BJOG An International Journal of Obstetrics and Gynaecology

Royal College of Obstetricians & Gynaecologists

DOI: 10.1111/1471-0528.16840
www.bjog.org

Estetrol-Drospirenone combination oral contraceptive: a clinical study of contraceptive efficacy, bleeding pattern and safety in Europe and Russia

K Gemzell-Danielsson,[a] D Apter,[b] J Zatik,[c] S Weyers,[d] T Piltonen,[e] L Suturina,[f] I Apolikhina,[g] M Jost,[h] MD Creinin,[i] J-M Foidart[h,j]

[a] Department of Women's and Children's Health, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden [b] VL-Medi Clinical Research Centre, Helsinki, Finland [c] Gynaecological Praxis St Anna, Debrecen, Hungary [d] Department of Obstetrics and Gynaecology, University Hospital, Gent, Belgium [e] Department of Obstetrics and Gynaecology, PEDEGO Research Unit, Medical Research Center, Oulu University Hospital, University of Oulu, Oulu, Finland [f] Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk, Russia [g] Kulakov National Medical Research Centre for Obstetrics, Gynaecology, and Perinatology, Moscow, Russia [h] Estetra SRL, an affiliate Company of Mithra Pharmaceuticals, Liège, Belgium [i] Department of Obstetrics and Gynecology, University of California, Davis, Sacramento, CA, USA [j] Department of Obstetrics and Gynaecology, University of Liège, Liège, Belgium
Correspondence: M Jost, Estetra SRL, Rue Saint Georges 5, 4000 Liège, Belgium. Email: mjost@mithra.com

Accepted 20 May 2021.

This article includes Author Insights, a video abstract available at: https://vimeo.com/bjog/authorinsights16840

Objectives To assess the contraceptive efficacy, bleeding pattern and safety of a combined oral contraceptive containing estetrol (E4) 15 mg and drospirenone (DRSP) 3 mg.

Design Multicenter, open-label, phase 3 trial.

Setting Sixty-nine sites in Europe and Russia.

Population Sexually active women aged 18–50 years with regular menstrual cycles and body mass index ≤35 kg/m^2.

Methods E4/DRSP was administered in a 24 active/4 placebo regimen for up to 13 cycles. Visits were scheduled during Cycles 2, 4, 7 and 10 and after completing treatment during which adverse events (AEs) were collected. Participants recorded medication intake, vaginal bleeding/spotting, use of other contraceptive methods and sexual intercourse on a daily diary.

Main outcome measures Pearl Index (PI) for women 18–35 years (overall and method-failure), bleeding pattern and AEs.

Results A total of 1553 women aged 18–50 years, including 1353 from 18 to 35 years old, received the study medication. PI was 0.47 pregnancies/100 woman-years (95% CI 0.15–1.11); method failure PI was 0.29 pregnancies/100 woman-years (95% CI 0.06–0.83). Scheduled bleeding/spotting occurred in 91.9–94.4% of women over Cycles 1 to 12 and lasted a median of 4–5 days per cycle. The percentage of women with unscheduled bleeding/spotting episodes decreased from 23.5% in Cycle 1 to <16% from Cycle 6 onwards. The most common AEs were headache (7.7%), metrorrhagia (5.5%), vaginal haemorrhage (4.8%) and acne (4.2%). One treatment-related serious AE was reported, a lower extremity venous thromboembolism. One-hundred and forty-one (9.1%) women discontinued study participation because of treatment-related adverse events.

Conclusion E4/DRSP provides effective contraception, a predictable bleeding pattern and a favourable safety profile.

Keywords Bleeding pattern, combined oral contraception, contraceptive efficacy, drospirenone, estetrol, native estrogen, safety.

Tweetable abstract A phase 3 trial with E4/DRSP shows high contraceptive efficacy, a predictable bleeding pattern and favourable safety profile.

Please cite this paper as: Gemzell-Danielsson K, Apter D, Zatik J, Weyers S, Piltonen T, Suturina L, Apolikhina I, Jost M, Creinin MD, Foidart J-M. Estetrol-Drospirenone combination oral contraceptive: a clinical study of contraceptive efficacy, bleeding pattern and safety in Europe and Russia. BJOG 2021; https://doi.org/10.1111/1471-0528.16840.

Introduction

Combined oral contraceptives (COCs) contain a progestin to inhibit ovulation and an estrogen. The estrogen component contributes to the contraceptive activity and balances the progestin effect to provide an acceptable bleeding pattern and to counteract any potential estrogen deficiency symptoms. Ethinyl estradiol (EE), a potent synthetic estrogen with good oral bioavailability, is the most frequently used estrogen in COCs. EE can affect the synthesis of various liver proteins (related to coagulation, fibrinolysis and hypertension) leading to an increased risk of cardiovascular complications.[1,2] Early EE-containing COCs were associated with a variety of adverse effects and medical risks, including a significant increase in venous thromboembolism (VTE).[3,4] Over the past few decades, the EE dose has been reduced to improve the safety and risk profiles. More recently, COCs with natural estrogen derivatives, estradiol or estradiol valerate, have been developed,[5,6] with the prospect of decreasing cardiovascular risk.

Estetrol (E4) is a natural estrogen exclusively produced by the human fetal liver.[7] It acts, unlike EE, selectively in tissues, exhibiting mixed agonist and antagonist estrogenic activities, but with a mode of action that is distinct from that of selective estrogen receptor modulators.[8–11] In phase 2 trials, E4 has minimal impact on haemostasis biomarkers, triglycerides and breast stimulation.[12–14] Additionally, E4 15 mg in combination with drospirenone 3 mg (DRSP), administered in a 24/4-day regimen, completely inhibited ovulation,[15] had limited to no impact on hepatic metabolism[13] and exhibited a favourable bleeding pattern, high-user acceptability and good body weight control.[16,17]

To further evaluate the contraceptive efficacy and safety of E4/DRSP, two comparable pivotal phase 3 studies were conducted (E4 Freedom), one in Europe/Russia and the other in the USA/Canada.[18] This paper presents the results of the first study.

