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Pooled efficacy results of estetrol/drospirenone combined oral contraception phase 3 trials ☆,☆☆

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Data will be made available on request.

ABSTRACT

Objective: To evaluate overall and subgroup efficacy of an estetrol (E4) 15 mg drospirenone (DRSP) 3 mg oral contraceptive in a 24/4-day regimen.

Study design: We pooled efficacy outcomes from 2 pivotal phase 3 contraceptive trials with E4/DRSP conducted in the United States/Canada and Europe/Russia. We assessed Pearl Index (PI; pregnancies per 100 participant-years) and 13-cycle life-table pregnancy rates in at-risk cycles (confirmed intercourse and no other contraceptive use) among participants 16 to 35 years. We calculated PI by age and further subcategorization (contraceptive history and body mass index [BMI]). We performed multivariable analysis using Cox regression to assess impact of potential confounding factors.

Results: Analyses included 3027 participants, of whom 451 (14.9%) had a BMI ≥30 kg/m^2. The pooled PI was 1.52 (95% confidence interval 1.04-2.16) and the 13-cycle life-table pregnancy rate was 1.28% (0.83%–1.73%). We calculated unadjusted pooled PI in participants 16 to 25 years and 26 to 35 years of 1.61 (0.94–2.57) and 1.43 (0.78–2.40), respectively; in new starters and switchers of 1.88 (1.09–3.00) and 1.24 (0.68–2.08), respectively; and by BMI <25 kg/m^2, 25 to 29.9 kg/m^2, and ≥30 kg/m^2 of 1.14 (0.64–1.88), 2.19 (1.05–4.03), and 2.27 (0.83–4.94), respectively. In multivariable analysis, we found associations of prior pregnancy (hazard ratio [HR] 3.61[1.56–8.38]), Black race (HR 4.61[1.97–10.80]), age 16 to 25 years (HR 2.37[1.09–5.15]) and compliance <99% of expected pills (HR 4.21[2.04–8.66]) with conception.

Conclusion: E4/DRSP is an effective oral contraceptive overall and across subgroups stratified by age, contraceptive history, and BMI. Other than compliance, predictors of contraceptive failure are nonmodifiable.

Implications Statement: Pooled results from two phase 3 trials demonstrate high contraceptive efficacy of the novel estetrol-drospirenone oral contraceptive. Several non–modifiable risk factors, including prior pregnancy, race, and age, are associated with higher pregnancy risk. Additional research is needed to better understand predictors of combined oral contraceptive failure.

☆ Conflicts of Interest: JTJ: has received payments for consulting from Bayer Healthcare, Evofem, Mayne Pharma, Merck, Sebela, and TherapeuticsMD. OHSU has received research support from Abbvie, Bayer Healthcare, Daré, Mayne, 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. AK: has served on Advisory Boards for Merck, Mithra Pharmaceuticals and Pfizer. The University of Florida College of Medicine receives research funding from Merck

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1. Introduction

The United States (US) Food and Drug Administration (FDA), the European Medicines Agency (EMA), and Health Canada have all recently approved the first estetrol (E4)-based combined oral contraceptive (COC). E4 is a naturally occurring estrogen produced by the human fetal liver during pregnancy [1] and derived from plant sources for clinical use. E4 distinctly displays selective tissue activity due to agonistic activation in the nucleus and antagonistic action at the membrane estrogen receptor (ER) α [2–7]. Phase 2 clinical trials examining E4 combined with drospirenone (DRSP) found excellent ovulation suppression [8,9], a favorable bleeding pattern [10], and limited impact on endocrine, metabolic, and hemostasis parameters [6,7,11,12].

Two recent phase 3 clinical trials using E4 15 mg/DRSP 3 mg (E4/DRSP), one trial conducted in the US/Canada and one in Europe/Russia, demonstrated high contraceptive efficacy, a predictable bleeding pattern, and a good safety and tolerability profile in daily users [13,14]. In the current analyses, we have pooled results of these two phase 3 trials to analyze the contraceptive efficacy of the entire cohort of participants and to assess if contraceptive efficacy is modified by participant characteristics including age, prior contraceptive use, and body mass index (BMI). Pooled bleeding and safety results from the Phase 3 studies are presented in separate publications.

