



Original Research Article

Estetrol-drospirenone combination oral contraceptive: North American phase 3 efficacy and safety results[☆]



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ABSTRACT

Objective: To assess efficacy, cycle control, and safety of an oral contraceptive containing estetrol (E4) 15 mg and drospirenone (DRSP) 3 mg.

Study design: Women aged 16 to 50 years with a body mass index ≤ 35 kg/m² enrolled in this multicenter, open-label, 13-cycle, phase 3 trial evaluating E4/DRSP in a 24-active/4-placebo regimen. Follow-up was scheduled at Cycles 2, 4, 7, and 10 and within 3 weeks of completing Cycle 13. Participants used daily diaries to record pill use and vaginal bleeding. We evaluated efficacy outcomes in women 16 to 35 years and bleeding patterns and safety (adverse events [AEs]) in all participants. We assessed overall and method-failure pregnancy rates using the Pearl index (PI) and life-table analysis. Scheduled bleeding included spotting or bleeding starting during the 4-day placebo period or first 3 days of the next cycle.

Results: We enrolled 1864 women of whom 1674 were 16 to 35 years. Women 16 to 35 years had a PI of 2.65 (95% CI 1.73–3.88), method-failure PI of 1.43 (95% CI 0.7–2.39) and 13-cycle life-table pregnancy rate of 2.1%. Scheduled bleeding occurred in 82.9% to 87.0% of women per cycle; median duration was 4.5 days. Unscheduled bleeding decreased from 30.3% in Cycle 1 to 21.3% to 22.1% during Cycles 2 to 4 and remained stable (15.5% to 19.2%) thereafter. The most frequently reported AEs were headache (5.0%) and metrorrhagia (4.6%). One-hundred thirty-two (7.1%) women discontinued the study early for an AE, most commonly for metrorrhagia (0.9%) and menorrhagia (0.8%). No thromboembolic events occurred.

Conclusion: E4/DRSP is an effective oral contraceptive with a predictable bleeding pattern for most women and low AE rates.

Implications statement: A new oral contraceptive with a novel estrogen, estetrol, combined with drospirenone has efficacy and safety within the range of other available oral contraceptives. Large phase 4 studies will be needed to confirm if this combination is associated with an improved adverse event profile or lower thrombosis risk.

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1. Introduction

Ethinyl estradiol (EE) has been the primary estrogen used in combined oral contraceptives (COC) since the 1960s, primarily because of its high oral bioavailability, long half-life, and high potency, which allows small doses to be effective. However, EE affects the vascular endothelium as well as liver protein synthesis

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related to coagulation, fibrinolysis, and blood pressure, resulting in a small increased risk of cardiovascular complications [1,2]. Scientists have lowered the EE dose in COCs over time to minimize side effects and morbidity, specifically thromboembolism. However, evidence that EE doses ≤ 30 mcg formulated with levonorgestrel or desogestrel further lower thromboembolic risk is inconsistent [3]. For many estrogen/progestin combinations, lower EE doses result in less favorable bleeding patterns [4,5], an important undesired effect since one of the most common reasons combined oral contraceptive users discontinue is bleeding complaints [6,7].

Estetrol (E4) is a natural estrogen produced exclusively by the human fetal liver [8]; the E4 used clinically is manufactured from plant sources. Unlike other natural estrogens, it exhibits mixed agonist and antagonist activities, with a mode of action distinct from selective estrogen receptor modulators [9–12]. E4 has a low impact on hemostasis biomarkers, triglycerides, and breast tissue [13–15]. Phase 2 clinical development evaluated several E4 doses in combination with levonorgestrel or drospirenone (DRSP) [14–17], and selected E4 15 mg/DRSP 3 mg for further development based on low rates of unscheduled bleeding, excellent ovulation suppression, limited impact on triglycerides and surrogate hemostasis markers, and no safety signals [17–19].

Two phase 3 clinical studies (E4Freedom) evaluated E4/DRSP contraceptive efficacy and safety in Europe/Russia and in United States/Canada. Herein, we present the United States/Canada results.

2. Materials and methods

This multicenter, open-label, phase 3 study enrolled healthy women from August 2016 through November 2018 at 70 centers in the United States and 7 centers in Canada (online Appendix 1). The study team designed the trial in accordance with US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines [20,21], and Kapp's recommendations [22] for phase 3 trials; we conducted the study based on the Declaration of Helsinki and Good Clinical Practice guidelines [23,24]. Central and local Institutional Review Boards approved the trial. All participants signed a written informed consent before study entry. Estetra SRL (subsidiary of Mithra Pharmaceuticals), sponsored and designed the study and oversaw its conduct, including funding the trial. Participants received the study treatment free of charge.

