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Original Research Article

The efficacy, safety, and tolerability of an estrogen-free oral contraceptive drospirenone 4 mg (24/4-day regimen) in obese users☆,☆☆

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ABSTRACT

Objectives: This study aimed to compare contraceptive efficacy and safety of drospirenone 4 mg in a 24/4-day regimen in nonobese and obese users and describe pharmacokinetics according to bodyweight.
Study design: We analyzed data from three drospirenone 4 mg trials (2 European and 1 United States) to report outcomes in nonobese (body mass index < 30 kg/m^2) and obese (body mass index ≥30 kg/m^2) users. We used data from the US trial to calculate the Pearl Index (pregnancies per 100 woman-years) in non-breastfeeding participants aged ≤35 years at enrollment for confirmed pregnancies. We assessed safety outcomes from all trials based on reported treatment-emergent adverse events. We evaluated pharmacokinetics by bodyweight in the US trial.
Results: The three trials combined comprised 2152 nonobese and 425 obese participants, including 590 nonobese and 325 obese participants in the US trial. Eight nonobese and four obese participants had confirmed pregnancies in the US trial, resulting in Pearl Indices of 3.0 (95% CI: 1.3–5.8) and 2.9 (95% CI: 0.8–7.3), respectively. Two-hundred forty-four (11.3%) nonobese and 39 (9.2%) obese participants discontinued due to a treatment-emergent adverse event. The pharmacokinetic analysis included 814 participants with a median weight of 73 (interquartile range 61–89) kg and median plasma drospirenone exposure (AUC_{0-24ss}) of 661.3 (interquartile range 522–828) ng·h/mL. Changing bodyweight from the median to the fifth percentile (51 kg) or 95th percentile (118 kg) changed drospirenone exposure ($AUC_{0-24,ss}$) by 22.2% and −23.6%, respectively.
Conclusions: Drospirenone 4 mg demonstrated similar contraceptive efficacy for both nonobese and obese users despite a difference in exposure based on bodyweight.
Implications: Our limited comparison between obese and nonobese users of drospirenone-only oral contraception demonstrated no evidence that efficacy or discontinuation for adverse events differs between groups. Serum drospirenone levels vary by bodyweight and may correlate with bleeding outcomes.

1. Introduction

Obesity is a global health concern associated with poor health outcomes, including venous thromboembolism (VTE) [1,2]. The proportion of obese women in the United States is increasing, from 31% in 1999–2000 to 42% in 2017–2020) [3]. This pattern is seen globally, particularly among the poorest people in high-income countries [4]. Many older studies for hormonal contraceptives, including progestin-only pills (POPs), did not establish contraceptive efficacy, safety, or pharmacokinetics (PK) in obese users (body mass index [BMI] ≥30 kg/m^2) [5–7].

☆ Conflicts of interest: M.D.C. has received speaking honorarium from Gedeon Richter, Mayne, and Organon; serves on Advisory Boards for Gedeon Richter, GlaxoSmithKline, OLIC, and Organon; and is a consultant for Estetra SRL, Mayne, and Medicines360. The Department of Obstetrics and Gynecology, University of California, Davis, receives contraceptive research funding for Dr. Creinin from Chemo Research SL, Evofem, Medicines360, Merck, and Sebela. A.A. and E.C. are employees of Exeltis HealthCare, Madrid. D.F.A. is a consultant to Exeltis Health Care, Madrid, and has been the principal investigator for Exeltis clinical studies with funding provided to Eastern Virginia Medical School.
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Between 2015 and 2017 in the United States, 46.9 million women aged 15–49 years used contraception with oral contraceptive pills, used by 21.4%, being the most frequently used reversible method [8]. US national survey results from 2011–2015 found that female permanent contraception is nearly twice as likely to be used by obese compared to nonobese respondents [9]. Moreover, some health care professionals remain cautious about prescribing combined hormonal contraceptives to obese patients [10,11] because of concerns about weight gain and contraception failure [12], VTE risk associated with some combined oral contraceptives (COCs) [13], and a higher VTE incidence than nonobese patients [2,14,15]. These sentiments can result in obese pregnancy-capable people having fewer contraceptive choices, particularly if they have additional risk factors for VTEs or cardiovascular disease [16].