2. Materials and methods

We performed pooled analyses of data from two multicenter, open-label phase 3 trials to evaluate the contraceptive efficacy of E4/DRSP for up to 13 cycles. These trials enrolled participants from 70 centers in the US and 7 centers in Canada between August 2016 and November 2018, and from 59 centers in Europe and 10 centers in Russia between June 2016 and April 2018. Independent ethics committees or institutional review boards from each center reviewed and approved the study protocols. Investigators conducted the trials in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Participants signed written informed consent prior to study entry.

The studies treated healthy heterosexually active, premenopausal participants (16–50 years US/Canada trial [n=1864]; 18–50 years Europe/Russia trial [n=1553]) according to previously described inclusion and exclusion criteria [13,14], which included an upper BMI limit of 35 kg/m^2. Participants agreed to use E4/DRSP for up to thirteen 28-day cycles (12 months) as their only method of contraception. After providing informed consent and completing screening evaluations, participants received treatment with E4/DRSP (Haupt Pharma, Münster, Germany) packaged in a blister pack of 24 tablets containing E4 15 mg (as monohydrate, equivalent to 14.2 mg anhydrous)/DRSP 3 mg and 4 placebo tablets with instructions to take one tablet daily for up to thirteen 28-day cycles. Investigators instructed participants not currently using hormonal contraception to begin treatment on the first day of their next menses. Investigators instructed those that switched from another combined hormonal contraceptive or progestin-only pill to start treatment on the day that they would have initiated their next pill pack, patch, or ring. Participants performed a urine pregnancy test prior to starting the study drug.

Investigators conducted study follow-up visits at Cycles 2, 4, 7, 10, and at end of treatment (Cycle 13 or discontinuation). Participants completed a daily paper diary to record medication intake, use of other contraceptives (hormonal or barrier methods), and sexual intercourse. During each study visit, a study coordinator reviewed the diary and collected empty study drug packets to check treatment compliance. We considered any day without a diary entry as a day with no pill intake. Participants completed a urine pregnancy test before first pill intake, following any treatment cycle without withdrawal bleeding, and at the end of treatment.

We included all participants who used at least one E4/DRSP pill and had at least one follow–up contact in the analyses. We defined the primary efficacy endpoint as the Pearl Index (PI) in participants 16 to 35 years (at screening) in accordance with regulatory agency age criteria, calculated as the number of pregnancies per 100 woman-years of exposure during at-risk 28-day cycles. We defined any reported/confirmed pregnancy as “on-treatment pregnancy” if the investigator estimated the conception date $\leq$7 days after the last intake of study drug (with E4/DRSP or placebo pill), based on the FDA definition. We considered cycles at–risk if the participant self-reported study drug use in the diary, having intercourse $\geq$1 time in that cycle, and no use of other contraceptive methods. We also evaluated the overall PI using the EMA definition (conception date $\leq$2 days after the last intake of study drug), method-failure PI (pregnancy occurred with self-reported correct E4/DRSP intake and no use of excluded medications known to interact with oral contraceptives), life-table pregnancy rates, and PIs according to subcategories.

We calculated PIs by age group (16–25 years, 26–35 years, 36–50 years), along with further subcategorization by contraceptive history (starters, switchers), BMI class ($<$25 kg/m^2, $\geq$25–29.9 kg/m^2, $\geq$30 kg/m^2), race (Asian, Black, Other, White) and smoking status (former smokers, current smokers, nonsmokers) for age groups 16 to 25 years and 26 to 35 years. Starters included persons who had not used hormonal contraception within three months prior to E4/DRSP initiation (including those who had never used hormonal contraception [referred to as true new users]), while all others were defined as switchers.

For the primary efficacy group 16 to 35 years, we further evaluated PIs by subgroups of age (16–25 years vs 26–35 years), BMI ($\geq$30 kg/m^2 vs $<$30 kg/m^2), contraceptive history (starters vs switchers), gravidity (at least one pregnancy before study vs no pregnancies), smoking status (current or former smoker vs never smoker), race (Asian or Black or Other vs White), region (US/Canada vs Europe/Russia) and compliance (low compliance vs

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Table 1
Demographics of pooled efficacy population in phase 3 studies of estetrol/drospirenone combined oral contraceptive.