The study product, E4/DRSP, was manufactured by Haupt Pharma, Münster, Germany, and packaged in blister packs each containing 24 E4 15 mg/DRSP 3 mg tablets and 4 placebo tablets.

Investigators enrolled heterosexually active women, aged 16 to 50 years inclusive with a body mass index (BMI) ≤ 35.0 kg/m², a history of regular menstrual cycles (21–35 days) when not using hormonal contraception, and no use of medications or supplements that increase liver metabolism. Women agreed to use E4/DRSP as the only method of contraception for up to thirteen 28-day cycles (12 months). The protocol allowed switching from a hormonal contraceptive to the study drug except for 3-month injectable contraception users who received an injection within 10 months prior to screening. We used World Health Organization (WHO) exclusion criteria for COC use [25]; these included history of thromboembolic, cardiovascular or cerebrovascular disorder, or hypertension defined as systolic and diastolic blood pressure of ≥ 140 mm Hg and ≥ 90 mm Hg, and smoking nicotine-containing products for women ≥ 35 years.

After screening, eligible participants underwent an enrollment visit prior to onset of their next menses, and received a supply of study drug, urine pregnancy tests, and paper study diaries. Study staff instructed participants to perform a pregnancy test on the first day of menses, start study drug if the test was negative, and then take one study pill daily. Study staff scheduled follow-up visits at Cycles 2, 4, 7, and 10, and within 3 weeks of completing Cycle

13. Participants used the daily diary to record study drug intake, sexual activity, other contraceptive methods used, and all vaginal spotting/bleeding events. Staff instructed participants to perform a urine pregnancy test during any cycles without bleeding within 7 days of the last active tablet. At each visit, staff reviewed the diaries, collected used blister packs, dispensed new drug as needed, and asked participants about changes in medical conditions, medication use, and complaints/adverse events. Investigators collected blood for hematology, serum chemistry, and lipid profile testing at screening, Cycle 7, and study exit, and performed complete physical examinations at screening and study exit.

The study planned an enrollment of 2000 (with 1800 participants aged 16 to 35 years) to meet FDA-approval requirements with the assumption that 80% of the cycles would be at-risk, a dropout rate of 45%, and a Pearl index (PI) of 1.0. Poisson modeling of the confidence intervals around the expected PI demonstrated a requirement for at least 12,337 at-risk cycles to assure a 90% probability that the upper 95% confidence limit would not exceed the estimated PI by more than one-point. Efficacy calculations included women aged 16 to 35 years at screening; other analyses included all enrolled participants.

The primary contraceptive efficacy outcome was the 13-cycle PI (number of pregnancies per 100 woman-years of exposure) for women aged 16 to 35 years at screening computed for at-risk cycles; at-risk meant the participant self-reported using study drug, having intercourse at least once in that cycle, and using no other contraceptive methods (including condoms and emergency contraception). Any reported or confirmed pregnancy was 'on-treatment' when the estimated date of conception was ≤ 7 days after last E4/DRSP intake (FDA definition). Secondary efficacy end points included the method-failure PI and cumulative pregnancy rate of on-treatment and method-failure pregnancies through 13 cycles using life-table analysis (Kaplan-Meier estimates and 95% CIs). We evaluated PIs by age, BMI (<30 and ≥ 30 kg/m²), race, gravidity, prior hormonal contraceptive use, smoking status, and compliance using Cox regression models to assess confounding by these variables. The protocol defined a pregnancy as a 'method failure' when it occurred with reported correct E4/DRSP intake and no use of excluded medications or supplements. We defined "starters" as participants who had not used hormonal contraception within 3 months prior to E4/DRSP initiation, while "switchers" had used hormonal contraceptives within 3 months preceding study drug initiation. New users (a subset of starters) had never used hormonal contraception. We used diary entries per 28-day cycle to estimate study drug compliance; we assumed no pill intake on days with missing diary data. We defined treatment compliance as the reported number of pills taken divided by the number of pills expected to have been taken, high compliance as $\geq 99\%$ of expected pills, and low compliance as $<99\%$ of expected pills.