Drospirenone 4 mg (Slynd; Exeltis, Madrid, Spain), a progestogen-only oral contraceptive in a 24-day hormone/4-day placebo regimen, is a new POP available to women in many countries. Contraceptive efficacy, safety, and tolerability of this product have been demonstrated in three registrational trials [17–19]. The aims of this study are to summarize the efficacy, safety, PK, and tolerability of drospirenone 4 mg (24/4) when used by obese users.

2. Materials and methods

The three phase 3 trials for the drospirenone 4 mg 24/4 regimen (EudraCT: 2011-002396-42 and 2010-021787-15 and clinicaltrials.gov NCT02269241) included in this analysis have been previously reported and comprise two European trials (9 and 13 cycles) [17,18] and one US trial (13 cycles) [19]. All participants provided written informed consent, and study centers obtained institutional review board approval. The studies were conducted in accordance with good clinical practice guidelines for the conduct of clinical trials, the Declaration of Helsinki, and the recommendations of the United States Food and Drug Administration or the European Medicines agency, which both require efficacy and safety of steroid contraceptives to be established in a sufficiently representative population [20,21]. For this analysis, we excluded 63 participants enrolled at two study sites in the US trial due to major breaches of United States Food and Drug Administration regulations, current Good Clinical Practice guidelines, and the trial protocol procedures, as we could not verify the reliability of the data from these sites.

The European trials included sexually active, nonbreastfeeding participants aged 18–45 years with systolic blood pressure/diastolic blood pressure (SBP/DBP) of < 140/ < 90 mm Hg [17,18]. Obese participants could be included if they were nonsmokers and had no history of VTEs themselves or in a first-degree relative (sibling or parent) that occurred at < 55 years. The US study included sexually active participants aged ≥15 years with SBP/DBP ≤159/99 mm Hg and no BMI restrictions; investigators excluded participants with a history of or current VTE, diabetes with vascular involvement, or valvular heart disease with thrombogenic complications [19].

Participants received packets containing drospirenone 4 mg for 24 consecutive days followed by 4 days of placebo, with instructions to take one pill daily for up to nine [17] or 13 [18,19] cycles. The details of the first study drug dose for participants switching from COCs and instructions for missed tablets have been previously described [17–19].

Briefly, participants attended study visits at screening and randomization, then at day 24 ± 2 of cycles 1, 3, 5, and 9 for the nine-cycle trial [17] or cycles 1, 3, 6, 9, and 13 for the 13-cycle trials [18,19]. Participants who discontinued the trial early could attend a discontinuation visit. Investigators collected samples for laboratory safety evaluations at screening, at cycles 3 or 6 (for the nine-cycle and 13-cycle trials, respectively), and at the final/discontinuation visit. Investigators evaluated participants for VTE symptoms/risk factors at every visit and monitored for adverse events during each drospirenone cycle. Participants self-reported bleeding patterns and use of concomitant contraceptive (including emergency contraception) using a daily e-diary. Investigators in the US trial only conducted a PK substudy, which included collection of drospirenone plasma samples at day 24 ± 2 of the first and sixth cycles (two samples collected 45–120 minutes apart per visit) for central laboratory analysis.

In this secondary analysis, we assessed efficacy, safety, tolerability, and PK outcomes by BMI status at screening (< 30 kg/m^2 or ≥30 kg/m^2). We assessed efficacy outcomes by calculating the Pearl Index (pregnancies per 100 women-years) only from participants in the US trial for pregnancies confirmed by blood test or ultrasonography (a prespecified end point of the trial) [19]. For the efficacy analysis, we excluded participants who were breastfeeding, aged > 35 years at enrollment, or had a pregnancy that dating confirmed conception prior to study drug initiation. We assessed safety outcomes in all participants from all three trials based on reported adverse events and clinical laboratory parameters. We summarized treatment-emergent adverse events (TEAEs) by number of events and percentage of participants with each TEAE using MedDRA primary system class/preferred term in each of the three trials. We assessed tolerability by evaluating vaginal bleeding profiles (U.S. study only) and changes in bodyweight and BMI, including participants from all trials with weight recorded at the final study visit.