	16–25 years (n = 1632)	26–35 years (n = 1395)	Total 16–35 years (n = 3027)
Age (years)	21.8 ± 2.2	29.7 ± 2.8	25.4 ± 4.6
Body mass index	23.8 ± 4.2	25.2 ± 4.6	24.5 ± 4.4
<25.0 kg/m^2	1113 (68.2)	765 (54.8)	1878 (62.0)
25.0 to 29.9 kg/m^2	333 (20.4)	365 (26.2)	698 (23.1)
≥ 30.0 kg/m^2	186 (11.4)	265 (19.0)	451 (14.9)
Gravidity			
Nulligravid	1378 (84.4)	606 (43.4)	1984 (65.6)
History of dysmenorrhea	480 (29.4)	388 (27.8)	868 (28.7)
Past hormonal contraceptive use			
>3 months before initiating study drug (starters)	779 (47.7)	714 (51.2)	1493 (49.3)
None (true new users)	376 (23.0)	245 (17.6)	621 (20.5)
≤3 months before initiating study drug (switchers)	853 (52.3)	681 (48.8)	1534 (50.7)
Race			
Asian	53 (3.2)	37 (2.7)	90 (3.0)
Black	145 (8.9)	189 (13.5)	334 (11.0)
Other[a]	45 (2.8)	50 (3.6)	95 (3.1)
White	1389 (85.1)	1119 (80.2)	2508 (82.9)
Region			
Canada	83 (5.1)	60 (4.3)	143 (4.7)
Europe	680 (41.7)	433 (31.0)	1113 (36.8)
Russia	113 (6.9)	127 (9.1)	240 (7.9)
United States	756 (46.3)	775 (55.6)	1531 (50.6)
Smoking status			
Current smoker	242 (14.8)	226 (16.2)	468 (15.5)
Former smoker	90 (5.5)	153 (11.0)	243 (8.0)
Never smoker	1300 (79.7)	1016 (72.8)	2316 (76.5)

Data presented as mean ± standard deviation or n (%).
[a] Includes American Indian or Alaskan Native, Native Hawaiian or other Pacific Islanders and Other.

high compliance). Treatment compliance was defined as the reported number of pills taken divided by the expected number of pills taken based on the duration of participation, with ≥99% of expected pills defined as high compliance. We also evaluated compliance by subgroups.

We calculated PIs with a 95% confidence interval (CI) assuming an underlying Poisson distribution. We used life-table analysis (Kaplan–Meier estimates and 95% CIs) to calculate the cumulative pregnancy rate of on-treatment and method-failure pregnancies through 13 cycles. To adjust for the effects of confounding on these multiple efficacy comparisons in the primary efficacy group, we performed multivariable analysis using a Cox regression model with hazard ratios (HR) and 95% Wald Confidence Limits to assess confounding by age, BMI, past hormonal contraceptive use, gravidity, smoking status, race, region, and compliance. We used non–parametric tests (Wilcoxon for 2 levels and Kruskal Wallis for more than 2 levels) for subgroup comparisons for self–reported compliance. We performed all statistical analyses using SAS software (version 9.4) for Windows.

Clinical Trial Registrations: ClinicalTrials.gov NCT02817841, NCT02817828.