We assessed bleeding patterns based on criteria described by Mishell et al. [26] (online Appendix 2). We considered cycles evaluable for bleeding outcomes if the participant missed fewer than 4 active pills and never missed consecutive days of active pills during the cycle. "Scheduled bleeding" occurred between Day 25 of the current cycle and Day 3 of the next cycle. We included early-onset bleeding/spotting that continued into the scheduled period and bleeding/spotting that continued after Day 3 as scheduled bleeding and/or spotting. We could not report Cycle 13 bleeding data because participant diaries did not include Days 1 to 3 after completion of the cycle. We imputed missing bleeding diary data based on the reported information from the day preceding for 1 or 2 missing days; for 3 or more missing days, we used the heaviest flow (if any) on the days bordering the missing days.

Safety analyses included all enrolled participants who received at least one dose of study medication. The evaluation of frequency and nature of adverse events (AEs) included clinically rel-

Table 1

Characteristics of participants in a North American phase 3 study of estetrol/drospirenone oral contraception for up to 13 cycles (12 months).

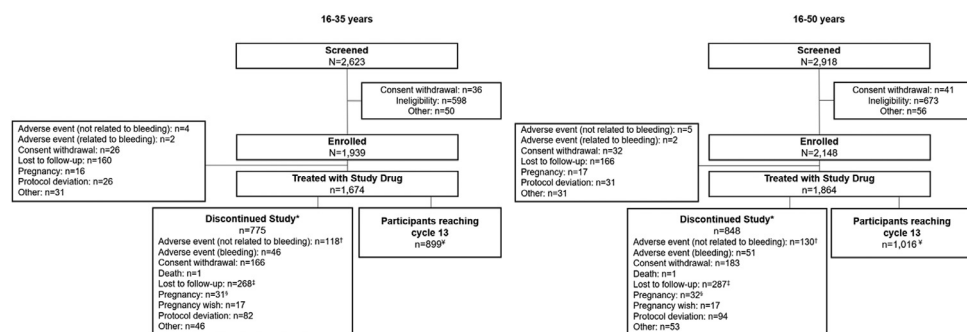
	16–35 years <i>n</i> = 1674	36–50 years <i>n</i> = 190	16–50 years <i>n</i> = 1864
Age (years)	25.8 ± 4.8	40.6 ± 3.9	27.3 ± 6.5
16–25	839 (50.1)		839 (45.0)
26–35	835 (49.9)		835 (44.8)
36–50		190 (100)	190 (10.2)
Body mass index (kg/m²)	25.8 ± 4.7	27.0 ± 4.4	25.9 ± 4.7
≥30.0	376 (22.5)	56 (29.5)	432 (23.2)
Race			
White	1174 (70.1)	126 (66.3)	1300 (69.7)
Black/African American	326 (19.5)	43 (22.6)	369 (19.8)
Asian	81 (4.8)	6 (3.2)	87 (4.7)
Other	93 (5.5)	15 (7.9)	108 (5.8)
Ethnicity			
Hispanic or Latina	429 (25.6)	59 (31.1)	488 (26.2)
Gravidity/parity			
Nulligravid	983 (58.7)	26 (13.7)	1009 (54.1)
Nulliparous	1134 (67.7)	42 (22.1)	1176 (63.1)
Past hormonal contraceptive use[†]			
Within 3 months before screening (switchers)	701 (41.9)	84 (44.2)	785 (42.1)
Past use, >3 months before screening	683 (40.8)	92 (48.4)	775 (41.6)
None	290 (17.3)	14 (7.3)	304 (16.3)
Smoking status			
Current smoker	222 (13.3)	0*	222 (11.9)
Former smoker	189 (11.3)	32 (16.8)	221 (11.9)
Never smoker	1263 (75.4)	158 (83.2)	1421 (76.2)
Country			
United States	1531 (91.5)	181 (95.3)	1712 (91.9)
Canada	143 (8.5)	9 (4.7)	152 (8.1)

Data are presented as *n* (%), mean ± standard deviation, or median (range).

16 to 35 years group included in the efficacy analyses and all participants (16 to 50 years) are included in all bleeding and safety assessments.

* Current smoking was an exclusion criterion for participants aged ≥35 years.

† Past use >3 months and no past use equals “starters” group.

**Fig. 1.** Disposition of participants in a phase 3 study of estetrol/drospirenone oral contraception for up to 13 cycles (12 months).

