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Original Research Article

Tolerability and safety of the estetrol/drospirenone combined oral contraceptive: Pooled analysis of two multicenter, open-label phase 3 trials ☆,☆☆

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ABSTRACT

Objectives: To evaluate tolerability and safety of estetrol (E4) 15 mg/drospirenone (DRSP) 3 mg oral contraceptive using pooled data from two, multicenter, phase 3 trials.
Study design: The two trials enrolled participants aged 16–50 years with a body mass index ≤35.0 kg/m^2 to use E4/DRSP in a 24/4-day regimen for up to 13 cycles. We pooled data from participants who used at least one E4/DRSP dose and had a follow-up assessment to analyze adverse events (AEs), vital signs, and laboratory parameters, including serum lipids, glucose, glycated hemoglobin, and potassium. We consolidated similar Medical Dictionary for Regulatory Activities preferred terms into groupings.
Results: Of 3725 participants enrolled, we included 3417 in the analyses of whom 1786 (52.3%) reported ≥1 AE. Most participants with reported AEs had AEs that investigators rated as mild or moderate (n = 1665, 93.2%); of participants reporting AEs, 1105 (61.9%) did so during cycles 1 to 3. In total, 981 (28.7%) participants experienced ≥1 treatment-related AE, most frequently related to bleeding complaints (n = 323, 9.5%), breast pain or tenderness (n = 136, 4.0%), acne (n = 113, 3.3%), and mood disturbance (n = 111, 3.2%). Discontinuation due to treatment-related AEs occurred in 272 participants (8.0%), with only bleeding complaints (n = 97, 2.8%) and mood disturbance (n = 38, 1.1%) at rates exceeding 1%. Three participants experienced serious AEs, which the site investigators considered treatment-related: one venous thromboembolism, one worsening of depression, and one ectopic pregnancy. We found no clinically relevant changes in weight, blood pressure, heart rate, or laboratory parameters during treatment.
Conclusions: E4/DRSP is associated with a favorable tolerability and safety profile.
Implications statement: Pooling data allowed for a robust assessment of tolerability and safety, including relatively infrequent events. Other than bleeding complaints and mood disturbance, no adverse event resulted in E4/DRSP discontinuation at rates >1%. Post-marketing surveillance studies are needed to evaluate long-term safety of the E4/DRSP COC and population-based venous thromboembolism risks.

1. Introduction

Combined oral contraceptives (COCs) are the most commonly used method of reversible contraception in North America and Europe [1,2], with most COCs comprised of ethinyl estradiol (EE) in combination with a progestin [3]. New COC formulations introduced over the past few decades have aimed to cause fewer side effects while maintaining efficacy; still, some users experience side-effects, including sexual dysfunction, mood changes, weight gain, breast tenderness, and unscheduled uterine bleeding [4–8]. Importantly, currently available COCs are associated with rare but serious cardiovascular adverse effects including venous thromboembolism (VTE) [9–11]. The adverse effects of COCs can be a barrier to use and result in discontinuation, with the potential for unintended pregnancies [12–15]. Therefore, a new COC with a favorable tolerability and safety profile could provide a beneficial option.

Estetrol (E4) is the estrogenic component of a new COC formulated with the progestin drospirenone (DRSP). E4 is naturally produced by the human fetal liver and is synthesized from a plant source for clinical use. This native estrogen has properties distinct from other natural and synthetic estrogens, displaying tissue-selective agonistic and/or antagonistic estrogenic properties elicited through selective nuclear estrogen-receptor (ER)α activation, but not membrane ERα activation in several tissues including the breast [16–19]. The selective receptor activity may result in a limited impact on hemostasis parameters, breast tissue, endocrine parameters, liver proteins, lipid profiles, and carbohydrate metabolism, while sustaining endometrial proliferation [20–24].

E4 15 mg (as monohydrate, equivalent to anhydrate 14.2 mg)/DRSP 3 mg has recently been approved in the United States (US), Canada, the European Union (EU), and Australia, with marketing authorization supported by the efficacy and safety results of two phase 3 studies [25,26]. We performed a pooled analysis of adverse events (AEs), laboratory data, and vital signs across the two phase 3 studies to further characterize the tolerability and safety profile of E4/DRSP in a larger spectrum of individuals.

