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ORIGINAL ARTICLE

Overall and bleeding-related discontinuation rates of a new oral contraceptive containing 4 mg drospirenone only in a 24/4 regimen and comparison to 0.075 mg desogestrel

Pedro-Antonio Regidor[a], Enrico Colli[b] and Santiago Palacios[c]

[a]Exeltis Europe, Ismaning, Germany; [b]Exeltis HealthCare Madrid, Madrid, Spain; [c]Instituto Palacios, Salud y Medicina de la Mujer, Madrid, Spain

ABSTRACT

Objectives: Progestin-only pills do not increase the risk of venous thromboembolism, stroke, and myocardial infarction but are associated with poor cycle control. A novel estrogen-free pill containing only drospirenone (DRSP) to improve bleeding patterns and tolerability and reduce discontinuation rates has been introduced into the market. The present study aims to describe the improvement in the acceptability of this DRSP-only pill, e.g. regarding the bleeding profile and the reduction in discontinuation rates due to unacceptable bleeding compared to desogestrel (DSG).

Study design: Double-blind, double-dummy prospective phase III study in healthy women aged 18–45 years evaluating a total of 858 women with 6691 DRSP and 332 women with 2487 DSG treatment cycles.

Results: Overall, 82 (9.6%) women in the DRSP group and 44 (13.3%) women in the DSG group experienced treatment-emergent adverse events (TEAEs) leading to premature termination of the trial meaning that 32% more women in the DRSP group finished the trial in comparison to the DSG group (based on the AUC of Kaplan–Meier's curves). Discontinuation rates due to abnormal bleeding were 3.7% for DRSP and 7.3% for DSG users. This is a 55.7% lower discontinuation rate in the DRSP group compared to the DSG group.

Conclusions: This report describes the improvement in acceptability and bleeding profile of women using the new DRSP-only oral contraceptive compared to DSG, providing a better quality of life and adherence to the contraceptive method as demonstrated by lower discontinuation rates of women using the estrogen-free DRSP-only pill.

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Drospirenone-only pill; discontinuation rates; contraception

Introduction

Shortly after introducing the first combined oral contraceptives (COCs) in the 1950s, researchers described the first cases of deep venous thromboembolism (VTE) under this contraceptive method [1]. Since the estrogen component of the COCs (ethinylestradiol) was primarily blamed as a possible cause of the onset of thrombosis, and due to other estrogen-related side effects such as weight gain, bleeding disorders, nausea, and bloating, a reduction in the dosage of the estrogens was continuously introduced in the 1970s. The decrease in the estrogen dose of the COCs correlated with a reduced risk of VTE events [2–4].

Efforts to further reduce the risk have also changed the progestin component over time. After introducing the first COCs (which included the progestins lynestrenol, and ethynodiol diacetate), new progestins like levonorgestrel were introduced in the 1970s, and gestodene and desogestrel (DSG) in the 1980s.

The next generation of progestins, such as DSG, gestodene, and drospirenone (DRSP), bind more specifically to the progesterone receptor and show a reduction in androgenic, estrogenic, and glucocorticoid-related side effects, with a more neutral impact on metabolic parameters [5]. Unfortunately, these new progestogens used in combination with ethinylestradiol have been associated with an increase in VTE risk in comparison to COC with levonorgestrel [6]. Therefore, the use of estrogen-free progestogens is increasing because of their cardiovascular safety profile.

All EU countries, the US Food and Drug Administration, and other agencies worldwide have recently approved a novel estrogen-free contraceptive with DRSP 4 mg [7,8].

For long, the problematic bleeding while using progestin-only pills (POPs) was challenging [9]. During a normal menstrual cycle, the endometrium is exposed to circulating sex steroids. The sequential exposure of the endometrium to natural steroids, estradiol, and progesterone leads to characteristic histological features [10].

The mechanisms involved in bleeding-associated disorders during the use of combined hormonal contraceptives or estrogen-free contraceptives are still unclear. Together with a superficial blood vessel permeability and the steroid hormone-induced change of endometrium receptors, local angiogenetic factors are the most accepted explanation for these bleeding disorders [11,12].

Women using contraceptives associate the occurrence of unscheduled bleeding or spotting negatively. Problematic bleeding is the most common quoted reason for user discontinuation

CONTACT Pedro-Antonio Regidor antonio.regidor@exeltis.com Exeltis Europe, Adalperostr. 84 85737, Ismaning, Germany
EudraCT: 2011-002396-42.

in up to 25% of users [13,14]. The objective of this study was to assess the effect of DRSP 4 mg vs. DSG 0.075 mg on the discontinuation rates due to adverse events and mainly due to bleeding disorders.

Materials and methods

Study design

This phase III study was a double-blinded, double-dummy, randomized controlled trial including 88 centers in Austria, Czech Republic, Germany, Hungary, Poland, Romania, Slovakia, and Spain

Ethics approval

The protocol was designed, and the study conducted according to existing legal regulations and following Good Clinical Practice in clinical trials and the Declaration of Helsinki, including recommendations in the European Medicines Agency Committee for Medicinal Products for Human Use Guideline on Clinical Investigation of Steroid Contraceptives in Women. Institutional review board approval was obtained for all study sites. All participants gave their written informed consent for participation in the clinical trial after obtention of the correspondent ethics committee approval for each of the investigational centers The overall approval for the trial was given in July 2012 by the leading ethics committee (Landesamt für Gesundheit und Soziales Berlin, Geschäftstelle der Ethik Kommission des Landes Berlin, number 11/0606 EK) (EudraCT 2011-002396-42). The study was performed between August 2012 and January 2014.

