRSP group and 2.9 in the E2V/DNG group ($p = .008$) (Fig. 5).

Early withdrawal bleeding (between cycle days 21 and 24) was variable across the cycles. The incidence decreased or remained stable over time and, by cycle 6, it was lowest for 15E4/DRSP (20.0%) and 20E4/LNG (17.0%). The incidence in the E2V/DNG reference group was 23.9% by cycle 6 (data not shown).

3.4. Safety parameters and vital signs

The frequency of TE-AEs was 64.6% for 15E4/DRSP and varied between 71.8% and 80.0% in the other groups (Table 3). The majority of women had mild or moderate TE-AEs. Between 23.1% and 45.5% of women reported a drug-related TE-AE in the various groups. The incidence of headache/migraine was 2.5–9.3%, and of anxiety/depression, it was 0%–6.5% across groups. One SAE was reported: thyroid neoplasm in the E2V/DNG group, considered by the investigator as not related to study treatment. No apparent dose- or drug-related trends were observed in standard safety laboratory parameters. There were no in-treatment pregnancies, and ovulation was inhibited for all treatments during the first four cycles tested.

Mean changes from baseline in systolic and diastolic blood pressure and heart rate were generally small throughout the study in all groups, without any obvious trends.

Table 1
Main demographics and baseline characteristics (AST population)

	15E4/DRSP *N*=79	20E4/DRSP *N*=75	15E4/LNG *N*=80	20E4/LNG *N*=77	E2V/DNG *N*=78	Overall *N*=389
Mean age, years (SD)	24.3 (4.6)	24.0 (4.5)	24.8 (4.8)	24.0 (3.6)	23.4 (3.5)	24.1 (4.2)
Mean BMI, kg/m^2 (SD)	22.9 (3.0)	23.1 (2.8)	22.6 (3.0)	22.6 (2.8)	22.4 (2.8)	22.7 (2.9)
Current smoking, *n* (%)	18 (22.8)	8 (10.7)	18 (22.5)	19 (24.7)	10 (12.8)	73 (18.8)
Switchers, *n* (%)	51 (64.6)	50 (66.7)	50 (62.5)	55 (71.4)	54 (69.2)	260 (66.8)
Starters, *n* (%)	28 (35.4)	25 (33.3)	30 (37.5)	22 (28.6)	24 (30.8)	129 (33.2)

BMI: body mass index; DNG: dienogest; DRSP: drospirenone; E4: estetrol; E2V: estradiol valerate; LNG: levonorgestrel; *n*: number of subjects with data; *N*: number of subjects in the AST population; SD: standard deviation.

Table 2
Primary and secondary bleeding outcome parameters (PP population)