Methods

E4 FREEDOM was a multicenter, open-label, phase 3 trial (protocol MIT-Es0001-C301; Clinicaltrials.gov, NCT02817828). The primary objective was to assess the contraceptive efficacy of E4/DRSP in women aged 18–35 years and at-risk of pregnancy (meaning at least one cycle with one act of intercourse per cycle with no other contraceptive use). Secondary objectives were to assess contraceptive efficacy, bleeding pattern and general safety in women aged 18–50 years.

The study design was based on the Declaration of Helsinki, ICH E6 (R2) Good Clinical Practice guidelines, US Food and Drug Administration and European Medicines Agency (EMA) guidelines,[19,20] and recommendations made by Kapp et al.[21] The trial centre Independent Ethics Committees approved the trial (Table S1). Participants signed written informed consents before study entry. The trial was funded by Estetra SRL, an affiliate company of Mithra Pharmaceuticals. Estetra SRL was involved in the phase 3 trial design. PRA Health Sciences managed the trial execution, including monitoring and reporting.

Participants

Study sites enrolled healthy heterosexually active, premenopausal women (18–50 years) with a body mass index (BMI) ≤35.0 kg/m^2, a history of regular menstrual cycles when not on hormonal treatment (21–35 days) and a negative serum pregnancy test before starting study treatment. Switching immediately from a previous hormonal contraceptive method was allowed except for injectable contraceptives, which required a washout period of 3, 6 or 10 months before screening for an injection with a 1-, 2- or 3-month treatment duration, respectively. Participants agreed to use E4/DRSP as their primary method of contraception for 13 cycles (12 months). We excluded persons with World Health Organization medical eligibility criteria category 3 or 4 contraindications to combined hormonal contraception use, such as smokers ≥35 years of age, history of thromboembolic, cardiovascular or cerebrovascular disorder, or hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg).[22]

Treatment

Haupt Pharma (Münster, Germany) manufactured and Almac (Craigavon, UK) distributed the study medication. Medication was provided in a blister pack containing 24 pink E4/DRSP tablets and 4 white placebo tablets for once-daily administration. Treatment duration was up to thirteen 28-day cycles. Participants who did not use any hormonal contraceptive method started study treatment on the first day of their menstrual bleeding. Participants switching from a COC or progestin-only pill initiated treatment on the day the next pill pack would have been started.

Measurements

Study visits were scheduled at Screening (Visit 1), at Enrolment (Visit 2), during the first 2 weeks of Cycle 2 (Visit 3), Cycle 4 (Visit 4), Cycle 7 (Visit 5) and Cycle 10 (Visit 6) and between 7 to 14 days after completing Cycle 13 (End of Treatment [EoT], Visit 7), or at Early Termination (ET).

Participants used a daily paper diary to record medication intake, vaginal bleeding/spotting episodes and use of other contraception. At the end of each cycle, participants recorded whether sexual intercourse occurred at least once during the cycle. A pregnancy test was performed before first pill intake, at cycles with no menstruation and at the end of treatment. At each visit, the diary was reviewed,

empty study drug packets were collected and new drug was dispensed as needed. General safety assessment was based on adverse events (AEs) and serious adverse events (SAEs), safety laboratory testing (haematology, serum chemistry and lipid profile) performed at Screening, Cycle 7 and EoT/ET; vital signs (blood pressure and heart rate) assessed at Screening, Cycles 2, 4, 7 and 10, and EoT/ET; and general physical, gynaecological and breast examinations performed at Screening and EoT/ET.

Outcome parameters

The Pearl Index (PI) for women aged 18–35 years was the primary efficacy endpoint. The PI was based on the following definitions:

- PI: pregnancies per 100 woman-years of exposure (13 cycles per year) calculated as: 1300 × number of 'on-treatment' pregnancies/number of women × 28-day equivalent at-risk treatment cycles
- At-risk cycles: no use of other contraceptive methods (including condoms and emergency contraception) and reported sexual intercourse.
- Modified at-risk cycles: no use of other contraceptive methods (including condoms and emergency contraception) (EMA definition).
- On-treatment pregnancy: pregnancy with an estimated date of conception up to 2 days after the last intake of study treatment (EMA definition).

The PI was assessed for at-risk cycles and modified at-risk cycles. Secondary contraceptive efficacy endpoints included method-failure PI (excluding 'user failure' [i.e. incorrect study treatment use]), cumulative pregnancy rate for women aged 18–35 years and PI endpoints for all women (18–50 years).

Other secondary endpoints were scheduled and unscheduled bleeding/spotting occurrence and duration, scheduled bleeding/spotting absence and the cumulative rate of scheduled bleeding/spotting absence. Safety endpoints included the number, frequency, type and severity of AEs and SAEs.

Analyses

A sample size of 1350 women aged 18–35 years was required for evaluation of the primary endpoint to meet EMA requirements for contraceptive efficacy with the assumption that 90% of the cycles would be at-risk and a dropout rate of 30%.[20,23] In addition, 200 women, aged 36–50 years, were enrolled to be included in secondary efficacy analyses and all non-efficacy analyses.

Safety analyses were performed for all women in the intention-to-treat (ITT) group who received at least one dose of investigational product. Contraceptive efficacy analyses were performed for women in the ITT group with at least one cycle in the denominator. Bleeding analysis was performed for women in the ITT set with at least one evaluable cycle. Statistical analyses were performed using SAS® software (version 9.4) for Windows® (SAS Institute Inc, Cary, NC, USA).

The PI was calculated with 95% CIs using a Poisson distribution. The cumulative pregnancy rate was determined by providing 1-year life-table pregnancy risks for each end point and was based on Kaplan–Meier estimates through Cycle 13. Treatment compliance with study drug use was based on diary entries per 28-day cycle; when diary data were missing, we assumed no pill intake that day. We defined treatment compliance as the reported total number of pills taken in the study across all participants, divided by the expected number of pills to be taken based on duration of participation.