2. Materials and methods

Investigators enrolled participants into two parallel phase 3 clinical trials from June 2016 through April 2018 (Europe/Russia) and from August 2016 through November 2018 (US/Canada). For this analysis, we included data from participants who had confirmed use of at least one dose of study drug and a follow-up visit and/or call. We analyzed AEs and serious AEs (SAEs), overall and treatment-related, by severity and cycle, together with vital signs and laboratory parameter abnormalities. In addition, we calculated the proportion of affected cycles against total number of cycles for treatment-related AEs.

The methods and outcomes of the individual trials have been previously reported [25,26]. Briefly, investigators enrolled healthy, heterosexually active, pre-menopausal participants (18–50 years Europe/Russia trial; 16–50 years US/Canada trial) with a body mass index (BMI) ≤35.0 kg/m^2, and a history of regular menstrual cycles (21–35 days) when not on hormonal contraception. Investigators excluded individuals with contraindications to COC use based on World Health Organization (WHO) medical eligibility criteria [27]. Specific exclusion criteria included a history of thromboembolic, cardiovascular or cerebrovascular disorder, hypertension (systolic blood pressure [SBP] ≥140 mmHg or diastolic blood pressure [DBP] ≥90 mmHg) and use of any nicotine-containing products for persons ≥35 years old. Participants received the study drug in a blister pack containing 24 active E4/DRSP tablets and 4 inactive tablets, to be taken once-daily for 28 days for up to thirteen cycles.

Study staff planned four follow-up study visits on-treatment (Cycles 2, 4, 7, and 10) and one at the end of treatment (Cycle 13 or early discontinuation). Participants used paper diaries to record medication intake, other contraceptive methods used, sexual activity, vaginal bleeding and/or spotting events, and AEs. At each visit, study staff reviewed the diaries, collected used study drug packets, dispensed new drug, and asked participants about any changes in medical conditions, other medication use, and the occurrence of AEs. Investigators assessed study drug compliance based on diary entries per 28-day cycle and counted any day with a missing entry

as no pill intake. For the analysis, we assessed treatment compliance as the reported number of pills taken divided by the expected number of pills taken based on duration of participation.

Investigators evaluated the frequency and severity of AEs, including clinically relevant changes or abnormalities in routine laboratory parameters or physical examination findings. Investigators assessed clinical laboratory parameters (including hematology, serum chemistry, and lipid profiles) at Screening, Cycle 7, and Cycle 13, and vital signs (SBP, DBP, heart rate, and weight) at Screening and Cycles 2, 4, 7, 10, and 13. For each AE, site investigators determined whether the AE should be categorized as an SAE and assessed the relationship of the AE to the study drug as treatment-related or not. The investigators determined that the AE was probably or possibly related to the study drug if there was a reasonable time relationship to the study drug intake and if it was unlikely to be due to an underlying illness or concurrent treatment. Site investigators recorded the intensity of each AE as mild (transient and well-tolerated by the study subject), moderate (temporary interference with daily living), or severe (substantially interfered with daily living to the point of being incapacitating and/or life-threatening). For the analysis, we classified AEs using version 20.0 of the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and consolidated similar preferred terms into groupings as presented in Supplemental Table 1. To calculate the number of affected cycles, we compared the beginning and end date of each treatment-related AE with the beginning and end date of each cycle. If a participant reported the event more than once within a single cycle, we counted it only once for the cycle. The proportion of affected cycles was calculated as the ratio of the number of impacted cycles and the total number of cycles of all participants during the study.

Clinical trial registration: Clinicaltrials.gov NCT02817828, NCT02817841

3. Results

3.1. Participants and compliance

Overall, we enrolled 3725 participants; 93 participants discontinued before study drug initiation, and we could not confirm intake in 215 participants as they had no follow-up contact, leaving 3417 participants in this pooled analysis (Fig. 1). The baseline characteristics of the participants are presented in Table 1. By the end of Cycle 3, 6, 9, and 13, 466 (13.6%), 771 (22.6%), 1035 (30.3%), and 1183 (34.6%) participants had discontinued, respectively. The disposition of participants through the two clinical trials is shown in Figure 1; the most common reasons for discontinuation were loss to follow-up (n = 328 [9.6%]) and consent withdrawal (n = 261 [7.6%]).