Years represents age at screening. *Primary reason for discontinuation from investigator. †Includes 2 on-treatment pregnancies in 16 to 35 years group and 1 on-treatment pregnancy in 36 to 50 years group. ‡Includes 1 subject with on-treatment pregnancy in 16 to 35 years group. §Includes 4 pretreatment, 22 on-treatment, and 5 post-treatment pregnancies in 16 to 35 years group and 1 on-treatment pregnancy in 36 to 50 years group. ¶Includes 1 on-treatment pregnancy in 16 to 35 years group.

event changes or abnormalities in routine laboratory parameters or physical examination findings. Study-site investigators assessed AE severity and any relationship to study drug. We classified AEs using version 20.0 of the Medical Dictionary for Regulatory Activities system organ classifications and preferred terms, and summarized events by system organ class and referred term. We performed statistical analyses using SAS software (version 9.4) for Windows.

3. Results

Investigators screened 2918 and enrolled 2148 participants, of whom 1864 started study drug (Fig. 1). Of those aged 16 to 35 years who received E4/DSRP 899/1674 (53.7%) completed 13 cycles. The most common reason for discontinuation among en-

rolled participants was loss to follow-up ($n = 428/1939$, [22.1%]). Table 1 presents participant characteristics. The mean reported treatment compliance was 98.7%; participants who reported missing none, 1, 2, or >2 pills across all cycles was 82.0%, 9.1%, 3.6%, and 5.3%, respectively.

The PI in women aged 16 to 35 years, was 2.65 (95% CI 1.73–3.88) based on 26 on-treatment pregnancies in 1524 women who reported 12,763 at-risk cycles. All pregnancies occurred in US women; 11 related to poor pill compliance, one followed use of a contraindicated supplement (St. John's Wort), and we considered 14 to be method failures. Twenty-five pregnancies occurred during pill use and one occurred after discontinuing study drug (conception estimated 5 days after last study drug intake, 9 days after last hormonal pill intake). The method-failure PI was 1.43 (95% CI 0.78–2.39). Cumulative 13-cycle life-table pregnancy rates were

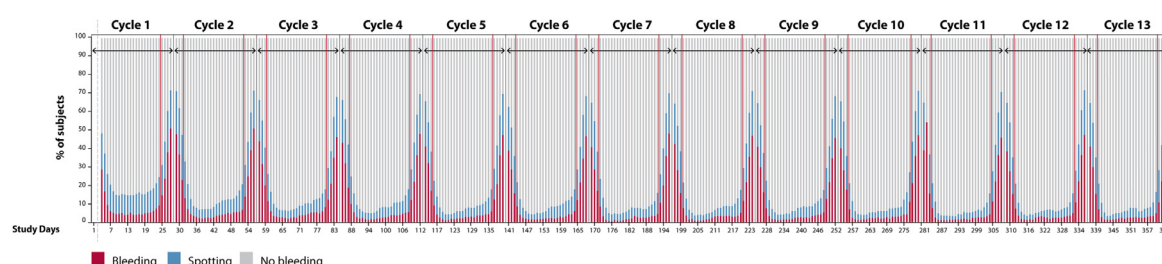
Table 2

Contraceptive efficacy by participant characteristic in a North American phase 3 study with etestrol/drospirenone oral contraceptive use* for up to 13 cycles (12 months).

	Number of participants	Number of 'at risk' cycles	Number of pregnancies	Pearl index (95% CI)	Adjusted Hazard Ratio [†] (95% CI)
Age					
16–25 years	748	5936	14	3.07 (1.68–5.14)	2.41 (1.05–5.54)
26–35 years	776	6827	12	2.29 (1.18–3.99)	Referent
BMI					
<30 kg/m ²	1187	10,113	20	2.57 (1.57–3.97)	1.18 (0.46–3.02)
≥30 kg/m ²	337	2650	6	2.94 (1.08–6.41)	Referent
Race¹					
White	1090	9570	13	1.77 (0.94–3.02)	Referent
Black	278	1911	10	6.80 (3.26–12.51)	3.14 (1.32–7.45)
Gravidity					
0	882	7679	8	1.35 (0.58–2.67)	Referent
≥1	642	5084	18	4.60 (2.72–7.27)	4.15 (1.65–10.46)
Prior HC use					
Switchers ²	656	6093	10	2.13 (1.02–3.92)	Referent
Starters ³	868	6670	16	3.12 (1.78–5.06)	1.06 (0.47–2.37)
Cigarette smoker					
Yes	198	1552	5	4.19 (1.36–9.77)	1.37 (0.49–3.81)
No	1326	11,211	21	2.44 (1.51–3.72)	Referent
Compliance⁴					
High	1160	10,046	13	1.68 (0.90–2.88)	Referent
Low	364	2717	13	6.22 (3.31–10.64)	3.17 (1.45–6.93)

BMI, body mass index; HC, hormonal contraception.