We analyzed PK parameters from the US trial to develop a population PK model. We excluded samples from the PK substudy analysis with no date or time records for any plasma sample or the drospirenone dose prior to sampling or those below the limit of quantification. The analysis used valid concentration values above the lower limit of quantification. We calculated the area under the curve (AUC), volume of distribution, and apparent clearance for drospirenone to determine steady-state AUC ($AUC_{0-24,ss}$). A model-based covariate analysis was performed to explore the effect of predefined covariates (bodyweight, BMI, number of bleeding days per cycle, age, race, alcohol use, and smoking status) that may affect clearance of drospirenone and exposure when drospirenone 4 mg was dosed once daily for 24 days followed by a 4-day break. We used a two-compartmental model using first-order elimination based on PK data from a phase I trial of intensively sampled healthy females (n = 24) [22] to describe the drospirenone steady-state plasma concentrations from participants in the US trial. We also used prior information to fit the parameters for central and peripheral volumes of distribution and intercompartmental clearance, while the absorption rate constant and lag time were fixed to the phase I values, and clearance and variability on the relative bioavailability fraction were estimated. Visual predictive checks and bootstrap analyses were used to test the variability and robustness of PK data.

3. Results

Overall, the three trials enrolled 1571 European participants and 1069 US study participants, with 1006 US study participants included in this analysis. Table 1 reports the characteristics of the study participants from the three trials included in this analysis. Very few (n = 71, 4.5%) participants in the European trials had BMI of ≥30 kg/m^2 compared with slightly more than one-third (n = 354, 35.2%) of the US trial participants. Two participants in the US trial had a pregnancy diagnosed during the first cycle of use that dating confirmed conception prior to study drug initiation; these participants are included in the safety analyses only.

For the efficacy assessment population, 11 pregnancies among 590 nonobese and four pregnancies among 325 obese participants in the US trial were reported, of which we excluded three and zero, respectively, from this analysis as unconfirmed. Pearl Indices for the eight confirmed pregnancies in nonobese participants and four pregnancies in obese participants are presented in Table 2.

Table 1
Demographics and baseline characteristics of participants in phase 3 trials of drospirenone 4 mg in a 24/4-d regimen

Characteristic	Europe trial 1 (RCT, nine 28-d cycles)[a] [17]	Europe trial 2 (noncomparative, thirteen 28-d cycles) [18]	US trial[b] (noncomparative, thirteen 28-d cycles) [19]
	n = 858	*n* = 713	*n* = 1006
Age ≤35 y at enrollment	682 (79.5)	569 (79.8)	928 (92.2)
Race			
American Indian or Alaska Native	0	0	13 (1.3)
Asian	0	1 (0.1)	20 (2.0)
Black or African-American	2 (0.2)	1 (0.1)	358 (35.6)
Native Hawaiian or another Pacific Islander	0	0	5 (0.5)
White	856 (99.8)	710 (99.6)	571 (56.8)
Other	0	1 (0.1)	39 (3.9)
Weight (kg)	61 (56–69)	62 (55–69)	72 (61–88)
BMI (kg/m^2)	23.0 ± 3.5	23.0 ± 3.8	28.6 ± 7.6
≥30	30 (3.5)	41 (5.8)	354 (35.2)
≥35	9 (1.0)	11 (1.5)	185 (17.7)
Blood pressure SBP/DBP ≥130/85	131 (15.3)	142 (19.9)	119 (11.8)
Breastfeeding at enrollment[c]	0	0	11 (1.1)
Baseline VTE risk factors[d]			
0 VTE risk factors	716 (83.4)	603 (84.6)	611 (60.8)
1 VTE risk factor	139 (16.2)	104 (14.6)	367 (36.5)
2 VTE risk factors	3 (0.3)	6 (0.8)	27 (2.7)
Missing data	0	0	1 (0.1)