Participants completed 35,093 E4/DRSP cycles with a median self-reported treatment compliance of 100% (interquartile range 99.5%–100%) across all cycles. Most participants reported not missing any pills, ranging from 82.9% at Cycle 2 to 90.8% at Cycle 13. The proportion of participants missing two pills ranged from 1.6% (Cycle 11) to 3.8% (Cycle 3), and more than two pills ranged from 4.6% (Cycle 2) to 1.5% (Cycle 13).

3.2. Adverse events

We provide an overview of AEs in Table 2. About half (n = 1786, 52.3%) of participants reported one or more AEs, of which most (n = 1665, 93.2%) were graded as mild or moderate intensity. Approximately one-third (n = 1105, 32.3%) of AEs occurred during Cycles 1–3. Investigators determined AEs to be treatment-related in 981 (28.7%) participants, which most frequently consisted of AEs related to bleeding complaints (n = 323, 9.5%), breast pain or tenderness (136, 4.0%), acne (n = 113, 3.3%), mood disturbance (n = 111, 3.2%), headache (n = 110, 3.2%), dysmenorrhea (n = 85, 2.5%), and increased weight (n = 74, 2.2%).

Overall, 338 (9.9%) participants reported an AE that led to early study discontinuation. Of these, investigators considered the AE to be treatment-related in 272 (8.0%) participants, most commonly bleeding complaints (n = 97, 2.8%), mood disturbance (38, 1.1%), acne (n = 28, 0.8%), and decreased or loss of libido (n = 21, 0.6%).

Table 1
Demographics and previous contraceptive, smoking and obstetric status of participants in the pooled safety population of estetrol/drospirenone users (N = 3417).

Characteristic	n (%) or mean ± standard deviation
Age (years)	27.2 ± 6.7
16 to 25	1632 (47.8)
26 to 35	1395 (40.8)
36 to 50	390 (11.4)
Body mass index (kg/m²)	24.6 ± 4.4
<18.5	115 (3.4)
18.5 to 24.9	1974 (57.8)
25.0 to 29.9	807 (23.6)
≥30.0	521 (15.2)
Race	
White	2832 (82.9)
Black	377 (11.0)
Asian	97 (2.8)
None of the above[a]	111 (3.2)
Past contraceptive use	
Switchers[b]	1732 (50.7)
Starters[c]	1685 (49.3)
None (true new users)	674 (19.7)
Smoking status	
Current smoker[d]	468 (13.7)
Former smoker	292 (8.5)
Never smoker	2657 (77.8)
Gravidity/Parity	
Nulligravid	2027 (59.3)
Nulliparous	2265 (66.3)

Data are for participants who received confirmed treatment with estetrol 15 mg/drospirenone 3 mg and had at least one follow-up call/visit.

[a] Includes America Indian or Alaska Native, Native Hawaiian or other Pacific Islanders and Other.

[b] Past contraceptive use within 3 months before initiating study drug (switchers).

[c] Past contraceptive use >3 months before initiating study drug (starters) and none (true new users).

[d] No current smokers were enrolled in age group >35 years.

3.2.1. Treatment-related adverse events by severity and cycle

We present the most common treatment-related AEs (bleeding complaints, breast pain or tenderness, acne, mood disturbance, headache, dysmenorrhea, and increased weight [self-reported and confirmed at study visit]) by 3-cycles and severity in Figure 2. Bleeding complaints, breast pain or tenderness, acne, mood disturbance, headache, and dysmenorrhea mainly occurred in Cycles 1–3 and decreased thereafter up to Cycles 10–13. Investigators assessed most of these treatment-related AEs as mild intensity; those events assessed as severe intensity included dysmenorrhea (n = 9 participants, 0.26%), headache (n = 8, 0.23%), mood disturbance (n = 8, 0.23%), breast pain or tenderness (n = 3, 0.09%), bleeding complaints (n = 4, 0.12%) and increased weight (n = 2, 0.06%); no participants reported severe intensity acne.