* Includes all enrolled participants 16 to 35 years old who received at least one dose of study treatment, and had at least one cycle in the denominator.

[†] Adjusted for all factors in the table using Cox regression analysis.¹ No differences comparing white to all non-white races; other races not included as numbers relatively small for comparison.² Switchers: use within 3 months before screening.³ Starters: use >3 months before screening or no prior use.⁴ High: ≥99% expected pills taken over all cycles; Low: <99% expected pills taken over all cycles.**Fig. 2.** Percentage of participants reporting bleeding and/or spotting by study day in women using etestrol/drospirenone oral contraceptive for up to 13 cycles*.

*Cycle 13 data are not reported because the last 3 days of the scheduled bleeding period of Cycle 13 (i.e., Days 1–3 after completion of the cycle) were not collected in the participants' diaries. Bleeding and spotting defined as per Mishell et al. (online Appendix 2) [26]. Calculations per cycle are based on the number of participants starting each cycle.

2.06% (95% CI 1.40–3.04%) overall and 1.18% (95% CI 0.69–2.01%) for method-failure pregnancies.

Table 2 reports univariate and multivariable assessments of pregnancy rates by age, BMI, race, gravidity, prior hormonal contraceptive use, smoking status, and compliance, demonstrating significant associations of efficacy with gravidity, compliance, race, and age. When we removed compliance from the model, the same outcomes remained significant (data not shown).

Bleeding and spotting showed a clear cyclic pattern (Fig. 2). Scheduled bleeding and/or spotting days remained stable throughout the study with a median duration of 4 to 5 days, consisting of a median of 2 days of spotting throughout and 3 days of bleeding from Cycles 1 to 8 and 2 days by Cycle 9. Absence of scheduled bleeding occurred in 13.1% of users in Cycle 1, peaked at 18.0% (Cycle 3), and declined to 13.3% by Cycle 12 (Fig. 3). The percentage of women with unscheduled bleeding and/or spotting episodes decreased from 30.3% in Cycle 1 to 21.3% to 22.1% during Cycles 2 to 4 and remained stable (15% to 20%) from Cycle 5 onward (Fig. 4). The number of unscheduled bleeding and/or spotting days remained stable throughout the study, with a median duration of 4 days among those women reporting unscheduled bleeding/spotting. Most unscheduled bleeding/spotting episodes con-

sisted of spotting only (55.2%), 6.8% bleeding only, and 38.1% both bleeding and spotting. The percentage with no scheduled or unscheduled bleeding and/or spotting was 7.7% at Cycle 1 and remained 10% or less per cycle throughout the study.

One thousand two (53.8%) women reported 2585 AEs, and 539 (28.9%) women reported 1017 AEs considered study-drug related. Table 3 reports the most common of these events, including those reported as a reason for early study discontinuation by 132 (7.1%) participants. The most common treatment-related AEs leading to premature discontinuation were metrorrhagia (0.9%), menorrhagia (0.8%), vaginal hemorrhage (0.5%), and increased weight (0.5%). At study completion, the mean change in BMI from baseline was 0.4 ± 1.7 kg/m². Of note, 2 (0.1%) participants had clinically significant elevated potassium levels (normal 3.5–5.0 nmol/L), 1 at Cycle 10 (6.0 nmol/L) and 1 post-Cycle 13 (6.3 nmol/L); neither participant experienced any clinical sequelae. Twenty-five (1.3%) participants experienced 30 SAEs, of which investigators considered 2 as treatment-related: 1 hospitalization for depression not leading to discontinuation and 1 ectopic pregnancy. One death unlikely related to the study drug occurred, involving a prescription drug overdose. No cases of venous thromboembolism (VTE) occurred.