BMI, body mass index; RCT, randomized controlled trial; VTE, venous thromboembolism.
All data presented as *n* (%), mean ± SD, or median (interquartile range).
[a] Comparator was desogestrel 75 mcg once daily; only participants who received drospirenone included in table.
[b] The study enrolled 1069 participants; this secondary analysis excluded 63 participants from two US study sites with major protocol and regulatory violations. Two participants initiated drospirenone treatment but had become pregnant prior to initiation and are included in the safety analysis only.
[c] Breastfeeding participants were not included inefficacy analysis (included in safety analysis only).
[d] VTE risk factors, comprised BMI ≥30 kg/m2, family history of thromboembolic illness, current smoker aged ≥35 y, or nonsmoker aged ≥40 y.

Table 3 reports TEAEs and TEAEs leading to study discontinuation separately for each trial. Overall, any drospirenone-related TEAE was reported by 493 (22.9%) nonobese and 133 (31.3%) obese participants. Any TEAE leading to discontinuation occurred in 244 (11.3%) nonobese and 39 (9.2%) obese participants. The most common TEAEs were headache and nasopharyngitis experienced by 103 (4.8%) and 98 (4.6%) nonobese participants and 31 (7.3%) and 30 (7.1%) obese participants, respectively. In the US study, the mean SBP/DBP absolute changes from baseline were minimal in both BMI subgroups (−0.8/−0.6 mm Hg and +0.5/+1.1 mm Hg, respectively). We observed similar patterns for the European-based studies, although these included few obese participants. No participants experienced a VTE in any of the studies.

In the US trial, we observed the highest number of bleeding/spotting days during the first cycle among the 650 nonobese (median 7 [interquartile range (IQR) 4–11] days) and 354 obese (median 6 [IQR 3–11] days) participants. In nonobese participants, the median number of bleeding/spotting days decreased to 1 (IQR 0–5) day by cycle 10 (*n* = 188) with no further changes during subsequent cycles. In obese participants, the median number of bleeding/spotting days decreased to 1 (IQR 0–5) day by cycle 7 (*n* = 112), 0 (IQR 0–5) days in cycle 12 (*n* = 80), and 0 (IQR 0–4.5) in cycle 13 (*n* = 86).

Bodyweight changes over time for both BMI subgroups are presented in Table 4. The mean change in bodyweight and BMI at each study visit for the US-based study are shown in Figure 1.

Drospirenone exposure outcomes in the PK models are reported in Table 5. The PK analysis included 1263 evaluable sample combinations in which investigators obtained both samples on a visit day and plasma concentrations were above the lower limit of quantification, including 805 at day 24 ± 2 in cycle 1 and 458 at day 24 ± 2 in cycle 6. Overall, 356 participants provided samples in only cycle 1, nine in only cycle 6, and 449 in both cycles. The median weight for participants in this PK data set was 73 kg (IQR 61–89 kg). The median plasma drospirenone exposure (AUC_{0-24ss}) was 661.3 ng·h/mL (IQR 522–828 ng·h/mL). We found no difference in mean distributions of exposure when restricting the analysis to participants who attended both PK sampling visits (data not shown). The covariates bodyweight and number of bleeding days per cycle were significantly associated with the relative bioavailability PK parameter, with the

Table 2
Pregnancy outcomes by BMI subgroups in nonbreastfeeding participants aged ≤35 y in a US [19] registration trial of drospirenone 4 mg in a 24/4-d regimen

Pregnancy outcomes	BMI subgroup		All participants[a]
	< 30 kg/m^2 (*n* = 590)	≥30 kg/m^2 (*n* = 325)	(*N* = 915)
Confirmed pregnancies[b]	8 (1.4%)	4 (1.2%)	12 (1.3%)
Evaluable cycles[c]	3520	1817	5337
Pearl index (pregnancies per 100 participant-years)	3.0 (95% CI 1.3–5.8)	2.9 (95% CI 0.8–7.3)	2.9 (95% CI1.5–5.1)

BMI, body mass index; CI, confidence interval.
All data presented as *n* (%).
[a] Includes all enrolled participants from 41 study sites, which had no major protocol or regulatory violations (63 participants were excluded from two US study sites) with exclusion of those who were breastfeeding (*n* = 11), aged > 35 old at enrollment (*n* = 84), or had a pregnancy that dating confirmed conception prior to study drug initiation (*n* = 2).
[b] Positive quantitative serum human chorionic gonadotropin test or ultrasonography was recorded.
[c] 28-d cycles with study medication use in which sexual intercourse occurred without the use of other contraceptives or any cycle in which pregnancy occurred even if other contraceptives used.

