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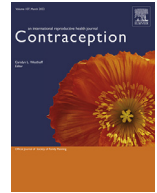
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Pooled analysis of two phase 3 trials evaluating the effects of a novel combined oral contraceptive containing estetrol/drospirenone on bleeding patterns in healthy women ☆,☆☆,★,★★,†,††,†,††,◇,◇◇,♦,♦♦,○○,„

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ABSTRACT

Objective: To evaluate the bleeding patterns of a new combined oral contraceptive containing estetrol (E4) 15 mg/drospirenone (DRSP) 3 mg in a 24/4-day regimen.

Study design: We pooled bleeding data from two parallel, open-label, 13-cycle phase 3 trials that enrolled participants 16 to 50 years old with body mass index (BMI) $\leq$35 kg/m^2. Participants reported vaginal bleeding/spotting in daily diaries. For this bleeding analysis, we included participants with at least one evaluable cycle. We calculated mean frequencies of scheduled and unscheduled bleeding/spotting episodes and median duration of bleeding/spotting episodes, and assessed associations between treatment compliance, BMI and recent hormonal contraceptive use on bleeding/spotting outcomes.

Results: We included 3409 participants with 33,815 cycles. Scheduled bleeding/spotting occurred in 87.2% to 90.4% of participants/cycle, with a median duration of 4 to 5 days. Unscheduled bleeding/spotting decreased from 27.1% in Cycle 1 to 20.6% in Cycle 2 to $\leq$17.5% from Cycle 5 onwards. Most (66.5%) unscheduled bleeding/spotting episodes were spotting-only. Between 5.8% and 7.8% of users/cycle experienced absence of any scheduled or unscheduled bleeding/spotting. Missing one or more active pills resulted in a higher occurrence of unscheduled bleeding/spotting (adjusted odds ratio [aOR] 2.13 [95% confidence interval 1.68–2.70]) and absence of scheduled bleeding/spotting (aOR 2.36 [1.82–3.07]). Participants with a BMI $\geq$30 kg/m^2 reported more absence of scheduled bleeding/spotting (aOR 1.68 [1.37−2.05]). Switchers and starters reported similar frequencies of unscheduled bleeding/spotting (aOR 0.94 [0.83−1.07]) and absence of scheduled bleeding/spotting (aOR 1.00 [0.85−1.19]). Three percent of participants discontinued for a bleeding-related adverse event.

Conclusion: E4/DRSP use results in a predictable bleeding pattern with limited unscheduled bleeding/spotting. Noncompliance and BMI affect bleeding patterns.

Implications statement: Most estetrol/drospirenone users experience a predictable and regular bleeding pattern. Providers can educate patients about the expected bleeding patterns and should advise users that they may infrequently experience no scheduled bleeding/spotting. This information may improve user acceptability and continuation of this new oral contraceptive.

1. Introduction

Combined oral contraceptives (COCs) are among the most commonly used contraceptives worldwide [1]. Most COCs contain ethinyl estradiol (EE) in combination with a progestin. While the progestin component is primarily responsible for the contraceptive effect, the main function of the estrogen component is to balance the impact of the progestin on the endometrium, thereby providing an acceptable bleeding pattern.

Early EE-containing COCs were associated with medical risks such as a significant increase in incidence of venous thromboembolism (VTE) [2–4]. To reduce these risks, researchers and pharmaceutical companies worked to lower the EE dose or replace it with naturally-occurring estrogens, including estradiol (E2) or E2 valerate (E2V) [5]. However, doses of $\leq$20 mcg EE are generally associated with a less favorable bleeding profile [6, 7], and current combinations of 17ß-E2 with nomegestrol acetate (E2/NOMAC) and E2V with dienogest (E2V/DNG) both have relatively high rates of absence of scheduled bleeding/spotting, ranging from 18% to31% over cycles in users of E2/NOMAC [8] and from 19% to 24% over cycles in users of E2V/DNG [9]. Elimination of the estrogen component minimizes medical risks [10] and avoids EE-related side effects of COCs, however, use of progestin-only pills (POPs) is often associated with suboptimal bleeding profiles [11,12].

Estetrol (E4) is a human-specific native estrogen produced in the fetal liver [13] and manufactured for clinical use from plant sources. In a phase 2 trial, E4 15 mg/drospirenone (DRSP) 3 mg users experienced less unscheduled bleeding/spotting and absence of withdrawal bleeding compared to users of E4/levonorgestrel and E2V/DNG pills [14]. Two pivotal phase 3 trials of E4/DRSP for contraception, one in the United States (US)/Canada and another in Europe/Russia, each demonstrated high contraceptive efficacy, a regular bleeding pattern, and a favorable safety and tolerability profile [15,16].