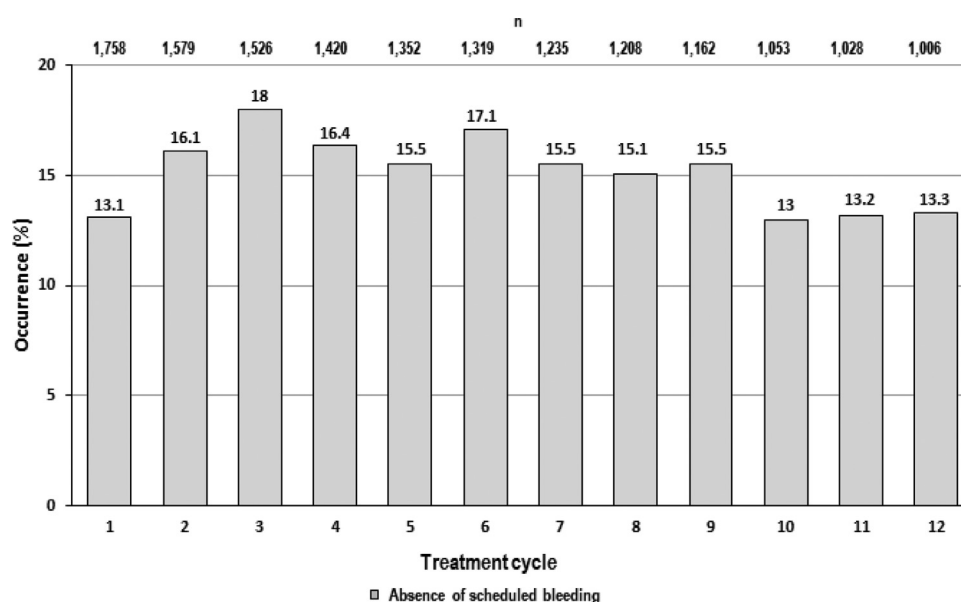


Fig. 3. Percentage of participants with the absence of scheduled bleeding per cycle in women using estetrol/drospirenone oral contraceptive for up to 13 cycles*. The number of cycles at the top represents the number of participants starting each cycle. *Cycle 13 data are not reported here since the last 3 days of scheduled bleeding in Cycle 13 (i.e., Days 1–3 after completion of the cycle) were not collected in the participants' diaries.

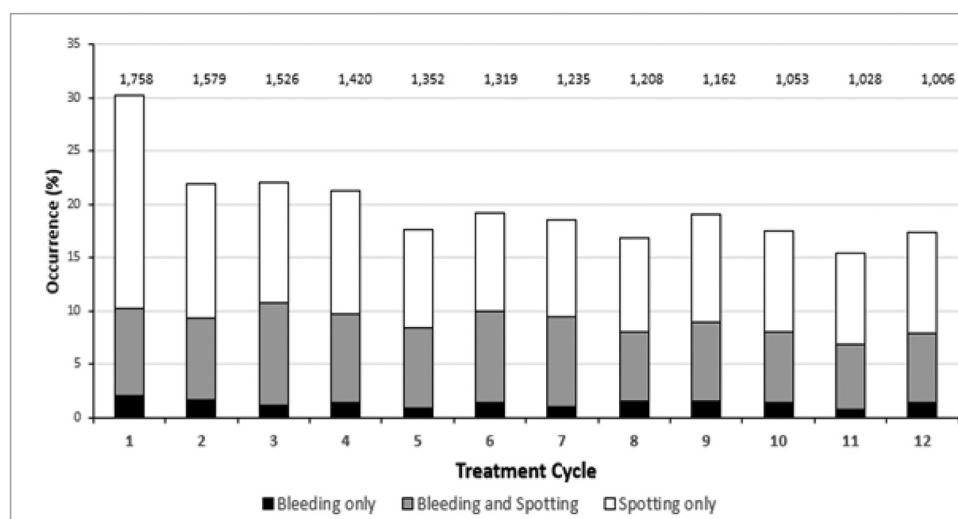


Fig. 4. Percentage of participants with unscheduled bleeding and/or spotting per cycle in women using estetrol/drospirenone oral contraceptive for up to 13 cycles*. The number of cycles at the top represents the number of participants starting each cycle. *Cycle 13 data are not reported here since the last 3 days of scheduled bleeding in Cycle 13 (i.e., Days 1–3 after completion of the cycle) were not collected in the participants' diaries.

4. Discussion

The PI for E4/DRSP of 2.65 (95% CI 1.73–3.88) demonstrates the efficacy of this combined oral contraceptive in US and Canadian women and is similar to reported PI for other contemporary combined-estrogen-progestin oral contraceptives. An ultra-low-dose combined oral contraceptive (EE 10 mcg/norethindrone acetate 1 mg), also with 24 days of estrogen-progestin, reported a PI of 2.6 (95% CI 1.6–3.8) with a discontinuation rate of 41.7%, comparable to the present study [4]. Similarly, a pooled analysis of 2 studies evaluating a contraceptive vaginal system delivering EE 13 mcg and segesterone acetate 150 mcg per day (21/7 design, 13 cycles) had an overall PI of 2.98 (95% CI 2.13–4.06) [27]. Trussell and Portman [28] described 'the Creeping Pearl' in 2013, discussing higher PIs in recent as compared to older hormonal contraception trials. They considered use of more frequent and more sensitive pregnancy testing combined with less adherent study participants

compared to those in older studies as the 2 most likely important contributors to the PI increase.