	15E4/DRSP *N*=77	20E4/DRSP *N*=73	15E4/LNG *N*=77	20E4/LNG *N*=76	E2V/DNG *N*=75
Occurrence of unscheduled bleeding and/or spotting					
Treatment cycle 2					
• Bleeding/spotting, *n*/*N* (%)	34/75 (45.3)	28/68 (41.2)	43/71 (60.6)	38/68 (55.9)	40/66 (60.6)
• Difference from E2V/DNG, rate (95% CI)	−15.3 (−31.6, 1.0)	−19.4 (−36.0, −2.8)	0.0 (−16.4, 16.3)	−4.7 (−21.4, 12.0)	
• Treatment cycle 3					
• Bleeding/spotting, *n*/*N* (%)	39/72 (54.2)	29/67 (43.3)	35/65 (53.8)	39/66 (59.1)	39/68 (57.4)
• Difference from E2V/DNG, rate (95% CI)	−3.2 (−19.6, 13.3)	−14.1 (−30.8, 2.6)	−3.5 (−20.4, 13.4)	1.7 (−15.0, 18.4)	
Treatment cycle 6					
• Bleeding/spotting, *n*/*N* (%)	22/65 (33.8)	29/57 (50.9)	28/58 (48.3)	22/53 (41.5)	32/67 (47.8)
• Difference from E2V/DNG, rate (95% CI)	−13.9 (−30.5, 2.7)	3.1 (−14.5, 20.8)	0.5 (−17.0, 18.1)	−6.2 (−24.1, 11.6)	
Occurrence of unscheduled bleeding					
Treatment cycle 2					
• Bleeding, *n*/*N* (%)	20/75 (26.7)	16/68 (23.5)	29/71 (40.8)	20/68 (29.4)	30/66 (45.5)
• Difference from E2V/DNG, rate (95% CI)	−18.8 (−34.4, −3.2)	−21.9 (−37.6, −6.2)	−4.6 (−21.2, 12.0)	−16.0 (−32.2, 0.1)	
• Treatment cycle 3					
• Bleeding, *n*/*N* (%)	22/72 (30.6)	15/67 (22.4)	24/65 (36.9)	22/66 (33.3)	29/68 (42.6)
• Difference from E2V/DNG, rate (95% CI)	−12.1 (−28.0, 3.8)	−20.6 (−35.7, −4.8)	−5.7 (−22.3, 10.9)	−9.3 (−25.7, 7.0)	
Treatment cycle 6					
• Bleeding, *n*/*N* (%)	11/65 (16.9)	13/57 (22.8)	21/58 (36.2)	10/53 (18.9)	24/67 (35.8)
• Difference from E2V/DNG, rate (95% CI)	−18.9 (−33.6, −4.2)	−13.1 (−28.8, 2.8)	0.4 (−16.5, 17.3)	−17.0 (−32.5, −1.4)	
Absence of withdrawal bleeding					
Treatment cycle 2					
• No withdrawal, *n*/*N* (%)	1/75 (1.3)	1/68 (1.5)	7/71 (9.9)	2/68 (2.9)	8/66 (12.1)
• Difference from E2V/DNG, rate (95% CI)	−10.8 (−19.1, −2.5)	−10.6 (−19.0, −2.3)	−2.3 (−12.8, 8.2)	−9.2 (−18.0, −0.3)	
Treatment cycle 3					
• No withdrawal,. *n*/*N* (%)	2/72 (2.8)	1/67 (1.5)	7/65 (10.8)	9/66 (13.6)	11/67 (16.4)
• Difference from E2V/DNG, rate (95% CI)	−13.6 (−23.3, −4.0)	−14.9 (−24.3, −5.6)	−5.6 (−17.3, 6.0)	−2.8 (−14.9, 9.4)	
Treatment cycle 6					
• No withdrawal, *n*/*N* (%)	2/57 (3.5)	2/53 (3.8)	10/54 (18.5)	7/50 (14.0)	16/59 (27.1)
• Difference from E2V/DNG, rate (95% CI)	−23.6 (−35.9, −11.3)	−23.4 (−35.8, −10.9)	−8.6 (−24.0, 6.8)	−3.1 (−28.0, 1.8)	

CI: confidence interval; DNG: dienogest; DRSP: drospirenone; E4: estetrol; E2V: estradiol valerate; LNG: levonorgestrel; *n*: number of subjects with data; *N*: number of subjects in the PP population.

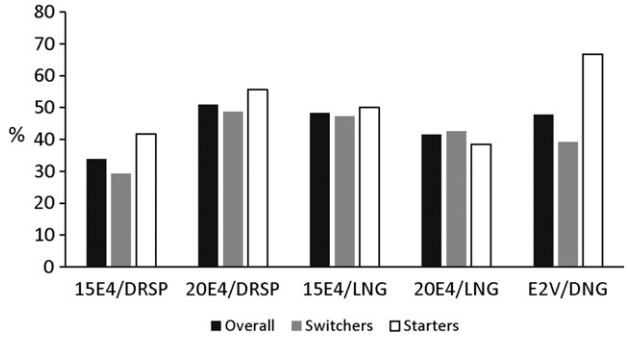

Fig. 2. Frequency (%) of women with unscheduled bleeding/spotting in cycle 6. Percentage of women with unscheduled bleeding/spotting in each treatment group in cycle 6. The data are presented overall and in the subsets of switchers and starters (PP population). DNG: dienogest; DRSP: drospirenone; E4: estetrol; E2V: estradiol valerate; LNG: levonorgestrel.