We evaluated the percentage of affected cycles for treatment-related AEs with only bleeding complaints (3.7%), acne (1.6%), breast pain or tenderness (1.6%), weight increased (1.4%), mood disturbance (1.2%), and headache (1.1%) occurring in more than 1% of all cycles (Table 3).

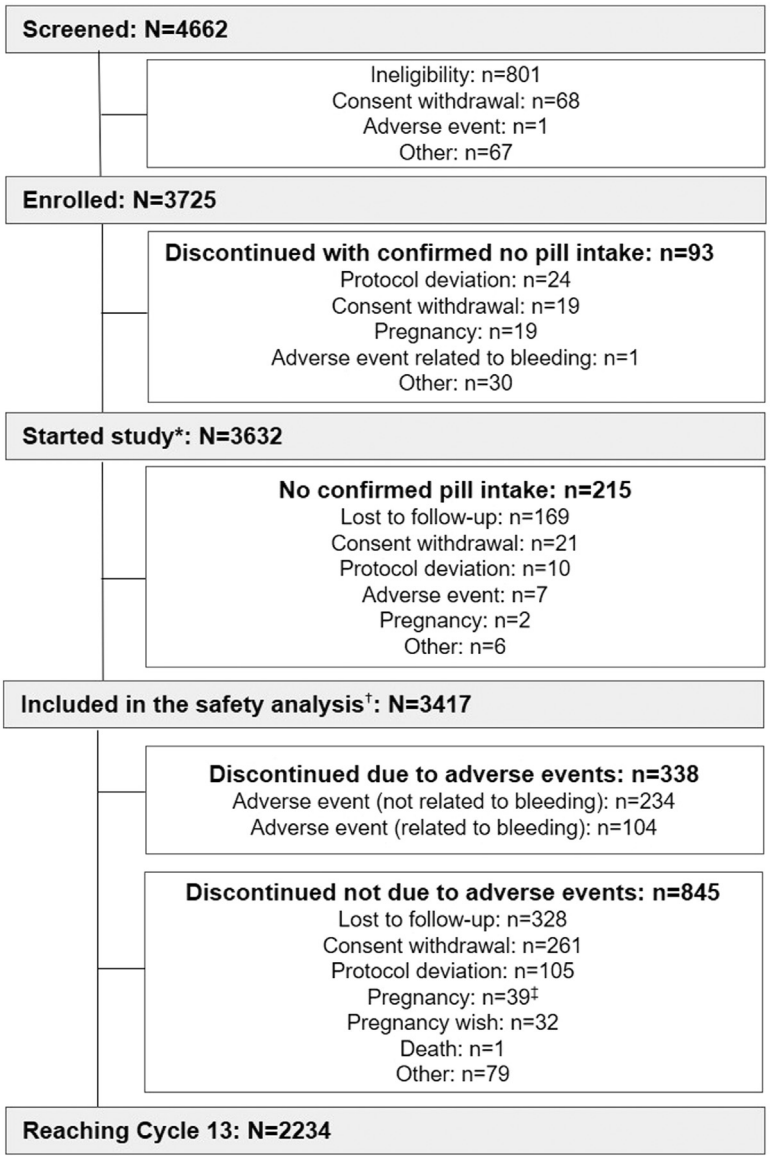

Fig. 1. Disposition of participants in the pooled phase 3 studies of estetrol/drospirenone oral contraception for up to 13 cycles (12 months). * Received study drug †Pooled safety population=participants who received at least one dose of estetrol 15 mg/drospirenone 3 mg and had at least one follow-up visit/call. ‡ This category includes participants with a confirmed pregnancy (pre-treatment, on-treatment and post-treatment) listed as their primary reason for discontinuation.