We evaluated overall PIs by age (18–25; 26–35 years), BMI (<30; ≥30 kg/m^2), past hormonal contraceptive use (starters; switchers) and smoking. Starters were defined as women that had not used hormonal contraceptive(s) within the 3 months before E4/DRSP initiation while switchers were women who had used hormonal contraceptives in that period.

Bleeding pattern parameters were summarised according to Mishell et al.[24] (Table S2). The bleeding pattern was analysed by cycle, defined as the period of 28 consecutive days from Day 4 of the current cycle to Day 3 of the next cycle, with a scheduled bleeding period between Day 25 of the current cycle and Day 3 of the next cycle. Early (bleeding/spotting that started before Day 25 and continued into the scheduled period) and continued (bleeding/spotting that started in the scheduled period but continued after Day 3) bleeding and/or spotting episodes were classified as scheduled bleeding and/or spotting. Cycle 13 data are not reported because the last 3 days of the scheduled bleeding period of Cycle 13 (i.e. days 1 to 3 after study treatment completion) were not collected in the participants' diaries. Duration of bleeding and/or spotting episodes was based on a post-hoc analysis of data from women who experienced bleeding and/or spotting events.

General safety analysis was based on the safety set that included all enrolled participants who received at least one dose of study medication. General safety evaluation was based on frequency and nature of AEs, which included clinically relevant changes or abnormalities in routine laboratory parameters or physical examination findings. AEs were classified using version 19.0 of the Medical Dictionary for Regulatory Activities system organ classifications and preferred terms. AEs were defined as AEs occurring after the first dose of E4/DRSP. Related AEs included AEs with a possible, probable or definite relationship to E4/DRSP as assessed by the investigator. The annual event rate was defined as the total number of events divided by the total duration of exposure across all women in years. Safety

variables were summarised for the safety population using descriptive statistics and frequency distributions, and/or change from baseline if appropriate.

Results

Study population

The study was performed from June 2016 until April 2018 at 69 sites in Europe (Belgium [eight sites], Czech Republic [12 sites], Finland [eight sites], Germany [seven sites], Hungary [11 sites], Norway [four sites], Poland [six sites], Sweden [three sites]) and Russia (ten sites). Out of 1744 screened women aged 18–50 years, 1577 were enrolled (Figure 1). A total of 1553 women (1353 aged 18–35 years) started E4/DRSP use and 1218 (78.4%) (1052 [77.7%] aged 18–35 years) reached Cycle 13. The most common reasons for discontinuation in all women after the start of study treatment were AEs not related to bleeding (n = 104, 6.7%), withdrawal of consent (n = 78, 5.0%) and AEs related to bleeding (n = 53, 3.4%) (Figure 1). For the subset of women aged 18–35 years, the most common reasons for discontinuation were similar: AEs not related to bleeding (n = 97, 7.2%), withdrawal of consent (n = 72, 5.3%) and AEs related to bleeding (n = 47, 3.5%). At Cycle 13, the cumulative discontinuation rate was 21.6% (22.2% for women aged 18–35 years).

Characteristics of all women are presented in Table 1. Among women aged 18–35 years, the mean age was 25.0 (±4.5) years (58.6% were ≤25 years), the mean BMI was 22.9 (±3.5) kg/m^2 (94.5% were <30 kg/m^2), 38.4% were starters (24.5% were true new users), 77.8% had never smoked and 18.2% were current smokers.

Treatment compliance

In women aged 18–35 years, compliance based on expected pill intake averaged 99.4% across all cycles, the lowest mean compliance rate in any cycle was 99.3% (Cycles 3 and 6). Overall, 90.1% of participants missed no pills with 6.1, 2.0 and 1.8% missing an average of one, two or more than two pills per cycle, respectively.

Contraceptive efficacy

The PI and cumulative pregnancy rates for women aged 18–35 years and for women aged 18–50 years are summarised