Providing accurate information on anticipated bleeding profiles to new COC users supports treatment acceptability and adherence (compliance) [17–19]. To provide evidence-based information to clinicians for patient education, we evaluated pooled E4/DRSP bleeding data from the two phase 3 trials, including an analysis stratified by compliance, Body Mass Index (BMI), previous combined hormonal contraceptive (CHC) use on bleeding and country. Pooling of outcomes from the two parallel studies provides more robust data in a larger population, allowing us to perform a more powerful statistical analysis and gaining relevant conclusions.

2. Materials and methods

This pooled analysis includes bleeding data from two multicenter, open-label phase 3 trials that evaluated contraceptive efficacy, bleeding patterns, and safety associated with use of E4 15 mg/DRSP 3 mg oral contraceptive pills. The primary methodology and results from each trial has been published previously [15,16].

Briefly, investigators enrolled healthy heterosexually active, premenopausal participants (16–50 years US/Canada trial; 18–50 years Europe/Russia trial) with a BMI of 18.0 to 35.0 kg/m^2 and regular menstrual cycles. Women who had switched from a previous hormonal contraceptive method, except for injectable contraceptives, were allowed to participate. Eligible participants received E4 15 mg (as monohydrate, equivalent to 14.2 mg anhydrous)/DRSP 3 mg once daily in a 24/4-day regimen for up to thirteen 28-day cycles. Switchers from another COC started study treatment when the next pill pack of the previous formulation would have been due, and new users started treatment on the first day of menstruation. Participants used a daily paper diary to record the study medication intake and vaginal bleeding or spotting. Study staff reviewed diaries and asked about adverse events (AEs) at each scheduled follow-up visit during cycles 2, 4, 7, 10, and 13 and, when applicable, during an early discontinuation visit.

For this pooled analysis, we evaluated bleeding outcomes in participants who started treatment and provided any bleeding outcome data. We adopted bleeding analysis definitions from Mishell et al. (2007) [20] as outlined in Supplemental Table 1; notably, we defined spotting as minimal blood loss that did not require any sanitary protection, including pantyliners. We used participants' diary entries to assess pill intake and analyze bleeding patterns by cycle, including frequencies of unscheduled bleeding/spotting episodes and number of unscheduled bleeding/spotting days, frequency of scheduled bleeding/spotting episodes and number of scheduled bleeding/spotting days, frequency of absence of scheduled bleeding/spotting and frequency of absence of any bleeding/spotting.

For all bleeding assessments, we excluded any cycles with a duration >28 days which occurred when participants skipped one or more days of pills but continued intake once daily through to the end of the pack, instead of doubling up and discarding pills that were missed ≥48 hours since last intake. For the assessment of scheduled bleeding/spotting, we excluded the last treatment cycle (Cycle 13) because the diaries did not include bleeding data beyond the end of Cycle 13 when, with a 24/4 regimen, we would have expected the continuation of the scheduled bleeding/spotting episode. For participants who discontinued for any reason, we included evaluable cycles up to the time of discontinuation.

We assessed treatment compliance based on diary entries. When participants did not complete pill intake information on the diary, we assigned that day as a missed pill.

We created two multivariable models to evaluate the effect of BMI (<30 kg/m^2, ≥30 kg/m^2), prior contraceptive use (starters vs switchers from CHCs), compliance overall and by cycle (0 to ≥5 active pills missed/cycle) and country on (1) the absence of scheduled bleeding/spotting and (2) unscheduled bleeding/spotting across valid cycles 2 through 12. We chose these outcome variables as the parameters most relevant to analyze bleeding data. We fitted a longitudinal generalized linear mixed model including cycle and interaction between cycle and compliance as covariates. In the model we adjusted for age group, smoking status, race and gravidity, as these variables may have confounding effects, and accounted for repeated random effects within participant (first-order autoregressive correlation structure).

We classified all AEs according to the Medical Dictionary for Regulatory Activities (MedDRA Version 20.0) system. We performed statistical analyses using SAS software (version 9.4) for Windows.

Clinical trial registrations: Clinicaltrials.gov NCT02817841 and NCT02817828

3. Results

3.1. Participants and compliance

Among 3725 enrolled participants, 3417 had confirmed initiation of E4/DRSP treatment; 7 participants did not provide evaluable bleeding data and one participant withdrew consent, leaving 3409 (99.8%) participants (Fig. 1). We excluded 1231 (3.5%) cycles >28 days resulting in a total of 33,815 evaluable cycles in the analysis population. For participants who discontinued, we included evaluable cycles up to the time of discontinuation. The demographic and baseline characteristics of the participants are presented in Table 1.

Overall, 2234 (65.4%) participants completed 13 treatment cycles. The most frequently reported bleeding-related AEs (in $\geq2\%$ of participants) included irregular bleeding (MedDRA term: metrorrhagia, 4.7%), vaginal bleeding (MedDRA term: vaginal hemorrhage, 3.0%), and dysmenorrhea (2.5%). One-hundred and four (3.0%) participants discontinued due to bleeding-related adverse events.