Table 3
Treatment emergent adverse events by BMI subgroup in registration trials of drospirenone 4 mg in a 24/4-d regimen

Treatment emergent adverse events	BMI subgroup	
	< 30 kg/m^2 *n* (%)	≥30 kg/m^2 *n* (%)
Europe trial 1 [17] (nine 28-d cycles)	*n* = 828	*n* = 30
Any TEAE	320 (38.6)	12 (40.0)
Any related TEAE	128 (15.5)	7 (23.3)
Any severe TEAE	22 (2.7)	2 (6.7)
Any serious TEAE	15 (1.8)	0
Any TEAE leading to discontinuation	79 (9.5)	3 (10.0)
TEAEs occurring in ≥5% of either subgroup		
Headache	35 (4.2)	3 (10.0)
Vaginal hemorrhage	30 (3.6)	2 (6.7)
Bodyweight increase	17 (2.1)	4 (13.3)
Europe trial 2 [18] (noncomparative, thirteen 28-d cycles)	*n* = 672	*n* = 41
Any TEAE	330 (49.1)	18 (42.9)
Any related TEAE	147 (21.9)	3 (7.3)
Any severe TEAE	23 (3.3)	2 (4.9)
Any serious TEAE	9 (1.3)	1 (2.4)
Any TEAE leading to discontinuation	88 (13.1)	0
TEAEs occurring in ≥5% of either subgroup		
Nasopharyngitis	19 (2.8)	3 (7.3)
Headache	29 (4.3)	3 (7.3)
Acne	44 (6.5)	1 (2.4)
United States trial [19] (noncomparative, thirteen 28-d cycles)	*n* = 652	*n* = 354
Any TEAE	405 (62.1)	209 (59.0)
Any related TEAE	218 (33.4)	123 (34.7)
Any severe TEAE	29 (4.4)	17 (4.8)
Any serious TEAE	12 (1.8)	3 (0.8)
Any TEAE leading to discontinuation	77 (11.8)	36 (10.2)
TEAEs occurring in ≥5% of either subgroup		
Nasopharyngitis	51 (7.8)	26 (7.3)
Headache	39 (6.0)	25 (7.1)
Nausea	39 (6.0)	24 (6.8)
Metrorrhagia	34 (5.2)	19 (5.4)
Dysmenorrhea	30 (4.6)	28 (7.9)

BMI, body mass index; RCT, randomized controlled trial; TEAE, treatment emergent adverse event.

interindividual variability decreasing from 51.7% to 39.6%. Increasing bleeding/spotting days per cycle correlated with lower drospirenone systemic exposure. As drospirenone 4 mg had its efficacy assessed in obese users, we also analyzed an alternative covariate model using BMI and number of bleeding days per cycle, but the model using bodyweight was statistically a better fit for the data. Changing bodyweight from the median to the 5th percentile (51 kg) or 95th percentile (118 kg) caused a change in systemic exposure of 22.2% and −23.6%, respectively, with each additional day of bleeding associated with a 0.8% drop in systemic exposure ($AUC_{0-24,ss}$). We found similar results with the alternative model using BMI. Drospirenone PK parameters in the final and alternative models are presented in an online Appendix. The PK parameter values for cycle 6 were comparable to cycle 2, suggesting no change in the drospirenone PK profile over time.