3. Results

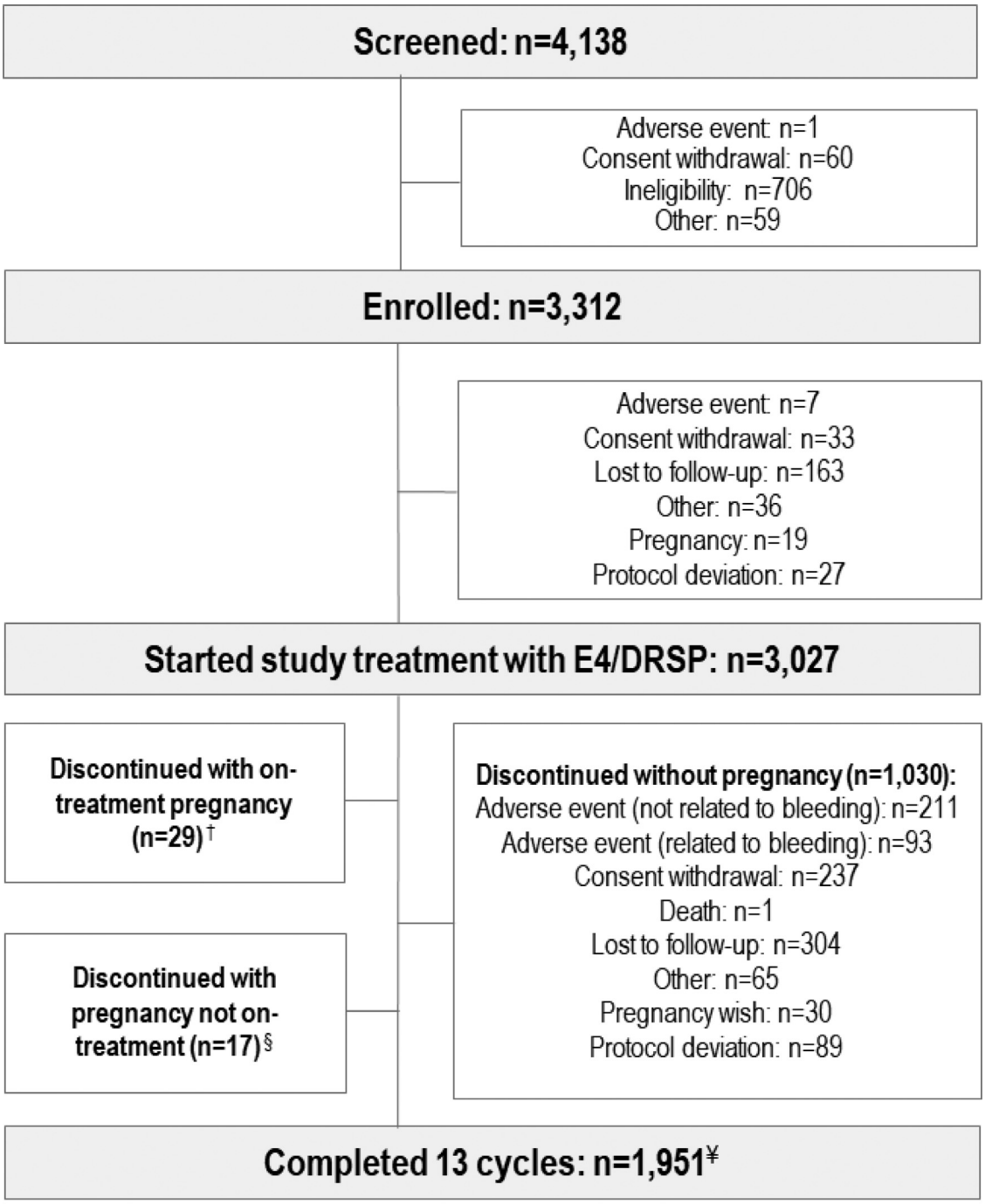
The primary efficacy population included one thousand six hundred seventy-four 16 to 35 year old participants in the US/Canada trial and one hundred three hundred fifty three 18 to 35 year old participants in the Europe/Russia trial. Participant characteristics for the primary efficacy analyses are presented in Table 1 with additional data for participants 36 to 50 years and by study location in Supplemental Tables 1 and 2, respectively. Overall, 2508 (82.9%) participants were white and 1531 (50.6%) were from the United State. About two-thirds (1951 [64.5%]) of participants completed cycle 13. The most common reasons for discontinuation were lost to follow-up (n=306 [10.1%]), consent withdrawal (n=238 [7.9%]), and adverse events not related to bleeding (n=215 [7.1%]) (Fig. 1). Among 16 to 35-year olds, the median self-reported compliance with daily pill intake was 100% (interquartile range [IQR] 99.5%–100%) across all cycles and 100% with the lower IQR >99% for all subgroups.

The pooled PI in the primary efficacy group was 1.52 (95% CI 1.04–2.16) pregnancies per 100 women-years based on 31 pregnancies in 2837 women with 26,455 cycles of use. The method-failure PI was 0.84 (0.49–1.34) pregnancies per 100 women–years. Cumulative 13-cycle life-table pregnancy rates were 1.28% (0.83%–1.73%) overall and 0.73% (0.38%–1.08%) for method-failure pregnancies (Table 2).

The PI was 1.61 (0.94–2.57) pregnancies per 100 women-years in participants 16 to 25 years and 1.43 (0.78–2.40) pregnancies per 100 women-years in those 26 to 35 years (Table 2). Overall, we found no clinically important differences in the unadjusted PIs for the primary efficacy group age categories with further stratification by subgroups (BMI, past hormonal contraceptive use, race, and smoking status; Table 3). The efficacy results from the pooled analyses of participants >35 years at screening are presented in Supplemental Table 3.