3.2.2. Serious adverse events

Thirty-eight (1.1%) participants experienced an SAE, of which 6 (0.2%) discontinued the study related to the event. Investigators assessed 3 (0.1%) as treatment-related: one hospitalization for worsening of depression (no discontinuation of study drug), one ectopic pregnancy, and one lower extremity VTE. The VTE event resolved without sequelae after anticoagulant treatment. One death occurred, related to a self-administered fentanyl and alprazolam overdose, which the investigator assessed as unlikely related to the study drug.

3.3. Body weight, vital signs and laboratory parameters

We did not observe clinically significant changes from baseline in mean values of SBP, DBP, and heart rate during treatment (Cycle 7 and Cycle 13) and measured changes in body weight from baseline to end of treatment were minimal (Supplemental Figure 1). Overall, 111 (3.3%) participants had an SBP of ≥140 mmHg and/or a DBP ≥90 mmHg during the treatment period. In addition, 745 (21.8%) participants gained ≥5% of their baseline weight and 483 (14.1%) lost ≥5% of their baseline weight during treatment. Eleven (0.3%) participants experienced hypertension or increased blood pressure as an AE, of which investigators considered 6 (0.2%) to be related to the study drug and two discontinued for the event (Supplemental Table 2).

We also did not observe clinically significant mean changes from baseline in serum lipids, glucose, glycated hemoglobin (HbA1c), and potassium during treatment (Supplemental Figure 1). Investigators reported hyperkalemia/increased blood potassium as an AE in 7 (0.2%) participants (Supplemental Table 2) which included one participant with a value in the normal range (5.2 mmol/L, normal 3.5-5.3 mmol/L); none had any associated symptoms. One participant, with a potassium of 4.4 mmol/L at baseline, had a value of 8.0 mmol/L 18 days after last study drug use. The other 5 participants had potassium values of 5.5 to 6.0 mmol/L, one of whom (6.0 mmol/L) discontinued.