4. Discussion

In this secondary analysis, we evaluated outcomes by obesity status from three trials used for regulatory registration of drospirenone 4 mg (24/4), a progestin-only oral contraceptive [17–19]. We found similar contraceptive efficacy n both non-obese and obese nonbreastfeeding participants aged ≤ 35 years in the US trial, despite approximately 20% lower systemic exposure. We chose to only use the US study data for comparing efficacy outcomes between obese and nonobese users because of the low proportion of participants in the European studies (71/1571 [4.5%]) with obesity, none of whom experienced a pregnancy. As such, we felt that using a pooled population for the efficacy outcome would be misleading.

We found no relevant differences in the safety profile for the two BMI subgroups, including changes in blood pressure (BP), heart rate, or bodyweight. In the US study, the only TEAE that occurred with a difference of more than 3% between BMI subgroups was dysmenorrhea (4.6% and 7.9% for nonobese and obese users, respectively). We also found a low proportion of serious TEAEs among participants in both BMI subgroups overall. As expected, due to study duration, participants in the two 13-cycle trials had slightly more TEAEs compared with the nine-cycle trial. Importantly, trials for product development (phases 2 and 3) typically have more stringent entry criteria than those used in clinical practice because of regulatory agency requirements that include first proving efficacy and safety in lower-risk populations. The European trials excluded potential participants with a BP > 140/90 or those with obesity if they smoked or had a personal or family history of VTE before the age of 55 years, and the US trial excluded potential participants with diabetes or BP ≥160/100 [17–19]. As such, these trials minimized the inclusion of patients at risk for significant health issues who might, in clinical practice, be considered candidates for progestin-only oral contraceptives. Indeed, evidence-based advice from the World Health Organization and US Medical Eligibility Criteria for Contraceptive Use state that progestin-only contraceptives, including oral pills, have no safety concerns for obese women [23,24]. Thus, these findings may not be generalizable to all obese patients who may receive drospirenone 4 mg oral contraception.

Participants in both BMI subgroups had similar median number of bleeding/spotting days despite a lower drospirenone systemic exposure in the obese compared to nonobese users. It is possible that peripheral aromatization of androstenedione in obese participants results in higher circulating estrone compared to nonobese participants [25]. Because estrone is converted to estradiol, both estrone and estradiol levels could be elevated. These hormonal

Table 4
Absolute changes in weight and BMI by BMI subgroups in the registration trials of drospirenone 4 mg in a 24/4-day regimen[a]

Changes in weight or BMI	BMI < 30 kg/m^2	BMI ≥30 kg/m^2
Europe trial 1 [17] (nine 28-d cycles)	*n* = 823	*n* = 30
Weight changes from baseline to study exit/final visit (kg)	0.1 ± 3.0	−0.2 ± 6.5
BMI changes base from baseline to study exit/final visit (kg/m^2)	0.04 ± 1.11	−0.7 ± 2.41
Europe trial 2 [18] (thirteen 28-d cycles)	*n* = 644	*n* = 41
Weight changes from baseline to study exit/final visit (kg)	0.38 ± 3.35	−1.95 ± 7.91
BMI changes base from baseline to study exit/final visit (kg/m^2)	0.14 ± 1.22	−0.77 ± 3.00
United States trial [19] (thirteen 28-d cycles)	*n* = 424	*n* = 222
Weight changes from baseline to study/final visit (kg)	1.1 ± 3.83	-0.1 ± 6.15
BMI changes base from baseline to study exit/final visit (kg/m^2)	0.41 ± 1.44	−0.03 ± 2.32

BMI, body mass index.
Data are mean ± SD.
[a] Only includes participants with bodyweight recorded at the final study visit; no data for five (0.6%) participants with BMI < 30 kg/m^2 in Europe trial 1; 28 (4.2%) participants with BMI < 30 kg/m^2 in Europe trial 2; 228 (35.0%) participants with BMI < 30 kg/m^2 in US trial, and 132 (37.3%) participants with BMI ≥ 30 kg/m^2 in US trial.