In women 16 to 35 years, the corresponding PIs for BMI classes <25 kg/m^2, 25 to 29.9 kg/m^2 and ≥30 kg/m^2, were 1.14 (0.64–1.88), 2.19 (1.05–4.03), and 2.27 (0.83–4.94) pregnancies per 100 women-years, respectively. We observed the highest PI in women 26 to 35 years with a BMI ≥30 kg/m^2 and 3.10 (1.01–7.24) pregnancies per 100 women-years and the lowest PI in those 26 to 35 years with a BMI in the normal range <25 kg/m^2 and 0.71 (0.19–1.83) pregnancies per 100 women-years.

Starters had a PI of 1.88 (1.09–3.00) pregnancies per 100 women-years, and switchers had a PI of 1.24 (0.682.08) pregnancies per 100 women-years. The highest PI was noted for starters aged 16 to 25 years (2.63 [1.36–4.60] pregnancies per 100 women-years) and the lowest PI was seen in switchers 16 to 25 years (0.83 [0.27–1.94] pregnancies per 100 women-years).



† Primary reason for discontinuation from investigator: 2 adverse events (not related to bleeding), 1 subject lost-to follow-up, 26 pregnancies.
§Includes 6 pretreatment (all listed as primary reason for discontinuation) and 11 post-treatment (of which 6 listed as primary reason for discontinuation) pregnancies.
¥Includes 2 on-treatment pregnancies and 2 post-treatment pregnancies .

Fig. 1. Disposition of participants 16 to 35 years enrolled in phase 3 trials of estetrol 15 mg/drospirenone 3 mg.

Table 2
Pearl Index[a] and cumulative pregnancy rate in pooled analysis of E4/DRSP oral contraception for up to 12 months (16–35 years).

Contraceptive efficacy assessments	16–25 years	26–35 years	Total 16–35 years
PI for 'at risk cycles' according to FDA[b]			
Subjects (n)	1518	1319	2837
Cycles (n)	13,759	12,696	26,455
On-treatment pregnancies (n)	17	14	31
PI (95% CI)	1.61 (0.94–2.57)	1.43 (0.78–2.40)	1.52 (1.04–2.16)
PI for 'at risk cycles' according to EMA[c]			
Subjects (n)	1,573	1,362	2935
Cycles (n)	15,013	13,725	28,738
On-treatment pregnancies (n)	17	14	31
PI (95% CI)	1.47 (0.86–2.36)	1.33 (0.72–2.22)	1.40 (0.95–1.99)
Method failure PI for 'at risk cycles' according to FDA[b,d]			
Subjects (n)	1518	1319	2837
Cycles (n)	13,759	12,696	26,455
On–treatment pregnancies (n)	9	8	17
PI (95% CI)	0.85 (0.39–1.61)	0.82 (0.35–1.61)	0.84 (0.49–1.34)
Cumulative pregnancy rate at cycle 13[e]			
Cumulative on-treatment pregnancy rate (% [95% CI])	1.29 (0.80–2.08)	1.26 (0.75–2.13)	1.28 (0.83–1.73)
Cumulative on-treatment method failure pregnancy rate (% [95% CI])	0.69 (0.36–1.34)	0.77 (0.38–1.54)	0.73 (0.38–1.08)

CI: confidence interval; EMA: European Medicines Agency; FDA: Food and Drug Administration; PI: Pearl Index.
[a] Pregnancies per 100 women-years.
[b] At risk cycles FDA: no other methods of birth control (including condoms and emergency contraception), and intercourse confirmed, pregnancy considered 'on-treatment' when estimated date of conception was ≤7 days after last study treatment.
[c] At risk cycles EMA: regardless of intercourse, no other methods of birth control (including condoms and emergency contraception), pregnancy considered 'on-treatment' when estimated conception date was ≤2 days after last study treatment.
[d] Method failure: excluding pregnancies due to user failure, i.e., not taking E4/DRSP as per protocol during the conception cycle, or co–medication use interacting with combined oral contraceptives.
[e] Kaplan-Meier life-table analysis.

In multivariable analysis of markers of efficacy in the primary efficacy group (Table 4), we found clinically important and statistically significant associations of pregnancy risk in women with a history of prior pregnancy (HR: 3.61 [1.56–8.38]), Black race (HR: 4.61 [1.97–10.80]), age 16–25 years (HR: 2.37 [1.09–5.15]), and low compliance (HR: 4.21 [2.04–8.66]).