Table 1

Demographic and baseline characteristics of participants treated with E4/DRSP in a pooled analysis of two phase 3 clinical trials.

Characteristic	Pooled population* $n = 3409$
Age (years)	27.2 ± 6.7
16–25	1629 (47.8)
26–35	1393 (40.9)
36–50	387 (11.4)
BMI (kg/m^2)	24.6 ± 4.4
<30.0	2891 (84.8)
≥30.0	518 (15.2)
Smoking status	
Current smoker†	467 (13.7)
Former smoker	291 (8.5)
Never smoker	2651 (77.8)
Gravidity/parity	
Nulligravid	2024 (59.4)
Nulliparous	2262 (66.4)
Recent hormonal contraceptive use	
Switchers‡	1729 (50.7)
Starters§	1680 (49.3)
True new users	673 (19.7)
Race	
Asian	97 (2.8)
Black	374 (11.0)
White	2828 (83.0)
Other¶	110 (3.2)
Region	
Canada	152 (4.5)
Eastern Europe	746 (21.9)
Russia	280 (8.2)
Scandinavia	298 (8.7)
United States of America	1705 (50.0)
Western Europe	228 (6.7)

Data are presented as n (%) or mean ± standard deviation.

* Europe/Russia trial included 1552 treated participants; United States/Canada trial included 1857 treated participants.

† Current smokers aged >35 years were excluded.

‡ Switchers: Previous hormonal contraceptive use within 3 months before initiating study drug.

§ Starters: Previous hormonal contraceptive use >3 months before initiating study drug (starters) and none (true new users).

¶ Includes America Indian or Alaskan Native, Native Hawaiian, or other Pacific Islanders, and Other.

Most (>82%) treated participants did not report missing any pills. The proportion of participants who missed one pill ranged from 9.3% (Cycle 1) to 5.4% (Cycles 12 and 13), missed two pills ranged from 3.8% (Cycle 3) to 1.6% (Cycle 11) and missed more than two pills from 4.6% (Cycle 2) to 1.5% (Cycle 13), respectively.

3.2. Scheduled bleeding/spotting

Overall, bleeding and spotting days during the treatment period showed a clear cyclic pattern with bleeding at the end of each cycle (Fig. 2). Most (87.2–90.4%, mean 89.0 ± 0.9%) participants reported scheduled bleeding/spotting across cycles 1–12 (Fig. 3). The number of scheduled bleeding/spotting days remained stable throughout the cycles with a median duration of 4 to 5 days. Scheduled bleeding/spotting consisted of an approximately equal number (2–3) of spotting days and bleeding days (Supplemental Table 1).

3.3. Unscheduled bleeding/spotting

Of the 2234 participants who completed 13 cycles of treatment, 911 (40.8%) reported no unscheduled bleeding/spotting, and 754 (33.8%) experienced unscheduled bleeding/spotting in only 1 or 2 cycles.

The proportion of participants reporting unscheduled bleeding/spotting episodes decreased from 27.1% in Cycle 1 to 19.5% to

Fig. 1. Disposition of participants in pooled bleeding analysis of E4/DRSP oral contraception.
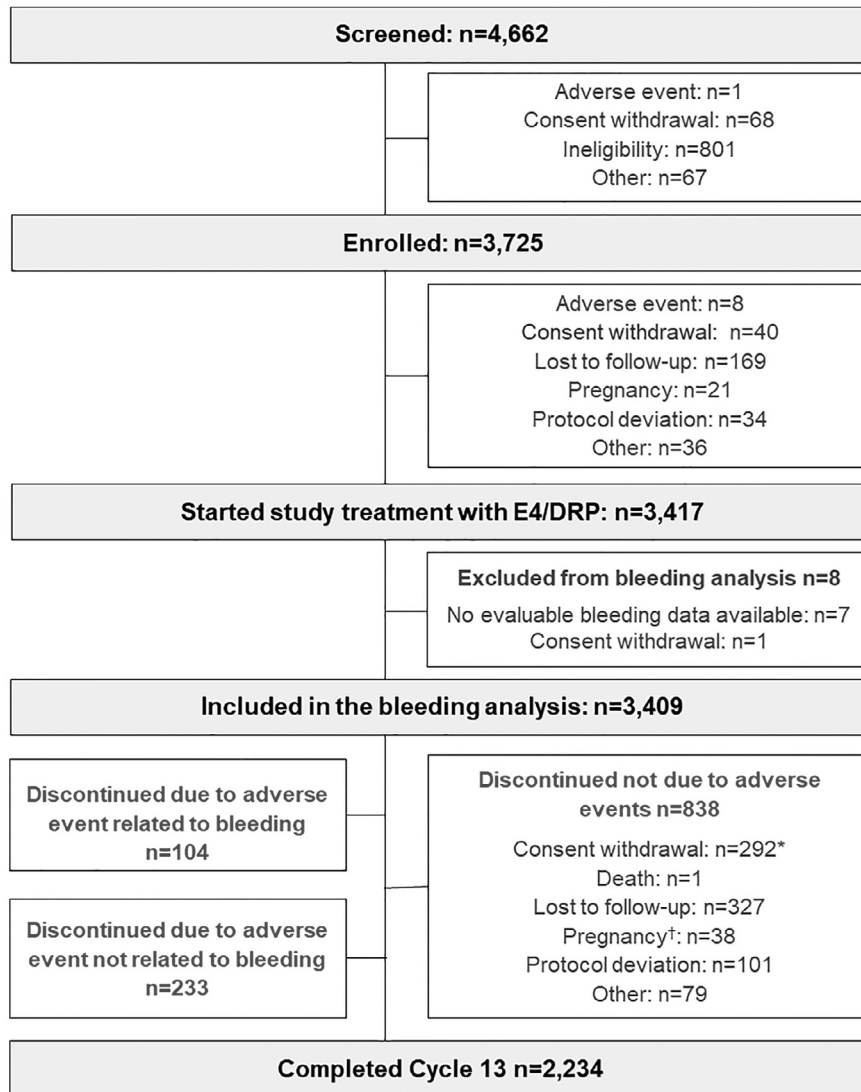
* Including 32 women with pregnancy wish
† This category includes participants with a confirmed pregnancy (pre-treatment, on-treatment, and post-treatment) listed as their primary reason for discontinuation