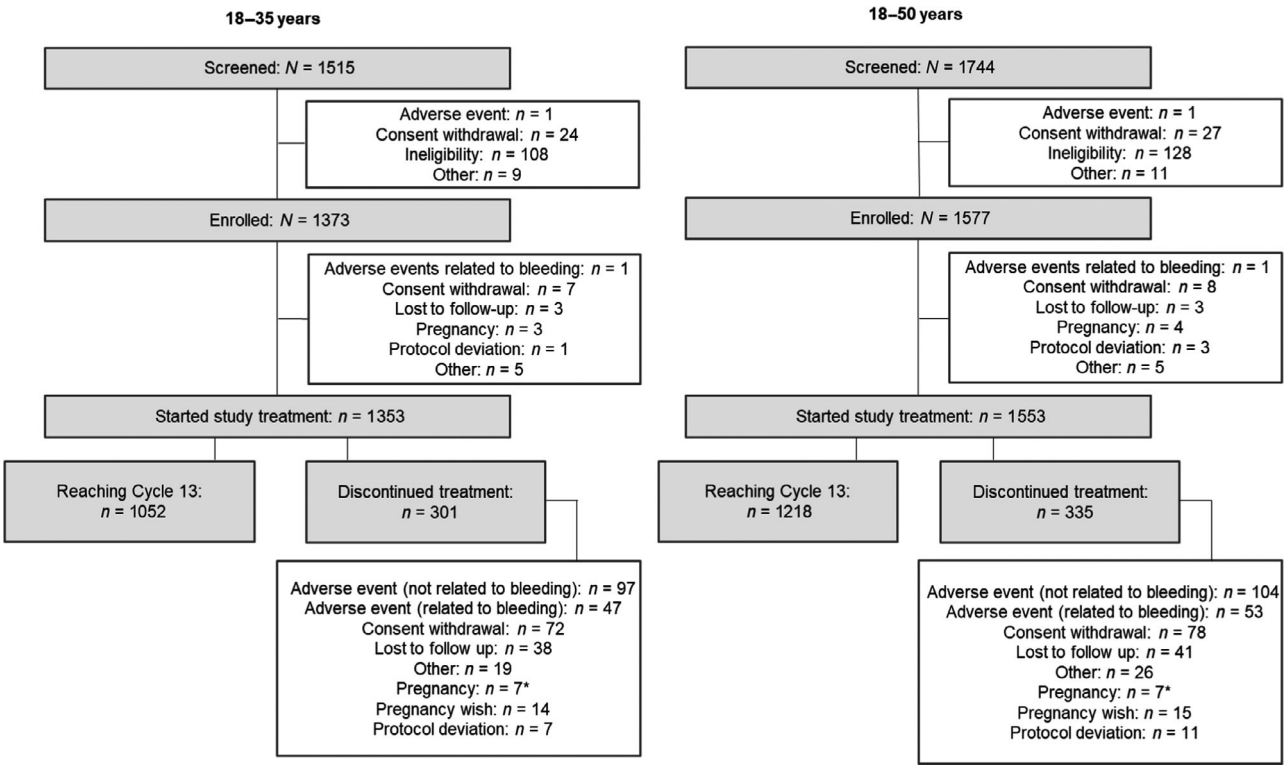

Figure 1. Disposition of participants in a phase 3 study of E4/DRSP oral contraception for up to 13 cycles (12 months). *Including two pregnancies with an estimated conception date before the start of study treatment. Screened: all women who signed an informed consent form. All women in the ITT population who received at least one dose of E4/DRSP were included in the safety population; all women in the ITT population who had at least one cycle in the denominator were included in the efficacy analysis; all women in the ITT population who had at least one evaluable cycle for bleeding were included in the bleeding analysis.

Table 1. Characteristics of participants in a phase 3 study of E4/DRSP oral contraception for up to 13 cycles (12 months)

	18–35 years *n* = 1353	18–50 years *n* = 1553
Age (years)	25.0 ± 4.5	27.1 ± 6.9
18–25	793 (58.6)	793 (51.1)
26–35	560 (41.4)	560 (36.1)
36–50	NA	200 (12.9)
Body mass index (kg/m^2)	22.9 ± 3.5	23.0 ± 3.5
<30	1278 (94.5)	1464 (94.3)
30–35	75 (5.5)	89 (5.7)
Race		
White	1334 (98.6)	1532 (98.6)
Black/African American	8 (0.6)	8 (0.5)
Asian	9 (0.7)	10 (0.6)
Other	2 (0.1)	3 (0.2)
Pregnancy history		
Nulligravid	1001 (74.0)	1018 (65.6)
Nulliparous	1068 (78.9)	1089 (70.1)
Past contraceptive use		
Switchers*	833 (61.6)	947 (61.0)
Starters**	520 (38.4)	606 (39.0)
None (true new users)	331 (24.5)	370 (23.8)
Smoking status		
Current smoker	246 (18.2)	246 (15.8)***
Former smoker	54 (4.0)	71 (4.6)
Never smoker	1053 (77.8)	1236 (79.6)

NA, not applicable.
Data are presented as n (%) or mean ± standard deviation.
Participants of 18–35 years old were included in the primary efficacy analyses and all participants (18–50 years old) are included in secondary efficacy analyses and all bleeding and safety assessments.
*Past contraceptive use within 3 months before screening (switchers).
**Past contraceptive use >3 months before screening (starters) and never use (true new users).
***Current smokers >35 years were excluded from the study.

Table 2. Pearl indices and cumulative pregnancy rates[a] in a phase 3 study of E4/DRSP oral contraception for up to 13 cycles (12 months)

	Aged 18–35 years	Aged 18–50 years
At-risk cycles[b]		
Participants	1313	1510
Cycles	13 692	15 849
PI		
On-treatment pregnancies	5	5
PI (95% CI)	0.47 (0.15–1.11)	0.41 (0.13–0.96)
Method failure PI[c]		
On-treatment pregnancies	3	3
PI (95% CI)	0.29 (0.06–0.83)	0.25 (0.05–0.72)
Modified at-risk cycles[d] PI		
Participants	1343	1542
Cycles	14 759	17 037
PI		
On-treatment pregnancies	5	5
PI (95% CI)	0.44 (0.14–1.03)	0.38 (0.12–0.89)
Method failure PI[c]		
On-treatment pregnancies	3	3
PI (95% CI)	0.26 (0.05–0.77)	0.23 (0.05–0.67)
Cumulative pregnancy rates at cycle 13 (95% CI)[e]		
On-treatment pregnancies	0.45% (0.19–1.09)	0.39% (0.16–0.94)
Method failure pregnancies	0.28% (0.09–0.86)	0.24% (0.08–0.74)

CI, confidence interval; PI, Pearl Index (pregnancies/100 woman-years).
[a]Includes all enrolled participants who received at least one dose of study treatment, and had at least one cycle in the denominator.
[b]At-risk cycle: no use of other methods of birth control (including condoms and emergency contraception), and intercourse reported, a pregnancy was considered 'on-treatment' when the estimated date of conception was ≤7 days after the last intake of study treatment.
[c]Method failure: excluding pregnancies due to user failure, i.e. not taking study treatment as per protocol during the cycle of conception, or use of co-medication interacting with COCs.
[d]Modified at-risk cycle (EMA definition): no use of other methods of birth control (including condoms and emergency contraception), a pregnancy was considered 'on-treatment' when the estimated date of conception was ≤2 days after the last intake of study treatment.
[e]Kaplan–Meier estimates.

in Table 2. Five on-treatment pregnancies occurred, all in women aged 18–35 years, of which three were considered method failures. The five pregnancies among 1313 women aged 18–35 years, with 13 692 at-risk cycles, resulted in a PI of 0.47 pregnancies/100 woman-years (95% CI 0.15–1.11). The modified at-risk PI was 0.44 pregnancies/100 woman-years (95% CI 0.14–1.03), based on five on-treatment pregnancies in 1343 women aged 18–35 years, with 14 759 modified at-risk cycles. The method failure PI in women aged 18–35 years was 0.29 pregnancies/100 woman-years (95% CI 0.06–0.83) and 0.26 pregnancies/100 woman-years (95% CI 0.05–0.77) for the at-risk and modified at-risk cycles, respectively. The cumulative on-treatment pregnancy rate at 13 cycles was 0.45% (95% CI 0.19–1.09).