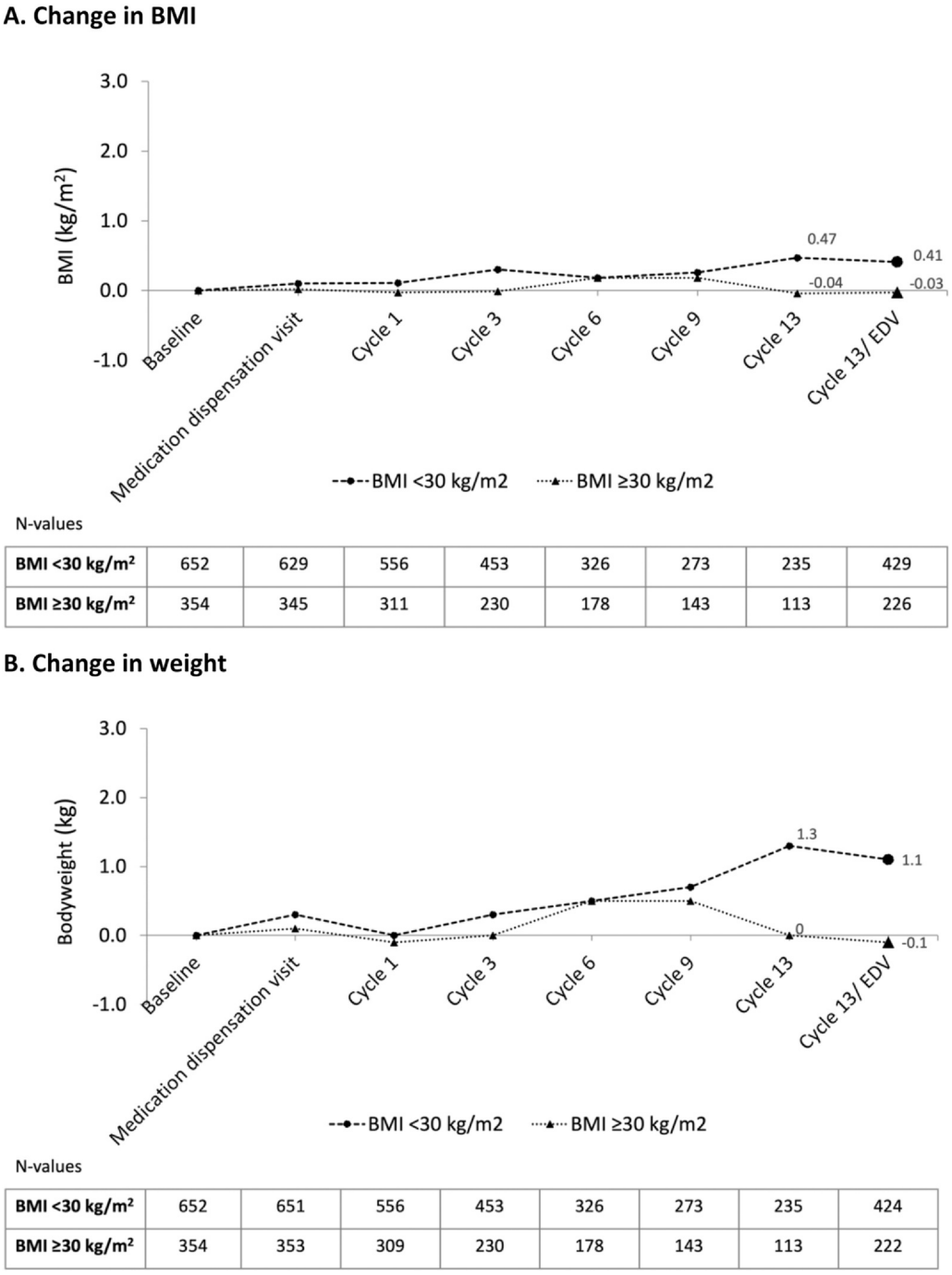

Fig. 1. Mean change in BMI and weight from baseline in a US registration trial of drospirenone 4 mg in a 24/4-d regimen [19]. (A) Change in BMI. (B) Change in weight. BMI = body mass index; EDV = early discontinuation visit. Study visits were conducted on cycle day 20 ± 2.

changes may influence bleeding and side effect outcomes. Future studies could evaluate these differences to provide a better understanding of any such differences.