Fig. 2. Percentage of participants reporting bleeding or spotting by study day during use of E4/DRSP oral contraception. Red vertical lines delineate the scheduled bleeding period that occurs between day 25 and day 3 of the next cycle.

Fig. 3. Percentages of participants reporting scheduled bleeding/spotting, unscheduled bleeding/spotting, and absence of any bleeding/spotting per cycle during use of E4/DRSP oral contraception. Note that the outcome does not add up to 100% in each cycle because participants may have scheduled bleeding and unscheduled bleeding in the same cycle and will thus be counted twice.

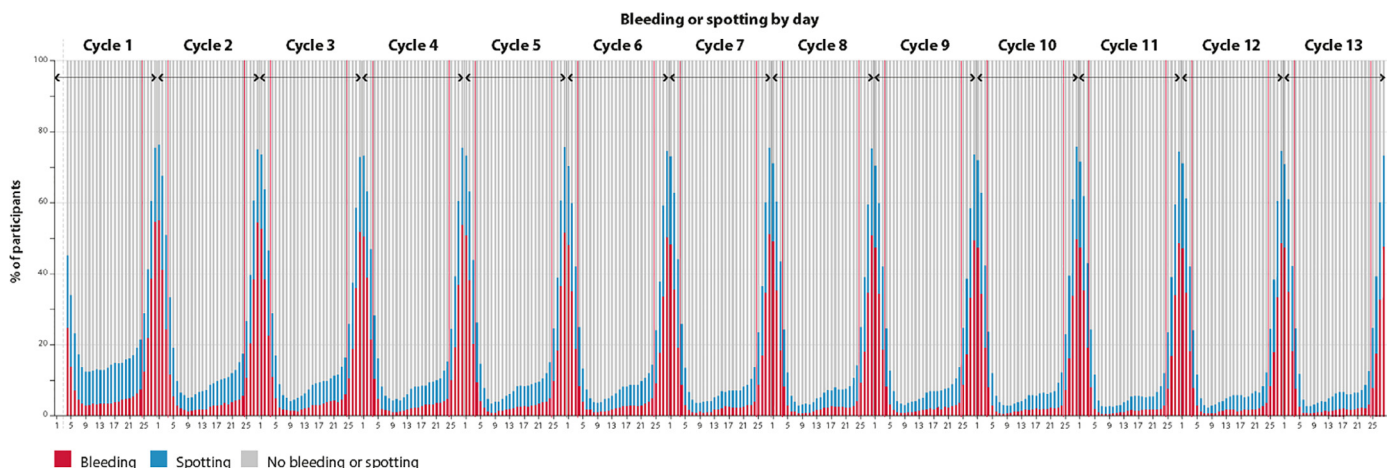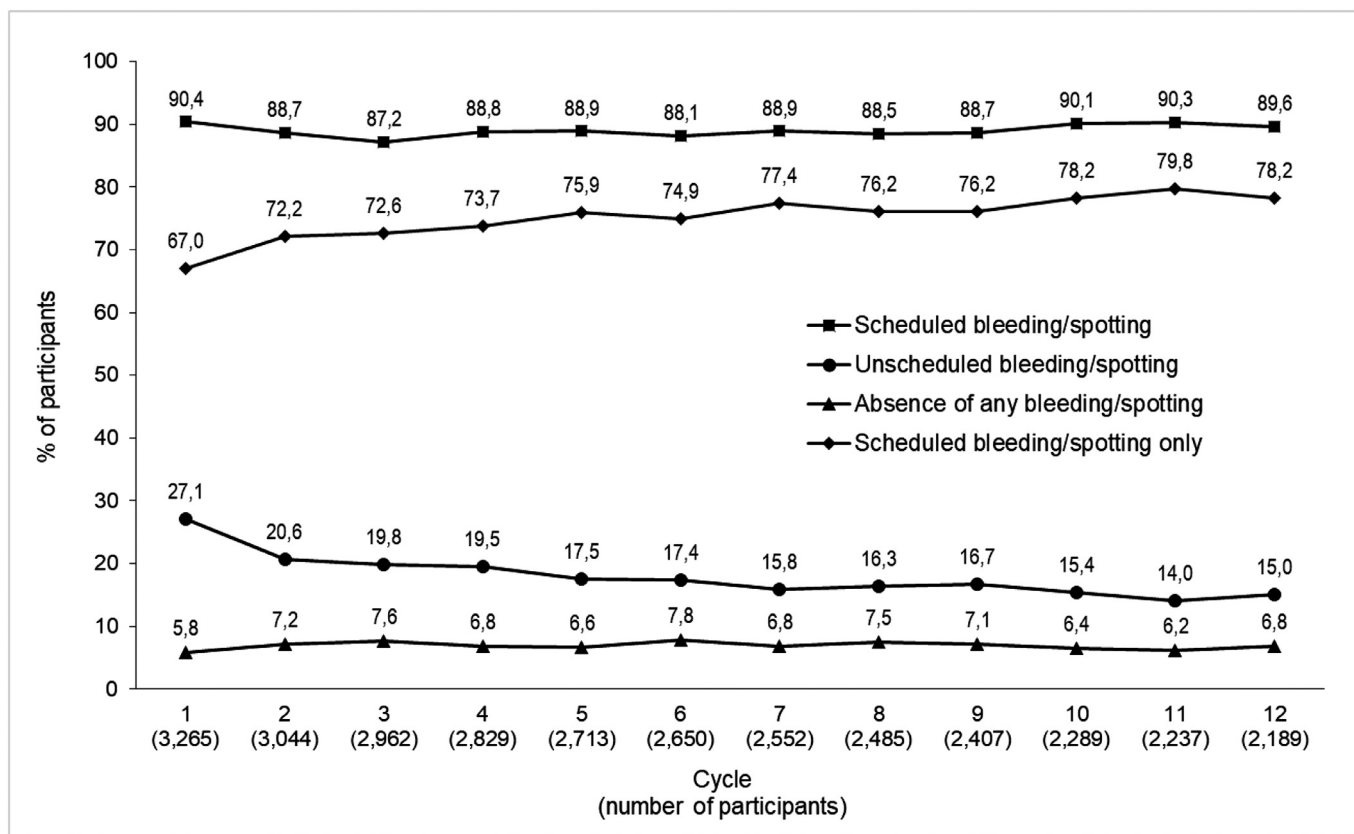20.6% during Cycles 2 to 4 and remained relatively stable thereafter, ranging from 17.5% at Cycle 5% to 14.0% at Cycle 11 (Fig. 3). The proportion of participants with unscheduled bleeding/spotting episodes over cycles 1–12 was 17.9%, of which 11.2% was spotting only, 5.6% was bleeding and spotting and 1.1% was bleeding only. With increased duration of use, participants reported fewer unscheduled spotting-only episodes (from 19.2% in Cycle 1 to 9.5% in Cycle 12), less unscheduled mixed-bleeding/spotting (from 6.5% to 4.5%) and less unscheduled