Table S3 reports the results of the descriptive analysis of pregnancy rates by subpopulations. Because only five on-treatment pregnancies occurred in this study, statistical analyses based on the subgroups were not possible.

Bleeding pattern

Figure 2 shows bleeding and spotting by cycle day, with a predominant cyclic pattern. Scheduled bleeding occurred in 91.9–94.4% of participants per cycle and generally occurred

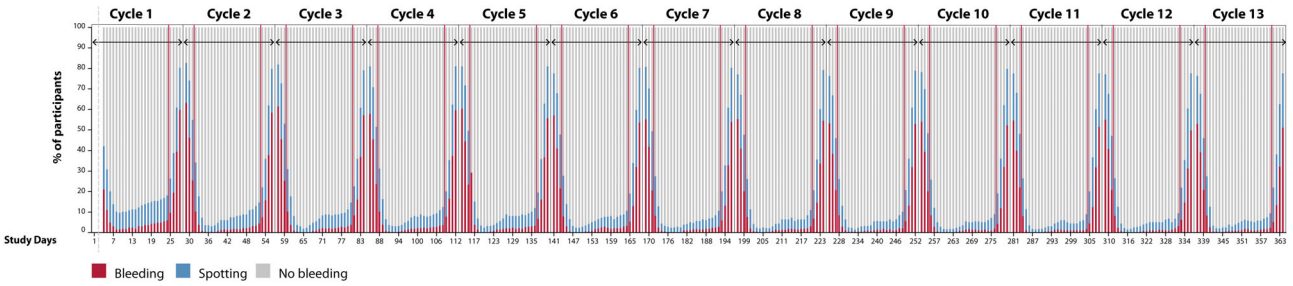

Figure 2. Percentage of participants with any type of bleeding and/or spotting over time by study day in phase 3 study of E4/DRSP oral contraception for up to 13 cycles (12 months). Arrows delineate pill cycles (from Day 1 to Day 28). Red lines delineate the scheduled bleeding period that occurs between Day 25 and Day 3 of the next cycle. *Cycle 13 data are not reported since the last 3 days of the scheduled bleeding period of Cycle 13 (i.e. days 1 to 3 after completion of the cycle) were not collected in the participants' diaries.

Table 3. Adverse events in a phase 3 study of E4/DRSP oral contraceptive use for up to 13 cycles (12 months)

	E4 15 mg/DRSP 3 mg *n* = 1553
Any AEs	784 (50.5)
AEs reported by ≥2% of participants	
Headache	120 (7.7)
Metrorrhagia	85 (5.5)
Vaginal haemorrhage	74 (4.8)
Acne	65 (4.2)
Nasopharyngitis	52 (3.3)
Dysmenorrhoea	47 (3.0)
Breast pain	42 (2.7)
Libido decreased	38 (2.4)
Abdominal pain	36 (2.3)
Weight increased	36 (2.3)
Any treatment-related AEs*	442 (28.5)
Treatment-related AEs reported by ≥2% of participants	
Metrorrhagia	77 (5.0)
Vaginal haemorrhage	67 (4.3)
Acne	59 (3.8)
Headache	44 (2.8)
Breast pain	37 (2.4)
Libido decreased	34 (2.2)
Dysmenorrhoea	33 (2.1)
Any treatment-related AEs leading to discontinuation	141 (9.1)
Treatment-related AEs leading to ≥0.5% of discontinuations	
Metrorrhagia	23 (1.5)
Acne	20 (1.3)
Vaginal haemorrhage	16 (1.0)
Libido decreased	12 (0.8)
Mood altered	8 (0.5)
Mood swings	7 (0.5)

Data presented as *n* (%). Safety population: all enrolled participants who received at least one dose of study treatment.
*Relatedness established by site investigator.

between Day 26 of each cycle and Day 3 of the next cycle. 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 3 days of bleeding from Cycles 1 to 9 and 2 to 3 days from Cycles 10 to 12 and a median of 2 days of spotting throughout.

The percentage of women with unscheduled bleeding and/or spotting episodes after Cycle 1 ranged from 19.2% in Cycle 2 to 12.8% in Cycle 11 (Figure S1). The number of unscheduled bleeding and/or spotting days remained stable throughout the study, with a median of 3 days, taking into account only women who experienced bleeding and/or spotting. Of the unscheduled bleeding/spotting episodes over all cycles, 71.8% were spotting-only, 22.7% were mixed bleeding/spotting and 5.4% were bleeding-only. The proportion of women with unscheduled spotting-only episodes decreased from Cycle 1 (18.3%) to around 10% for Cycles 6 to 12. The proportion of women with mixed bleeding/spotting episodes decreased from 4.4% in Cycle 1 to 2.8% in Cycle 13. The proportion of participants with unscheduled bleeding-only episodes was ≤1.4% over all the cycles.

The percentage of women with an absence of scheduled bleeding and/or spotting episodes ranged between 5.6 and 8.1% over all cycles.

Safety

Adverse events reported in this study are summarised in Table 3. The frequency of AEs and of treatment-related AEs was 50.5 and 28.5%, respectively. The majority (63%) of AEs were of mild intensity. The most common treatment-related AEs were metrorrhagia (5.0%), vaginal haemorrhage (4.3%), acne (3.8%) and headache (2.8%). At study completion, the mean change in body weight compared with baseline was +0.68 (±3.58) kg and the mean change in BMI was +0.25 (±1.29) kg/m^2. Overall, 9.1% of participants discontinued for treatment-related AEs, the

most common of which were metrorrhagia (1.5%), acne (1.3%) and vaginal haemorrhage (1.0%).