Obesity affects contraceptive steroid absorption, distribution (including drug binding), metabolism, and excretion [26]. Our PK analysis with daily oral drospirenone use showed obese users, compared with nonobese users, had approximately 20% lower drospirenone systemic exposure ($AUC_{0-24,ss}$). For comparison, levonorgestrel, when used as a single 1.5 mg dose for oral emergency contraception, demonstrates 40%–50% lower systemic exposure (AUC) in obese compared to nonobese users [27,28]. Levonorgestrel is a highly bound drug, mainly to sex hormone–-binding globulin (SHBG), with only about 1% unbound [28]. SHBG levels are lower in obese than nonobese women, which are further reduced upon exposure to levonorgestrel [28]. In obese users, lower SHBG levels are likely to lead to the rapid clearance of unbound levonorgestrel and thus reduce systemic exposure compared with nonobese users [28]. In contrast, we hypothesize that because drospirenone does not bind to SHBG [29], systemic exposure is not affected by SHBG levels, thus leading to smaller differences in drospirenone systemic exposure and bioavailability among nonobese and obese users and no differences in contraceptive efficacy in relation to BMI. A recent pooled analysis of estetrol 15 mg/drospirenone 3 mg (24/4) COC studies also showed no difference in contraceptive efficacy when participants were stratified by BMI [30].

Table 5
Drospirenone exposure statistics in pharmacokinetic models with covariates bodyweight (final model) and BMI (alternative model)

	$AUC_{0-24,ss}$ (ng·h/mL)			
Category	*n*	5th percentile	Median	95th percentile
Final model using bodyweight covariate				
All	1263	391.7	661.3	1239
≤51 kg	72	514.5	870.6	1521
> 51–117 kg	1123	403.5	659.2	1224
≥118 kg	68	294.1	471.9	926.2
Number of bleeding days per 28-day cycle				
0 days	251	432.9	727.8	1482
1–15 days	939	381.3	651.1	1202
≥16 days	73	383.5	600.7	1007
Alternative model using BMI covariate				
All	1263	380.3	660.8	1238
≤19.6 kg/m^2	66	467.9	784.8	1544
19.6–43.7 kg/m^2	1133	392.5	661.7	1229
≥43.8 kg/m^2	64	290.7	465.2	947.6
Number of bleeding days per 28-day cycle				
0	251	425.6	734.0	1486
1–15	939	376.5	647.5	1211
≥16	73	372.1	602.7	1007

$AUC_{0-24,ss}$, steady-state area-under-the-concentration-time curve; BMI, body mass index; *n*, number of visits in which both samples on a visit day were evaluable (samples obtained 45–120 min apart on day 24 ± 2 of cycles 1 and 6).
Data are from the US trial [19].

There is a small increased relative risk of VTEs associated with the use of COCs with ethinylestradiol, which has decreased only marginally over recent decades despite a large reduction in the dose of estrogen used in the pills [31]. Both COC use and higher BMI increase the risk for VTE [15]. Nonetheless, different progestins modulate the risk of VTE used in combination with the same estrogen [31]. These progestins, including drospirenone, do not interfere with coagulation protein synthesis when used on their own [32,33] and do not appear to affect VTE risk [32].

As a secondary analysis, this report has important limitations. Participants in the primary studies were not recruited with the goal of comparing obese and nonobese populations. Thus, for this secondary analysis, the overall sample of obese participants is relatively small, resulting in large 95% CIs. Even as a pooled population, the sample is not large enough to confirm event rates for rare outcomes such as VTE. Because the majority of obese participants were from the US, the results may not be generalizable to obese users in other countries. A strength of this analysis is that the obese population did not have an upper limit and 17.7% of participants in the US trial (7.8% overall) had a BMI ≥35 kg/m^2. In contrast, contemporary COC trials that include participants with obesity commonly use a BMI upper limit of 35 kg/m^2 [30,34].

In conclusion, our data summarizing drospirenone 4 mg POP use in nonobese and obese users shows no evidence of differences in efficacy or safety outcomes related to obesity status.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.contraception.2023.110136.

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