bleeding (from 1.4% to 1.0%) (Fig. 4). Overall, 66.5% of unscheduled bleeding/spotting episodes included only spotting, 26.7% mixed bleeding and spotting, and 6.8% only bleeding. The number of bleeding days was less than 2-fold the number of spotting days (Supplemental Table 1).

While the proportion of participants with unscheduled bleeding/spotting episodes decreased over time, the number of unscheduled bleeding/spotting days remained stable throughout the study, with a median duration of 3 to 4 days among those participants reporting unscheduled bleeding and/or spotting (Supplemental Table 2).

3.4. Absence of bleeding/spotting

Absence of scheduled bleeding/spotting occurred more frequently in participants with a BMI $\geq$30 kg/m^2 (13.4%–21.6% per cycle) than <30 kg/m^2 (7.6%–9.0% per cycle) (adjusted odds ratio [aOR] 1.68, 95% CI 1.37–2.05); we found no difference in unscheduled bleeding/spotting when stratified by BMI (aOR 1.16 95% CI 0.98–1.36) (Table 2). Prior use of CHC (starters vs switchers) did not affect absence of scheduled bleeding/spotting (aOR 1.00, 95% CI 0.85–1.19) or unscheduled bleeding/spotting (aOR 0.94 95% CI 0.83–1.07) when analyzed over all cycles, or, as shown in Table 2, when analyzed per cycle.