Serious AEs were reported in 13 women (0.8%), of which only one, a lower extremity VTE, was considered treatment-related. This SAE was reported during the fourth E4/DRSP treatment cycle in a 32-year-old white participant and a BMI of 21.5 kg/m^2, who had used hormonal contraception in the past (more than 3 months before enrolment). She had been using escitalopram for 3 years before enrolment and had no other known predisposing factors. E4/DRSP was discontinued and the SAE resolved after antithrombotic treatment without sequelae. Other SAEs reported during the study were not considered to be treatment-related. No deaths were reported.

Discussion

Main findings

In this study, E4/DRSP use resulted in high contraceptive efficacy with a low PI of 0.47 pregnancies/100 woman-years. The difference between this PI and the corresponding upper limit of the 95% CI was <1, confirming that the study achieved the required precision of the estimate according to EMA guidelines on steroid contraceptives.[20,23] In addition, E4/DRSP use resulted in a highly predictable vaginal bleeding pattern, with most women having their scheduled bleeding each cycle without experiencing unscheduled bleeding requiring the use of sanitary protection. No new safety concerns for E4/DRSP were noted during the study, no unexpected adverse events occurred and most (>90%) events were limited to one treatment cycle. One case of VTE was reported in a participant who did not use hormonal contraception for at least 3 months before the first E4/DRSP dose and who had been taking escitalopram for 3 years. Two case reports suggest a possible association with escitalopram and increased VTE risk at treatment initiation.[25,26]

Strengths and limitations

The study was adequately designed and powered to assess the contraceptive efficacy of E4/DRSP in women aged 18–35 years. Considering that this study occurred in Europe and Russia, the population is primarily white and not overweight; the data may not be generalisable to more diverse populations in other parts of the world. The assessments of this study, requiring participants to record the intake of the COC daily, may have impacted the adherence in this study compared with typical use. The sample size was too small to determine any relevant efficacy or safety conclusions on subpopulations. No comparator was included, so comparison of the contraceptive efficacy, bleeding pattern and safety of E4/DRSP with other contraceptives can only be inferred across studies.

Interpretation

E4/DRSP provides contraceptive efficacy based on PI (0.47 pregnancies/100 woman-years; 95% CI 0.15–1.11), which is similar to marketed DRSP-containing COCs, such as Yaz® (PI = 0.80 pregnancies/100 woman-years; upper limit 95% CI 1.30) and Yasmin® (PI = 0.57 pregnancies/100 woman-years; upper limit 95% CI 0.90). Moreover, E4/DRSP has a lower PI compared with recent studies performed in Europe with a DRSP-only 4 mg 24/4 contraceptive (Slynd®, Slinda®, pooled PI = 0.73 pregnancies/100 woman-years; 95% CI 0.31–1.43).[27] E4/DRSP bleeding pattern is comparable to EE-containing COCs and better than a DRSP-only 4 mg 24/4 contraceptive.[27] The adverse event profile was consistent with the use of other COCs, with the most common adverse events being menstrual irregularities, acne and headache.[28–30] The annual VTE incidence observed in this study (6/10 000 women) is reassuringly low in comparison with annual VTE risks reported in non-COC users of 0.7–5.8/10 000 women (varying by age), reported by Lidegaard et al.,[31] and 5–10/10 000 women reported by Heinemann and Dinger.[32] However, larger studies are still necessary because the sample size of this study does not allow an accurate population estimate of the VTE rate with E4/DRSP.

The combination of EE with DRSP has been associated with an increased risk of VTE with a relative VTE risk of 6.4 (95% CI 5.4–7.5) compared with COCs with EE/levonorgestrel (LNG) with a relative risk of 2.9 (95% CI 2.2–3.8).[31] This raises the question why E4 was developed in combination with DRSP as a new oral contraceptive and not with LNG. During phase 2 clinical development, E4/DRSP and E4/LNG formulations were evaluated to select the optimal combination for further development. E4/DRSP showed a more favourable bleeding pattern, satisfaction with treatment and wellbeing compared with E4/LNG.[16,17] Moreover, in the EE/LNG combination, the anti-estrogenic properties of LNG counteract the estrogenic effects of EE on the liver and reduce the total estrogenicity and thrombogenicity of this combination. This is an effect that is not needed and not present in an E4-containing COC, as E4 has a much lower estrogenic impact on the liver than EE. In a recent six-cycle study, changes in haemostasis parameters for E4/DRSP were indeed considerably smaller or similar to those observed for EE/LNG and significantly lower than those observed for EE/DRSP,[33] which is in line with the hypothesis that the effect of COCs on haemostasis parameters is mainly mediated by the estrogen component, and the fact that DRSP 4 mg, when used as a progestin-only contraceptive, is not associated with an increased VTE risk.[31,33,34] Finally, the anti-androgenic and mild diuretic profile of DRSP, which reduces the side effects of COCs, leads to an improved quality of life, supporting the choice of DRSP. The safety profile of E4/DRSP needs to be further assessed in post-marketing surveillance

studies. Based on the available data, the VTE risk-related contraindications for the use of E4/DRSP are anticipated to be similar to those of the most commonly used COCs.

Conclusions

The results of this study demonstrate that combining the native estrogen E4 with the anti-mineralocorticoid DRSP results in high contraceptive efficacy, a predictable bleeding pattern and a good safety profile. The present phase 3 investigation confirms that E4/DRSP could be a new and promising COC that combines the beneficial effects of E4 and DRSP.