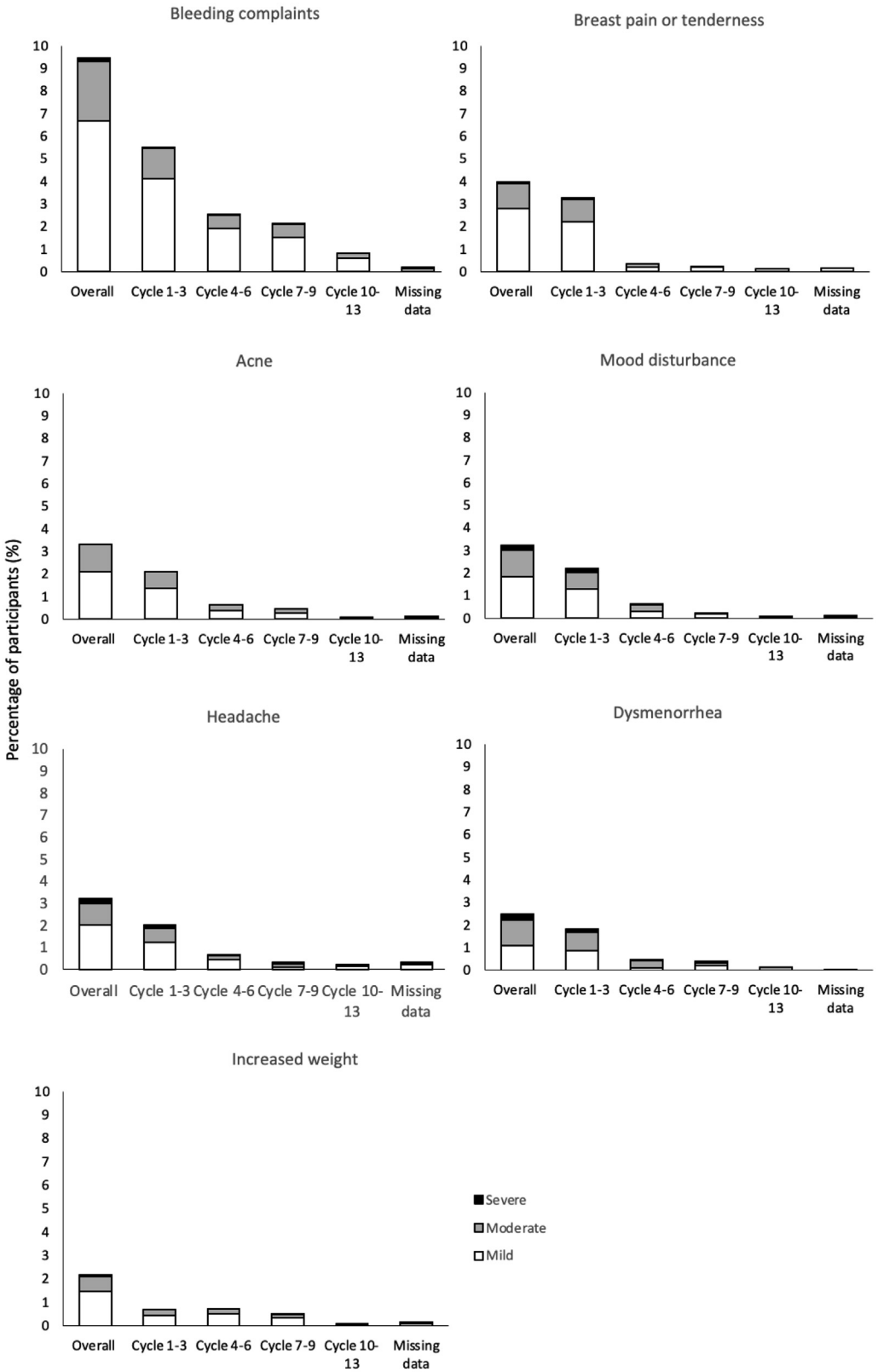

Fig. 2. Most common treatment-related adverse events (≥2%) by severity (overall and by 3-cycles) in participants using estetrol/drospirenone for up to 13 cycles. First bar indicates the overall % of subjects with treatment-related AEs by severity (mild [white]; moderate [grey]; severe [black]), followed by bars indicating the % of participants with treatment-related AEs by 3-cycles (4 cycles for 10-13) and missing data (AEs where we did not have information on the cycle). See Supplemental Table 1 for the MedDRA preferred terms of the groupings.

Table 2
Adverse events reported in the pooled safety population of estetrol/drospirenone users ($N = 3417$).

Event	*n* (%)
Adverse events	
Any AE	1786 (52.3)
AEs by severity[a]	
Mild	924 (27.0)
Moderate	741 (21.7)
Severe	121 (3.5)
AEs by cycle	
Cycle 1-3	1105 (32.3)
Cycle 4-6	621 (18.2)
Cycle 7-9	487 (14.3)
Cycle 10-13	332 (9.7)
Treatment-related adverse events[a]	
Any treatment-related AEs	981 (28.7)
Treatment-related AEs[b] in ≥ 2% of participants	
Bleeding complaints	323 (9.5)
Breast pain or tenderness	136 (4.0)
Acne	113 (3.3)
Mood disturbance	111 (3.2)
Headache	110 (3.2)
Dysmenorrhea	85 (2.5)
Increased weight	74 (2.2)
Any treatment-related AEs leading to premature study discontinuation	272 (8.0)
Treatment-related AEs[b] leading to premature study discontinuation in ≥ 0.5% of participants	
Bleeding complaints	97 (2.8)
Mood disturbance	38 (1.1)
Acne	28 (0.8)
Decreased/loss of libido	21 (0.6)

AE, adverse event.
Data are for participants who received confirmed treatment with estetrol 15 mg/drospirenone 3 mg and had at least one follow-up call/visit.
[a] Severity and relatedness established by site investigator.
[b] See Supplemental Table 1 for the MedDRA preferred terms of the groupings.

Table 3
Proportion of cycles with treatment-related AEs in participants using estetrol/drospirenone for up to 13 cycles ($N = 3417$)[a].