4. Discussion

The pooled PI for E4/DRSP in 16 to 35 year olds of 1.52 (1.04–2.16) pregnancies per 100 women–years and life–table contraceptive protection of 98.7% demonstrates high contraceptive efficacy over 1 year of use. We found higher PIs in the individual primary efficacy study conducted in the US/Canada (2.65, 95% CI 1.73–3.88) [13] compared with that conducted in Europe/Russia (0.47, 95% CI 0.15–1.11) [14], a phenomenon reported previously [15–17]. Fundamental differences in sexual education and health service provision between US and Europe may explain some of the differences in pregnancy rates [18], as well as other differences in socioeconomic and education status in study participants [15]. In our pooled analysis, we found a significant difference in self-reported compliance between Europe vs US participants.

More recently approved combined hormonal contraceptives tend to have higher PIs than those approved decades earlier. Trussell and Portman [19] coined the term "Creeping Pearl" in a 2013 review of increased rates of contraceptive failures in recent versus older hormonal contraceptive trials. They identified more frequent and sensitive pregnancy testing and less adherent participants as the two most likely important contributors to the increased PI in recent trials.

Our results provide evidence of high contraceptive efficacy across a diverse group of users. Strengths of this pooled analyses include a large number of participants and a diverse population, including women with BMI ≥30 kg/m^2. Although we identified small PI differences within subgroups, all remain in a highly effective range. We did not find an association between obesity and lower efficacy of E4/DRSP in our multivariable analysis. The inclusion of a relatively large proportion (15%) of obese participants supports contraceptive efficacy in this subgroup. Previous studies examining other hormonal contraceptives suggest an association between obesity and oral contraception failure [11,20]. Studies have not clarified whether these differences occur due to progestin-specific pharmacokinetic differences, adherence, or both [11,21].

Multivariable analysis in the primary efficacy group found prior gravidity, Black race, younger age, and low compliance as independent risk factors for pregnancy in this pooled cohort. The lower PI with increasing age likely reflects decreasing fecundity and more consistent pill taking [22]. The association between Black race and efficacy likely reflect other unmeasured variables, such as socioeconomic status and other social factors, or genetic variants affecting hormone metabolism [23–25]. The majority of Black race participants were from the US (98%), suggesting that race itself may not be an independent risk factor but, instead, is reflective of underlying social issues that may include systemic racism within healthcare [26].

Limitations include the open-label noncomparator design common to phase 3 contraceptive efficacy studies. While pooling of results from two large phase 3 trials of the same contraceptive formulation with internal consistency improves confidence in the efficacy findings, direct comparison to other contraceptive formulations require caution. The compliance data comes from participant reported diaries; accordingly, we have no objective means to confirm the accuracy of this self-reported information. Most participants were white (82.9%) and from the United States (50.6%); therefore, all results may not be generalizable. The majority of nonwhite and obese participants were enrolled in US study sites; thus, associations between race and obesity may not be generalizable. The study enrolled participants with an upper BMI limit of 35 kg/m^2, so the findings do not reflect a population with very high BMI.

The E4/DRSP formulations represents the first pharmaceutical compound formulated with the natural estrogen E4 that has been approved for clinical use. In this pooled analysis of two phase 3 clinical trials examining E4/DRSP in a 24/4-day regimen for 1 year of usage, this oral contraceptive showed high contraceptive efficacy

Table 3
Unadjusted Pearl Index[a] by subgroups in pooled analysis of E4/DRSP oral contraception for up to 12 months (16–35 years).