Disclosure of interests

KGD has served as an ad hoc speaker and/or member of advisory boards for Exelgyn, Campus Pharma and HRA Pharma, Exeltis, Bayer AG, MSD/Merck, MedinCell, Gedeon Richter, Natural Cycles and Myovant, is a member of the former ICCR, Population council and an investigator of ongoing NICDH male contraception trial. DA participated in advisory board meetings. His institution has received support for clinical trials from Bayer AG, Mithra and Myovant. DA has been an invited speaker on an ad hoc basis for Bayer and Mithra. JZ has no conflict of interests to declare. SW serves on an advisory board for Bayer and MSD. TP serves on an Advisory Board for Exeltis, Merck and has received honoraria from Astra Zeneca, Exeltis, Ferring, Merck and MSD. Her research is funded by the Finnish Academy, Sigrid Jusélius Foundation, the Finnish Medical Foundation and Roche. LS serves as a consultant for Bayer Pharmaceuticals (Russia) and for Gedeon Richter (Russia). IA has served as an ad hoc speaker for Bayer Pharma AG (Russia), TEVA (Russia), Astellas (Russia), Roche Diagnostics Rus LLC (Russia), Avexima, Bionorica (Russia), CSC Pharma and Aspen Health LLC. MJ is employee of Estetra SRL, an affiliate company of Mithra Pharmaceuticals, Liège, Belgium. MDC serves on an Advisory Board for Evofem, Lupin, Mayne, Merck & Co., Searchlight and Therapeutics MD and is a consultant for Exeltis, Estetra, Mayne, Medicines 360, and Merck & Co. The Department of Obstetrics and Gynecology, University of California, Davis, receives research funding for MDC's contraceptive research from HRA Pharma, Medicines 360, Merck & Co. and Sebela. JMF is a member of the board at Mithra and received financial support for the supervision of this study. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

KGD and DA were study investigators, interpreted and discussed the data, and edited and approved the manuscript. JZ, SW, TP, LS and IA were study investigators and reviewed and approved the manuscript. MDC was a medical and safety monitor for the study, interpreted and discussed the data, and edited and approved the manuscript. MJ and JMF designed the study, interpreted and discussed the data, and edited and approved the manuscript.

Details on ethical approval

Ethical approval was provided either by the local ethics committee per study site and/or by a central ethics committee per country, whichever was applicable according to local regulations. The dates of first ethical approval per study site are included in Table S1.

Funding

The study was funded by Estetra SRL, an affiliate company of Mithra Pharmaceuticals. Estetra SRL was involved in the phase 3 trial design. PRA Health Sciences managed the trial execution, including monitoring and reporting, as well as data analysis. Study treatment was provided free of charge to participants.

Acknowledgements

The authors would like to acknowledge the contributions of the principal investigators and staff at the 69 centres in Europe and Russia (see Table S1) and thank the members of the Estelle Scientific Advisory Boards for their valuable advice. Medical Writing support was provided by Mireille Gerrits at Terminal 4 Communications, Hilversum, the Netherlands. PRA Health Sciences was involved as clinical research organization in organising the study. Statistical support was provided by Fabrice Nollevaux, Maud Hennion and Clément Laloux (Pharmalex, Belgium).

Data availability statement

Data are available on request from the authors.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Percentage of participants with unscheduled bleeding and/or spotting episodes over time in a phase 3 study of with Estetrol/ Drospirenone oral contraception for up to 13 cycles (12 months)

Table S1. Ethics committees and approval dates.

Table S2. Bleeding definitions used to assess bleeding patterns/flow during a phase 3 study of Estetrol/Drospirenone oral contraception for up to 13 cycles (12 months).

Table S3. Pearl index by subgroup in a phase 3 study of Estetrol/Drospirenone oral contraception for up to 13 cycles (12 months).