Treatment-related AE[b]	Number of participants (%)	Number of affected cycles	Percentage of affected cycles against total number of cycles[c]
Bleeding complaints	323 (9.5)	1294	3.7
Acne	113 (3.3)	579	1.6
Breast pain or tenderness	136 (4.0)	561	1.6
Increased weight	74 (2.2)	482	1.4
Mood disturbance	111 (3.2)	429	1.2
Headache	110 (3.2)	388	1.1
Dysmenorrhea	85 (2.5)	337	1.0
Decreased/loss of libido	62 (1.8)	299	0.9

AE, adverse event.
[a] Includes AEs with a percentage of affected cycles ≥0.5%.
[b] See Supplemental Table 1 for the MedDRA preferred terms of the groupings.
[c] Calculated as the ratio between the number of cycles affected by the treatment-related AE and the total number of cycles for all the patients (35,093 cycles); for example, for bleeding complaints 1294/35,093=3.7%.

4. Discussion

We demonstrated that most E4/DRSP users experienced high tolerability with a favorable safety profile based on the combined data from two pivotal phase 3 trials involving 3417 participants with 35,093 cycles of exposure. Regulatory agencies pooled safety data for safety considerations during drug approval. We grouped similar AEs to provide more clinically meaningful information for healthcare professionals and COC users. Overall, about 29% of participants reported AEs assessed by investigators as treatment-related, the most common of which were typical of those self-reported for other COCs including bleeding complaints, breast pain or tenderness, acne, mood disturbance, headache, dysmenorrhea, and increased weight [6,28]. Increased potassium, a potential consequence of the weak potassium-sparing diuretic effect of DRSP, occurred uncommonly; this finding was reported in 7 (0.2%) asymptomatic participants.

The background annual VTE incidence for EE-containing COC users is 5 to 10/10,000 woman-years [29,30]. In our pooled analysis, a single participant with no known baseline risk factors experienced a lower extremity VTE. The overall estimated annual VTE incidence rate across the full E4/DRSP clinical program (pooled phase 2 and 3 trials) is 3.66/10,000 woman-years [31]. The risk of VTE is considered highest in the first 12 months of using a new COC [32], with multiple studies reporting a small increased risk in new users compared to switchers [32–34], perhaps because switchers have already demonstrated a lower risk for VTE [34]. A similar increased risk has also been observed in those re-starting a COC after an absence [35]. While nearly half of the participants in this pooled analysis were starters, that is, past contraceptive use >3 months before initiating study drug or no prior use, only 19% of participants were true new users. A study with a larger population of true new users may have different results, although the low proportion of true new users our studies are in-line with other phase 3 COC trials [36,37]. Because VTE is rare with COC use, a population-based post-marketing study is needed to confirm VTE risk with the E4/DRSP formulation.

We found no clinically relevant changes with E4/DRSP use in parameters that indicate cardiovascular risk including blood pressure, heart rate, lipids, glucose, HbA1c, and potassium. Clinical studies have consistently demonstrated that E4 has a limited effect on lipids, hemostasis, and carbohydrate metabolism [20,22,24,38]. However, these trials of E4/DRSP use excluded participants with major cardiovascular risk factors in accordance with WHO eligibility criteria for COCs [27]. Until further data are available, the contraindications related to cardiovascular risk should remain the same as other COCs [39,40].

A strength of this analysis is that we used pooled data from the two pivotal trials, allowing an evaluation of the risks and benefits of E4/DRSP in a large number of participants. Pooling data allowed for a robust assessment of tolerability and safety, including relatively infrequent events. In addition, the trials, conducted in North America, Europe, and Russia, included participants with a range of different demographic factors. However, some limitations are worth noting. Most participants were white (82.9%), and only 15% were obese. Therefore, the results of the pooled analysis may not be generalizable to populations with different characteristics. Furthermore, as is standard for pivotal contraceptive regulatory trials, the study did not include a comparator contraceptive, and therefore we cannot provide any direct comparison with other COCs or methods.

In conclusion, this pooled analysis adds to the body of evidence supporting E4 in combination with DRSP as a COC with a favorable tolerability and safety profile. Post-marketing surveillance studies will provide additional data to evaluate the long-term safety of the E4/DRSP COC.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.contraception.2022.10.004.

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