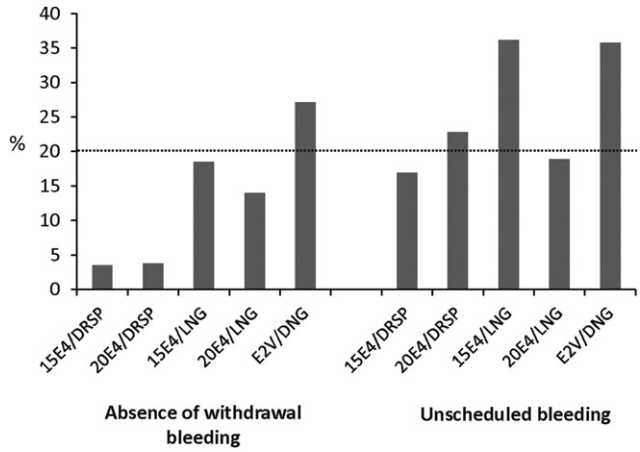

Fig. 3. Frequency (%) of women with absence of withdrawal bleeding/spotting in cycle 6. Percentage of subjects with absence of withdrawal bleeding and unscheduled bleeding in each treatment group in cycle 6 (PP population). Absence of withdrawal bleeding ≤20%, and/or ≤20% unscheduled intracyclic bleeding after six treatment cycles, was set as a limit (dotted bar). DNG: dienogest; DRSP: drospirenone; E4: estetrol; E2V: estradiol valerate; LNG: levonorgestrel.

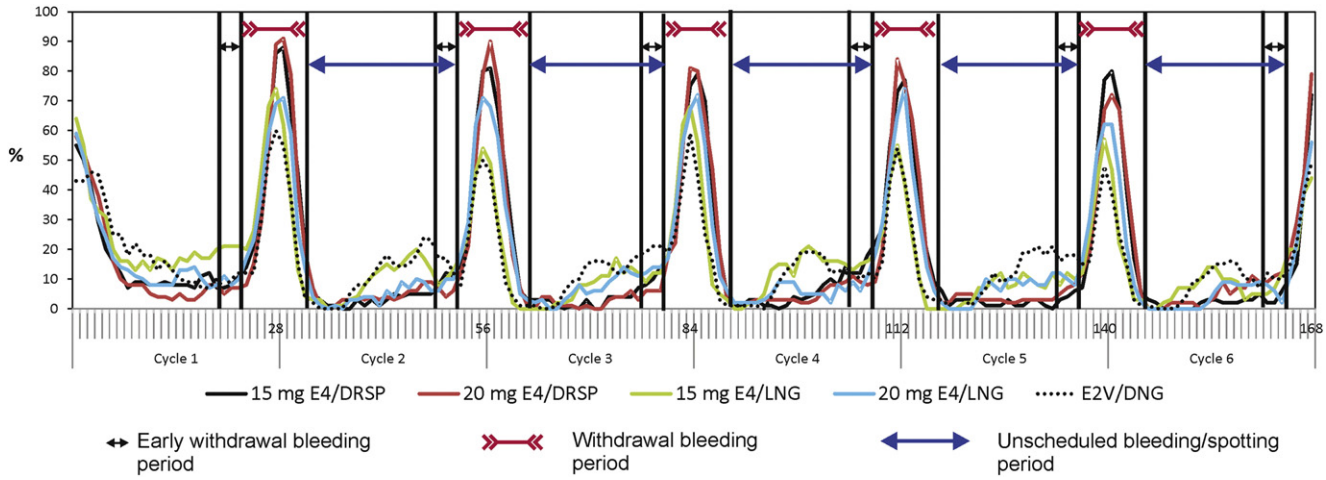

Fig. 4. Incidence of scheduled and unscheduled bleeding/spotting on a daily basis during the six treatment cycles (PP population). Bleeding or spotting reported during cycle days 5–24 was considered unscheduled. Early withdrawal bleeding/spotting occurs between cycle days 21 and 24. DNG: dienogest; DRSP: drospirenone; E4: estetrol; E2V: estradiol valerate; LNG: levonorgestrel.

4. Discussion

Firstly, there were no safety concerns for any of the treatments in this study.

The aim of the present study was to select the E4/progestin dosing regimen for phase III development, based on an optimal bleeding pattern and cycle control. For this reason, absence of withdrawal bleeding for at most 20% of the women and unscheduled intracyclic bleeding without spotting for at most 20% of the women were set as limits. After six cycles, the 15 mg E4/DRSP and the 20 mg E4/LNG combinations were the only ones meeting both criteria: absence of withdrawal bleeding was observed for 3.5% and 14.0%, respectively, and unscheduled intracyclic bleeding was observed for 16.9% and 18.9%, respectively.