As shown in Fig. 3, 9.6% to 12.8% of users per cycle reported no scheduled bleeding/spotting and 67.0% to 79.8% of users reported only scheduled bleeding/spotting, without unscheduled bleeding/spotting. Additionally, 5.8% to 7.8% (mean 6.9% $\pm$ 0.6%) of users across cycles 1–12 reported no bleeding/spotting (scheduled or unscheduled).

3.5. Bleeding patterns by treatment compliance and region

Participants who reported missing one or more active pills in a cycle, compared to those who missed no pills, more frequently reported unscheduled bleeding/spotting (adjusted odds ratio [aOR] 2.13, 95% confidence interval [CI] 1.68–2.70) and absence of scheduled bleeding/spotting (aOR 2.36, 95% CI 1.82–3.07). The odds increased with the number of missed pills (Table 2).

Because the characteristics of participants varied by study location, we further evaluated absence of scheduled bleeding/spotting and unscheduled bleeding/spotting by study region (Table 3). Participants in Canada and the U.S. more frequently reported cycles with absence of scheduled bleeding/spotting and those from Scandinavian countries more frequently reported unscheduled bleeding/spotting. Russian participants less frequently reported both of these bleeding/spotting outcomes.

4. Discussion

This pooled analysis aggregates data from over 3200 participants and demonstrates that the novel E4/DRSP COC is most frequently associated with a regular bleeding pattern, with most participants (87.2%–90.4%) experiencing scheduled bleeding/spotting each cycle. The median duration of the scheduled
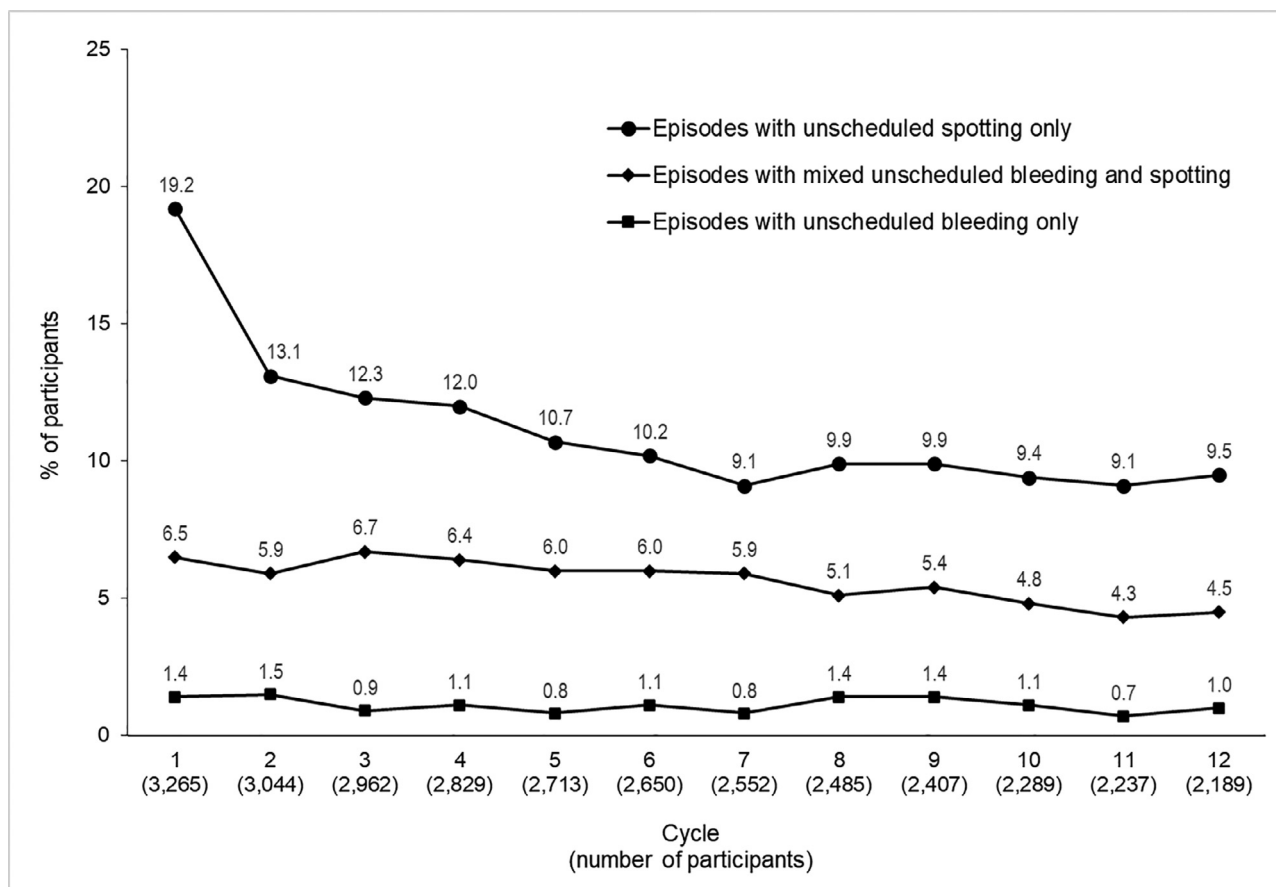
Fig. 4. Percentage of participants with unscheduled bleeding/spotting episodes during use of E4/DRSP oral contraception.