We found gravidity, compliance, race, and age were independent risk factors for pregnancy in this predominantly US population. Compliance is the only potentially modifiable risk factor. While older studies have suggested an association of obesity with higher oral contraceptive failure rates [29,30], we did not find this association with the E4/DRSP combination. Some progestins, including levonorgestrel, have a weight-dependent distribution, which could potentially account for this difference [31,32]. We presume the association between race and efficacy indicates that race is a marker for other unmeasured factors (e.g., socioeconomic and other social factors, or genetic variants affecting hormone metabolism) [33–35].

Most women experienced scheduled withdrawal bleeding; approximately 15% of users per cycle experienced unscheduled bleeding/spotting, although most was spotting alone. Very few (<1%)

Table 3

Adverse events* in a phase 3 study of estetrol/drospirenone oral contraceptive use for up to 13 cycles (12 months).

Adverse Event	E4 15 mg/ DRSP 3 mg N=1864
Any adverse event	
Headache	94 (5.0)
Metrorrhagia	86 (4.6)
Dysmenorrhea	66 (3.5)
Nausea	70 (3.8)
Acne	63 (3.4)
Urinary tract infection	64 (3.4)
Weight increased	62 (3.3)
Upper respiratory tract infection	62 (3.3)
Viral upper respiratory tract infection	61 (3.3)
Breast tenderness	54 (2.9)
Bacterial vaginosis	45 (2.4)
Anxiety	45 (2.4)
Fatigue	42 (2.3)
Vaginal hemorrhage	41 (2.2)
Menorrhagia	39 (2.1)
Abdominal pain	39 (2.1)
Mood swings	38 (2.0)
Related adverse event†	
Metrorrhagia	82 (4.4)
Headache	65 (3.5)
Acne	53 (2.8)
Dysmenorrhea	52 (2.8)
Breast tenderness	51 (2.7)
Weight increased	46 (2.5)
Nausea	40 (2.1)
Adverse event leading to discontinuation	
Metrorrhagia	16 (0.9)
Menorrhagia	14 (0.8)
Vaginal hemorrhage	10 (0.5)
Weight increased	9 (0.5)

Data presented as n (%).

Safety population: all enrolled participants who received at least one dose of study treatment.

DRSP = drospirenone; E4 = estetrol.

* Reported by 2% or more of participants for adverse events, 0.5% or more for discontinuation.

† Relatedness established by site investigator.

women discontinued due to bleeding between periods. In contrast, the proportion of women reporting unscheduled bleeding/spotting with a new EE/levonorgestrel contraceptive patch was 60% in Cycle 1 and 42% in Cycle 13 [36]. Complete absence of any bleeding (scheduled or unscheduled) with E4/DRSP occurred in 10% or less users per cycle, allowing most women to expect some bleeding. For comparison, no bleeding occurred in 32% of EE 10 mcg/norethindrone acetate 1 mg users in the first cycle, increasing to 49% in Cycle 13 [4].

The clinical safety profile was reassuring in terms of the frequency, nature and severity of AEs. We observed favorable body-weight control (associated with the known antimineralocorticoid activity of DRSP [18]) with a minimal mean BMI change of 0.4 ± 1.7 kg/m². Only 9 (0.5%) women discontinued for weight gain. Elevated potassium, a theoretical concern with DRSP use, occurred in only 2 (0.1%) participants with no clinically relevant issues. Most noticeable was the lack of venous thromboembolic events among the 1864 women who initiated E4/DRSP in this study, of whom 23% had a BMI >30.0, a risk factor for VTE [37]. In comparison, among 1683 US women in the phase 3 trial of EE 10 mcg/norethindrone acetate 1 mg, 18% of whom were obese, 3 (0.2%) thrombotic events occurred [4]. Among 1188 US women in phase 3 studies of a vaginal ring delivering EE 13 mcg and segesterone acetate 150 mcg per day, 4 (0.3%) thrombotic events occurred [38]. Most recently, a US phase 3 study with 2031 women, 35% of whom were obese, who used a new contraceptive patch with dosing equivalent to an EE 30 mcg/levonorgestrel 120 mcg oral contraceptive, 4 (0.2%) thrombotic events occurred (all in

obese women) [36]. Thus, even with low-dose EE short-acting combination contraceptives, thrombosis risk is still elevated substantially. Large phase 4 studies will be needed to confirm the phase 3 findings that suggest E4/DRSP use is associated with low clinical thrombosis risk. Interestingly, these findings correlate with phase 2 data demonstrating smaller or similar changes in hemostatic parameters after 6 treatment cycles with E4/DRSP as compared to EE/DRSP and EE/LNG pills [19].