Video S1. Authors' insight. ■

References

1 Bitzer J. Pharmacological profile of estrogens in oral contraception. *Minerva Ginecol* 2011;63:299–304.
2 Hugon-Rodin J, Gompel A, Plu-Bureau G. Epidemiology of hormonal contraceptives-related venous thromboembolism. *Eur J Endocrinol* 2014;171:R221–30.
3 de Bastos M, Stegeman BH, Rosendaal FR, Van Hylckama VA, Helmerhorst FM, Stijnen T, et al. Combined oral contraceptives: venous thrombosis. *Cochrane Database Syst Rev.* 2014;3: CD010813.
4 Stegeman BH, de Bastos M, Rosendaal FR, van Hylckama VA, Helmerhorst FM, Stijnen T, et al. Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis. *BMJ* 2013;347: f5298.
5 Fruzzetti F, Tremollieres F, Bitzer J. An overview of the development of combined oral contraceptives containing estradiol: focus on estradiol valerate/dienogest. *Gynecol Endocrinol* 2012;28:400–8.
6 Shulman LP. Changing convention in combination oral contraceptives: estradiol and nomegestrol acetate in a monophasic 24/4 regimen. *J Fam Plann Reprod Health Care* 2013;39:211–6.
7 Hagen AA, Barr M, Diczfalusy E. Metabolism of 17-beta-oestradiol-4-14-C in early infancy. *Acta Endocrinol (Copenh)* 1965;49:207–20.
8 Abot A, Fontaine C, Buscato M, Solinhac R, Flouriot G, Fabre A, et al. The uterine and vascular actions of estetrol delineate a distinctive profile of estrogen receptor alpha modulation, uncoupling nuclear and membrane activation. *EMBO Mol Med* 2014;6:1328–46.
9 Arnal JF, Lenfant F, Metivier R, Flouriot G, Henrion D, Adlanmerini M, et al. Membrane and nuclear estrogen receptor alpha actions: from tissue specificity to medical implications. *Physiol Rev* 2017;97:1045–87.
10 Guivarc'h E, Buscato M, Guihot AL, Favre J, Vessieres E, Grimaud L, et al. Predominant role of nuclear versus membrane estrogen receptor alpha in arterial protection: implications for estrogen receptor alpha modulation in cardiovascular prevention/safety. *J Am Heart Assoc* 2018;7:e008950.
11 Foidart JM, Arnal JF, Lenfant F, Taziaux M, Houtman R, Jost M, et al. Estetrol (E4) is a unique estrogen with selective actions in tissues which are distinctly different from the actions of SERMs. *J Endocrine Soc*. 2019;3(Suppl. 1). SUN-LB001.
12 Gerard C, Blacher S, Communal L, Courtin A, Tskitishvili E, Mestdagt M, et al. Estetrol is a weak estrogen antagonizing estradiol-dependent mammary gland proliferation. *J Endocrinol* 2015;224:85–95.
13 Mawet M, Maillard C, Klipping C, Zimmerman Y, Foidart JM, Coelingh Bennink HJ. Unique effects on hepatic function, lipid metabolism, bone and growth endocrine parameters of estetrol in combined oral contraceptives. *Eur J Contracept Reprod Health Care* 2015;20:463–75.
14 Kluft C, Zimmerman Y, Mawet M, Klipping C, Duijkers I, Neuteboom J, et al. Reduced haemostatic effects with drospirenone-based oral contraceptives containing estetrol versus ethinyl estradiol. *Contraception* 2017;95:140–47.
15 Duijkers IJ, Klipping C, Zimmerman Y, Appels N, Jost M, Maillard C, et al. Inhibition of ovulation by administration of estetrol in combination with drospirenone or levonorgestrel: results of a phase II dose-finding pilot study. *Eur J Contracept Reprod Health Care* 2015;20:476–89.
16 Apter D, Zimmerman Y, Beekman L, Mawet M, Maillard C, Foidart JM, et al. Bleeding pattern and cycle control with estetrol-containing combined oral contraceptives: results from a phase II, randomised, dose-finding study (FIESTA). *Contraception* 2016;94:366–73.
17 Apter D, Zimmerman Y, Beekman L, Mawet M, Maillard C, Foidart JM, et al. Estetrol combined with drospirenone: an oral contraceptive with high acceptability, user satisfaction, well-being and favourable body weight control. *Eur J Contracept Reprod Health Care* 2017;22:260–67.
18 Creinin MD, Westhoff CL, Bouchard C, Chen MJ, Jensen JT, Kaunitz AM, et al. Estetrol-drospirenone combination oral contraceptive: North American phase 3 efficacy and safety results. *Contraception* 2021;104:222–28.
19 FDA draft Guidance for Industry. *Establishing Effectiveness and Safety for Hormonal Drug Products Intended to Prevent Pregnancy*. 2019. [https://www.fda.gov/media/128792/download]. Accessed 22 December 2020.
20 The EMEA CHMP guideline on clinical investigation of steroid contraceptives in women. [https://www.ema.europa.eu/en/clinical-investigation-steroid-contraceptives-women]. Accessed 22 December 2020.
21 Kapp N, Curtis KM, Borgatta L. Study design to evaluate the safety and effectiveness of hormonal contraception for women. *Clin Obstet Gynecol* 2007;50:850–67.
22 World Health Organization. *Medical eligibility criteria for contraceptive use*, 4th edn. WHO Press; 2009. pp. 15–44.
23 Gerlinger C, Endrikat J, van der Meulen EA, Dieben TO, Dusterberg B. Recommendation for confidence interval and sample size calculation for the Pearl Index. *Eur J Contracept Reprod Health Care* 2003;8:87–92.
24 Mishell DR Jr, Guillebaud J, Westhoff C, Nelson AL, Kaunitz AM, Trussell J, et al. Recommendations for standardization of data collection and analysis of bleeding in combined hormone contraceptive trials. *Contraception* 2007;75:11–5.
25 Kurne A, Ertugrul A, Anil Yagcioglu AE, Yazici KM. Venous thromboembolism and escitalopram. *Gen Hosp Psychiatry* 2004;26:481–3.
26 Yong WK, Sang HL, Tae KC, Ki HY, Shin YS. A case of pulmonary embolism associated with escitalopram. *Psychiatr Invest* 2007;4:52–4.
27 Palacios S, Regidor PA, Colli E, Skouby SO, Apter D, Roemer T, et al. Oestrogen-free oral contraception with a 4 mg drospirenone-only pill: new data and a review of the literature. *Eur J Contracept Reprod Health Care* 2020;25:221–27.
28 De Leo V, Musacchio MC, Cappelli V, Piomboni P, Morgante G. Hormonal contraceptives: pharmacology tailored to women's health. *Hum Reprod Update* 2016;22:634–46.
29 Ahrendt HJ, Makalova D, Parke S, Mellinger U, Mansour D. Bleeding pattern and cycle control with an estradiol-based oral contraceptive: a seven-cycle, randomized comparative trial of estradiol valerate/dienogest and ethinyl estradiol/levonorgestrel. *Contraception* 2009;80:436–44.
30 Palacios S, Wildt L, Parke S, Machlitt A, Romer T, Bitzer J. Efficacy and safety of a novel oral contraceptive based on oestradiol (oestradiol valerate/dienogest): a Phase III trial. *Eur J Obstet Gynecol Reprod Biol* 2010;149:57–62.
31 Lidegaard O, Nielsen LH, Skovlund CW, Skjeldestad FE, Lokkegaard E. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001–9. *BMJ* 2011;343:d6423.
32 Heinemann LA, Dinger JC. Range of published estimates of venous thromboembolism incidence in young women. *Contraception* 2007;75:328–36.
33 Mantha S, Karp R, Raghavan V, Terrin N, Bauer KA, Zwicker JI. Assessing the risk of venous thromboembolic events in women taking progestin-only contraception: a meta-analysis. *BMJ* 2012;345:e4944.
34 Regidor PA, Colli E, Schindler AE. Drospirenone as estrogen-free pill and hemostasis: coagulatory study results comparing a novel 4 mg formulation in a 24 + 4 cycle with desogestrel 75 mug per day. *Gynecol Endocrinol* 2016;32:749–51.