Table 2
Absence of scheduled bleeding/spotting (Table A) and unscheduled bleeding/spotting (Table B) by subgroup in participants treated with E4/DRSP in a pooled analysis of two phase 3 clinical trials.

Table A. Absence of scheduled bleeding/spotting

Parameter	Comparator	Cycles	Proportion*	Reference	Cycles	Proportion*	Adjusted OR (95% CI)
Compliance[†]	1 missed pill	402	11.9%	No missed pills	25,584	9.4%	1.31 (1.00–1.71)
	2 missed pills	131	16.0%				1.82 (1.25–2.64)
	3 missed pills	59	18.6%				1.79 (0.96–3.33)
	4 missed pills	40	37.5%				3.23 (1.60–6.51)
	≥5 missed pills	52	55.8%				5.35 (2.95–9.72)
BMI	≥30 kg/m²	3,541	17.8%	<30 kg/m²	22,727	8.3%	1.68 (1.37–2.05)
Recent CHC use[‡]							
Cycle 2[§]	Switcher from CHC	1,445	8.2%	Starter	1383	10.1%	1.01 (0.77–1.31)
Cycle 3[§]	Switcher from CHC	1,403	9.8%	Starter	1267	10.5%	1.06 (0.83–1.37)
Cycle 4[§]	Switcher from CHC	1,386	8.4%	Starter	1239	10.3%	0.93 (0.71–1.21)

Table B. Unscheduled bleeding/spotting

Parameter	Comparator	Cycles	Proportion*	Reference	Cycles	Proportion*	Adjusted OR (95% CI)
Compliance[†]	1 missed pill	402	25.4%	No missed pills	25,584	16.7%	1.40 (1.11–1.77)
	2 missed pills	131	26.0%				1.70 (1.13–2.56)
	3 missed pills	59	42.4%				3.15 (1.86–5.33)
	4 missed pills	40	40.0%				2.44 (1.26–4.71)
	≥5 missed pills	52	38.5%				2.40 (1.36–4.23)
BMI	≥30 kg/m²	3541	20.4%	<30 kg/m²	22,727	16.4%	1.16 (0.98–1.36)
Recent CHC use[‡]							
Cycle 2[§]	Switcher from CHC	1445	20.2%	Starter	1383	20.7%	0.95 (0.79–1.15)
Cycle 3[§]	Switcher from CHC	1403	20.5%	Starter	1267	17.3%	1.19 (0.97–1.45)
Cycle 4[§]	Switcher from CHC	1386	19.4%	Starter	1239	19.2%	0.98 (0.80–1.19)

BMI, body mass index; CHC, combined hormonal contraceptive; OR, Odds Ratio
Associations evaluated using a multivariable longitudinal model adjusted for age group, smoking status, race, country and gravidity.
* Proportion of cycles with outcome.
†Based on active pills only.
‡A separate analysis comparing starters vs switchers from combined oral contraceptives demonstrated similar results (data not shown).
§The outcome in Cycles 2 to 4 is included as the difference between starters and switchers is expected to be seen in the first few months of treatment.

Table 3

Absence of scheduled bleeding/spotting (Table A) and unscheduled bleeding (Table B) by region in participants treated with E4/DRSP in a pooled analysis of two phase 3 clinical trials.

A. Absence of scheduled bleeding/spotting

Region	N*	#	Proportion†	Reference	N	#	Proportion†	Adjusted
		Cycles				Cycles		OR (95% CI)‡
Canada	123	1008	10.0%	Non-Canada	2844	25,260	9.6%	1.57 (1.03–2.38)
Eastern Europe	712	6733	6.9%	Non-Eastern Europe	2255	19,535	10.5%	1.04 (0.82–1.32)
Russia	265	2653	1.9%	Non-Russia	2702	23,615	10.4%	0.21 (0.13–0.33)
Scandinavia	256	2150	7.9%	Non-Scandinavia	2711	24,118	9.7%	1.32 (0.92–1.90)
US	1400	11,640	13.5%	Non-US	1567	14,628	6.4%	1.93 (1.57–2.37)
Western Europe	211	2084	7.3%	Non-Western Europe	2756	24,184	9.8%	1.15 (0.77–1.70)