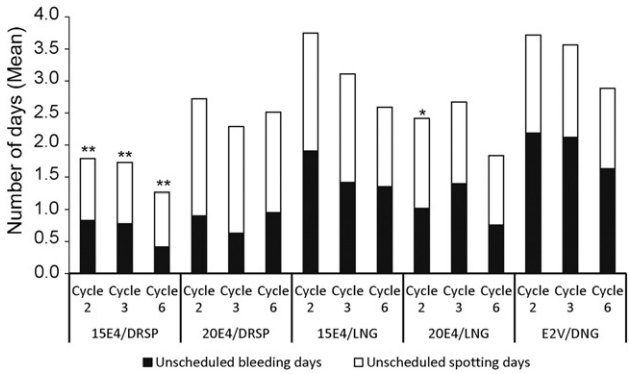

Fig. 5. Mean number of unscheduled bleeding/spotting days in cycles 2, 3 and 6. Bleeding or spotting reported during cycle days 5–24 was considered unscheduled. The mean number of unscheduled bleeding (black bars)/spotting (white bars) days was calculated for each treatment group in the PP population. *t* Test showed a significant difference at cycles 2, 3 and 6 between 15E4/DRSP and E2V/DNG treatment groups (*$p<.05$, **$p<.005$). DNG: dienogest; DRSP: drospirenone; E4: estetrol; E2V: estradiol valerate; LNG: levonorgestrel.

Regular monthly withdrawal bleeding is desirable as it reassures the user that she is not pregnant [24]. Therefore, the 3.5% absence of withdrawal bleeding in the 15E4/DRSP group is considered a very positive feature. By cycle 6, the lowest frequency of unscheduled bleeding and spotting was also observed in the 15E4/DRSP group (33.8%), which was considerably lower than the 47.8% observed in the E2V/DNG reference group. Only 8.9% of subjects in the 15E4/DRSP group discontinued prematurely (compared with a discontinuation rate of between 10.3% and 29.9% in the other groups), which may be related to the favourable cycle control with this treatment regimen.

Since E4 is a natural oestrogen, Qlaira® was chosen as reference COC in the present study because it also contains a natural oestrogen (E2V). It is noteworthy that the incidence of unscheduled bleeding in the E2V/DNG group (35.8%) is in contrast with the 14% reported by Ahrendt et al. [9]. An explanation may be the different definitions used for the term 'unscheduled': days 5–24 in the present study and days 3–21 in the E2V/DNG study [9]. This is also supported by the fact that, during E2V/DNG treatment, substantial bleeding was reported between days 21 and 24 (Fig. 4). A satisfactory cycle control has been described for combinations of DRSP or LNG with 20 mcg EE as the oestrogen [25,26]. The results observed with 15 mg E4/DRSP are in line with these findings.

In conclusion, the 15 mg E4/DRSP combination has been shown to be the most efficacious in terms of bleeding pattern and cycle control, compared with the other combinations investigated. Therefore, this COC seems to be the preferred combination for further phase III clinical development.

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Table 3
Incidence of TE-AEs, *n* (%) (AST population)

	15E4/DRSP *N*=79	20E4/DRSP *N*=75	15E4/LNG *N*=80	20E4/LNG *N*=77	E2V/DNG *N*=78
TE-AEs	51 (64.6)	60 (80.0)	60 (75.0)	57 (74.0)	56 (71.8)
Deaths	0	0	0	0	0
SAE	0	0	0	0	1 (1.3)
TE-AEs leading to withdrawal	5 (6.3)	8 (10.7)	10 (12.5)	12 (15.6)	4 (5.1)
TE-AEs of known severe intensity	3 (3.8)	2 (2.7)	1 (1.3)	2 (2.6)	3 (3.9)
Drug-related TE-AEs					
• Overall	20 (25.3)	31 (41.3)	28 (35.0)	35 (45.5)	18 (23.1)
• Headache/migraine	3 (3.8)	7 (9.3)	2 (2.5)	6 (7.8)	5 (6.4)
• Anxiety/depression	0	0	1 (1.3)	5 (6.5)	1 (1.3)

AST: all-subjects treated; DNG: dienogest; DRSP: drospirenone; E4: estetrol; E2V: estradiol valerate; LNG: levonorgestrel; *n*: number of subjects with data; *N*: number of subjects in the AST population; SAE: serious adverse event; TE-AEs: treatment-emergent adverse events.

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