This study included a large proportion of nulligravid, nulliparous, and obese women, and included black participants (19.8%) reflective of the racial demographics in the US population (13.4%) [39]. These features allowed a full evaluation of characteristics associated with efficacy. However, the reasons for the observed association of race and increased pregnancy risk require further evaluation. Although the study population included US and Canadian participants, most participants came from US sites; thus, the overall findings may not reflect Canadian users. As is standard for contraceptive phase 3 studies, this study did not include a comparator; therefore, efficacy and adverse events cannot be viewed as better (or worse) than other products without a randomized trial. Because pregnancy rates were low, the sample was not large enough to fully evaluate all efficacy confounders (Table 2); however, factors associated with pregnancy (gravidity, low compliance, race, and younger age) are important to consider in future analyses of oral contraceptive efficacy.

E4/DRSP (24/4) is an effective oral contraceptive associated with a regular bleeding pattern and low rates of adverse events. This contraceptive represents the first product formulated with the natural estrogen estetrol to be considered for marketing, with approval in April 2021 by the FDA.

Conflict of interest

MDC serves on an Advisory Board for Evofem, Mayne, Merck, and Searchlight and is a consultant for Danco, Estetra SRL (an affiliate company of Mithra Pharmaceuticals [includes support for medical and safety oversight of this study]), Mayne, Medicines360, and Merck. The University of California, Davis, receives contraceptive research funding from Daré, HRA Pharma, Medicines360, Merck, and Sebela. CLW serves on an Advisory Board for Mayne and TherapeuticsMD, is a consultant to HRA Pharma, and serves as a DSMB member for studies evaluating Merck and Bayer products. Columbia University receives research funding for contraceptive research from Medicines360 and Sebela. CB serves on an Advisory Board for Merck Canada, Pfizer, Searchlight, BioSynt Pharma Inc., Estetra SRL (an affiliate company of Mithra Pharmaceuticals), and has received honoraria for medical lectures from Merck Canada, and research grants from Astellas, Estetra SRL (an affiliate company of Mithra Pharmaceuticals), Ipsen, Inovio Pharmaceuticals. MJC has no personal financial disclosures to report. The University of California, Davis, receives contraceptive research funding from Daré, HRA Pharma, Medicines360, Merck, and Sebela. JTJ has received payments for consulting from Abbvie, Cooper Surgical, Bayer Healthcare, Evofem, Mayne Pharma, Merck, Sebela, and TherapeuticsMD. OHSU has received research support from Abbvie, Bayer Healthcare, Daré, Estetra SRL (an affiliate company of Mithra Pharmaceuticals), Medicines360, Merck, and Sebela. These companies and organizations may have a commercial or financial interest in the results of this research and technology. These potential conflicts of interest have been reviewed and managed by OHSU. AMK serves on Advisory Boards for Merck and Mithra Pharmaceuticals. Has served on Advisory Board for Pfizer. The University of Florida College of Medicine receives research funding from Merck and Estetra SRL (an affiliate company of Mithra Pharmaceuticals). SLA has received consulting fees from Mayne Pharma and Merck. Magee-Womens Research Institute receives research funding from Este-

tra SRL (an affiliate company of Mithra Pharmaceuticals), EvoFem, and Merck. J-MF is a member of the board at Mithra Pharmaceuticals and received financial support for the supervision of this study. DFA owns stock or options in Agile Therapeutics and InovaGyn, Inc., and is a consultant for AbbVie, Agile Therapeutics, Exeltis, Mayne Pharma, Mithra Pharmaceuticals, TherapeuticsMD. Eastern Virginia Medical School receives research funding from AbbVie, Bayer Healthcare, Estetra SRL (an affiliate company of Mithra Pharmaceuticals), Myovant, ObsEva, TherapeuticsMD.

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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.2021.05.002](https://doi.org/10.1016/j.contraception.2021.05.002).

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