B. Unscheduled bleeding/spotting

Region	N*	#	Proportion†	Reference	N	#	Proportion†	Adjusted
		Cycles				Cycles		OR (95% CI)‡
Canada	123	1008	19.4%	Non-Canada	2844	25,260	16.9%	1.27 (0.94–1.73)
Eastern Europe	712	6733	15.8%	Non-Eastern Europe	2255	19,535	17.4%	1.04 (0.88–1.23)
Russia	265	2653	7.8%	Non-Russia	2702	23,615	18.0%	0.39 (0.30–0.52)
Scandinavia	256	2150	22.3%	Non-Scandinavia	2711	24,118	16.5%	1.65 (1.33–2.06)
US	1400	11,640	18.7%	Non-US	1567	14,628	15.6%	1.13 (0.98–1.29)
Western Europe	211	2084	16.0%	Non-Western Europe	2756	24,184	17.1%	1.03 (0.80–1.33)

OR, odds ratio; US, United States.

*Number of participants in region or reference category (differs from Table 1 because only switchers from combined hormonal contraceptives were included).

†Proportion of cycles with outcome.

‡Adjusted for age, smoking status, race, gravidity, compliance, body mass index and prior/recent combined hormonal contraceptive use.

bleeding/spotting of 4 to 5 days is comparable to the duration reported for persons with regular cycles not using hormonal contraceptives [21]. As seen with other COCs, bleeding irregularities were more frequent at the start of the treatment and declined thereafter.

A regular bleeding pattern is an important factor influencing contraceptive selection, adherence, and treatment continuation [17–19]. Definitions for unscheduled bleeding/spotting can vary across studies but absence of scheduled bleeding-spotting is a consistent outcome. Pooled bleeding analyses of phase 3 trials conducted with other COCs demonstrate the frequency of absence of scheduled bleeding/spotting over cycles of between 8% and 12% with an EE 20 µg/DRSP 3 mg, 24/4 regimen [22], 18% to 32% with an E2 1.5 mg/NOMAC 2.5 mg, 24/4 regimen [8], and 19% to 24% with an E2V 1/2/3 mg/DNG 2/3 mg, 26/2 regimen [9]. The absence of scheduled bleeding/spotting with E4/DRSP (10%–13%) appears comparable to EE/DRSP and occurs less frequently compared to E2 formulations. However, these comparisons are indirect, and the potential impact of different assessments of bleeding patterns, definitions, and other trial design features should be considered. A reliable comparison with other products can only be made in a comparative trial using the same conditions, study methods, and analysis for the different treatment groups.

We were surprised to find that the bleeding profile of E4/DRSP was not impacted by prior use of CHCs, not even in the first treatment cycle. However, obese (BMI > 30 kg/m^2) participants appeared to experience more absence of scheduled bleeding (13.4%–21.6% per cycle) compared to nonobese participants (7.6%–9.0% per cycle). This finding is similar to those reported with E2/NOMAC which saw higher rates of absence of scheduled bleeding in participants with a BMI ≥25 kg/m^2 (46.9%) compared with a BMI <25 kg/m^2 (32.0%) [8]. Amenorrhea rates with use of a COC containing EE 10 µg and norethindrone acetate 1 mg demonstrated minimal difference in obese (50.1%), overweight (54.9%), and normal weight (54.6%) users [23]. With E4/DRSP use, missing one or more pills per cycle increased the frequency of both absence of scheduled bleeding/spotting and of unscheduled bleeding/spotting, and the pattern became less favorable when more pills were missed. Providing this information to users may help to improve treatment compliance, which is also important for efficacy.

Bleeding outcomes related to noncyclic bleeding (absence of scheduled bleeding/spotting and unscheduled bleeding/spotting) varied slightly by region. Of note, Russian participants reported

these outcomes significantly less than all other participants. These variations could reflect cultural differences or reporting compliance. Clinicians should be aware of these small differences in outcomes by region when counseling patients using E4/DRSP.

We performed this analysis using data from two similar pivotal phase 3 studies, which used the same methodology to assess the bleeding pattern of E4/DRSP and therefore provided robust bleeding information in a large population [15,16]. Our analysis includes several limitations: the study collected compliance and bleeding data from participant-reported diaries, accordingly, we had no objective means of confirming the accuracy of this self-reported information. In addition, as phase 3 contraceptive studies do not require a reference comparator, the Sponsor did not include one, limiting comparison with other contraceptives.

In conclusion this pooled analysis on bleeding data found that use of COC E4 15 mg/DRSP 3 mg in a 24/4-day treatment regimen is typically associated with a regular and predictable bleeding pattern that is similar to that reported with the use of other widely prescribed COCs. Importantly, the number of participants discontinuing participation due to bleeding-related adverse events was low (3.0%). These findings are important when counseling oral contraceptive users about anticipated bleeding patterns.

Acknowledgments

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.contraception.2022.07.010.

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