Variable	Statistic	16–25 years	26–35 years	Total 16–35 years
Body mass index				
<25.0 kg/m^2	Subjects, n	1044	727	1771
	Cycles	9809	7275	17,084
	On-treatment pregnancies	11	4	15
	Pearl Index (95% CI)	1.46 (0.73–2.61)	0.71 (0.19–1.83)	1.14 (0.64–1.88)
25.0 to 29.9 kg/m^2	Subjects, n	311	345	656
	Cycles	2610	3325	5935
	On-treatment pregnancies	5	5	10
	Pearl Index (95% CI)	2.49 (0.81–5.81)	1.95 (0.63–4.56)	2.19 (1.05–4.03)
≥30.0 kg/m^2	Subjects, n	163	247	410
	Cycles	1340	2096	3436
	On-treatment pregnancies	1	5	6
	Pearl Index (95% CI)	0.97 (0.025–5.40)	3.10 (1.01–7.24)	2.27 (0.83–4.94)
Past hormonal contraceptive use				
Starters[b]	Subjects, n	704	664	1368
	Cycles	5924	5859	11,783
	On-treatment pregnancies	12	5	17
	Pearl Index (95% CI)	2.63 (1.36–4.60)	1.11 (0.36–2.59)	1.88 (1.09–3.00)
Switchers[c]	Subjects, n	814	655	1469
	Cycles	7835	6837	14,672
	On-treatment pregnancies	5	9	14
	Pearl Index (95% CI)	0.83 (0.27–1.94)	1.71 (0.78–3.25)	1.24 (0.68–2.08)
Race				
Asian	Subjects, n	48	34	82
	Cycles	352	332	684
	On-treatment pregnancies	1	1	2
	Pearl Index (95% CI)	3.69 (0.09–20.58)	3.92 (0.10–21.82)	3.80 (0.46–13.73)
Black	Subjects, n	119	165	284
	Cycles	795	1161	1956
	On-treatment pregnancies	9	3	12
	Pearl Index (95% CI)	14.72 (6.73–27.94)	3.36 (0.69–9.82)	7.98 (4.12–13.93)
Other[d]	Subjects, n	41	44	85
	Cycles	312	380	692
	On-treatment pregnancies	0	1	1
	Pearl Index (95% CI)	0 (0 –15.37)	3.42 (0.09–19.06)	1.88 (0.05–10.47)
White	Subjects, n	1310	1076	2386
	Cycles	12,300	10,823	23,123
	On-treatment pregnancies	7	9	16
	Pearl Index (95% CI)	0.74 (0.30–1.52)	1.08 (0.49–2.05)	0.90 (0.51–1.46)
Smoking status				
Current smoker	Subjects, n	221	215	436
	Cycles	1,991	2,057	4048
	On-treatment pregnancies	3	4	7
	Pearl Index (95% CI)	1.96 (0.40–5.72)	2.53 (0.69–6.47)	2.25 (0.90–4.63)
Former smoker	Subjects, n	83	140	223
	Cycles	660	1,229	1889
	On-treatment pregnancies	2	2	4
	Pearl Index (95% CI)	3.94 (0.48–14.23)	2.12 (0.26–7.64)	2.75 (0.75–7.05)
Never smoker	Subjects, n	1,214	964	2178
	Cycles	11,108	9,410	20,518
	On-treatment pregnancies	12	8	20
	Pearl Index (95% CI)	1.40 (0.73–2.45)	1.10 (0.48–2.18)	1.27 (0.77–1.96)

CI: confidence interval.
[a] Pregnancies per 100 women-years.
[b] Past contraceptive use >3 months before initiating study drug (starters) and none (true new users).
[c] Past contraceptive use within 3 months before initiating study drug (switchers).
[d] Includes American Indian or Alaskan Native, Native Hawaiian or other Pacific Islanders and Other.

Table 4
Multivariable analysis (Cox regression model) for pregnancy in the primary efficacy group 16–35 years based on subgroup analysis.

Variable		Hazard ratio	% Wald confidence limits
Comparator	Reference		
Age			
16 to <25 years	25 to 35 years	2.37	1.09–5.15
Body mass index			
≥30 kg/m^2	<30 kg/m^2	0.79	0.31–2.01
Past contraceptive use			
Starters[a]	Switchers[b]	0.92	0.45–1.92
Gravidity[c]			
1	0	3.61	1.56–8.38
Smoking status			
Current smoker	Never Smoker	1.83	0.74–4.50
Former Smoker	Never Smoker	1.48	0.49–4.46
Race			
Asian	White	2.78	0.61–12.71
Black	White	4.61	1.97–10.80
Other[d]	White	1.03	0.13–8.05
Region			
United States/Canada	Europe/Russia	2.68	0.93–7.77
Compliance[e]			
Low	High	4.21	2.04–8.66

[a] Starters: Past contraceptive use >3 months before initiating study drug.
[b] Switchers: Past contraceptive use within 3 months before initiating study drug.
[c] Gravidity: Participant had at least one pregnancy before study (1) or no pregnancy (0).
[d] Includes American Indian or Alaskan Native, Native Hawaiian or other Pacific Islanders and Other.
[e] Compliance: categorical variable that defines if compliance was "High" (Total Compliance ≥99%) or "Low" (Total Compliance <99%).

overall and in subgroups stratified by age, contraceptive history and BMI.

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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.2022.07.009.

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