Study medication

The study medication was DRSP, one tablet of 4 mg non-micronized DRSP per day, via the oral route, with consecutive administration of 24 active pills and four placebo tablets with no tablet-free interval between two successive cycles (24/4 regimen).

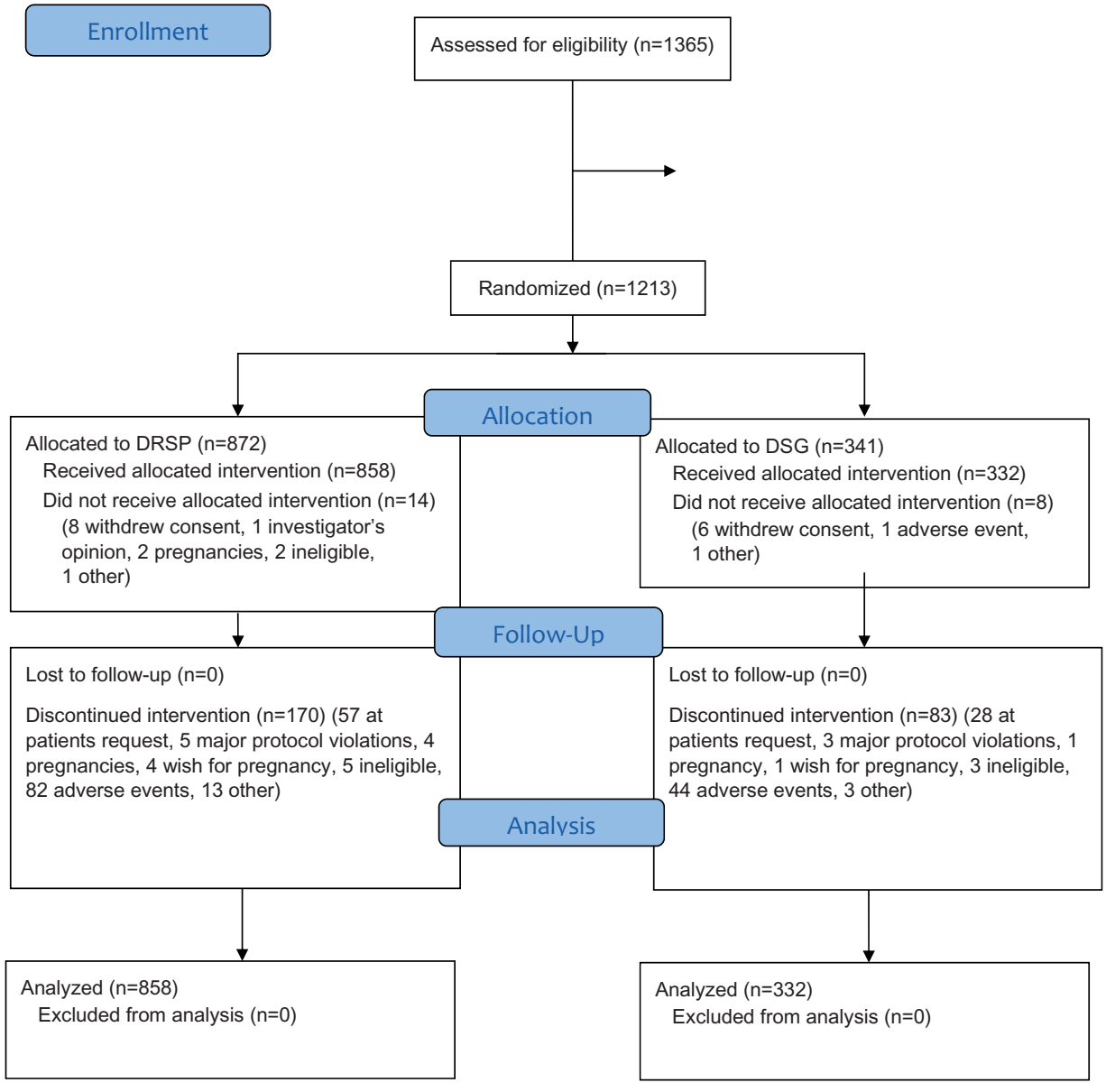


Figure 1. CONSORT diagram.

The comparator was DSG 0.075 mg in a regimen of 28 active pills, marketed under trade names such as Cerazette® and Cerazet®, as it also inhibits ovulation as a POP. It is also the first POP with a missed pill window of 12 h, instead of the 3 h allowed by conventional POPs, and is one of the leading POPs on the European market.

We assessed medication compliance using an electronic diary, providing time and hour of each tablet intake, allowing for calculation of the number of study medication delayed tablet intake for more than 12 h, i.e. more than 36 h after the last tablet intake.

Study population

A total of 858 women with 6691 DRSP and 332 women with 2487 DSG treatment cycles were analyzed. Women included in this study were all of child-bearing potential, at risk of pregnancy, agreeing to use only the study medication for contraception for the duration of the study treatment, aged 18–45, with systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg.

The medication groups were divided into starter = first administration of a hormonal contraceptive or at least 4-month break after the administration of another hormonal contraceptive or switcher = direct switch from another hormonal contraceptive to the studied drug with no gap in administration.

Sample size

To test non-inferiority of the discontinuation parameters between the two treatment groups (assuming a 24% proportion of the control group, a 9% non-inferiority margin, a one-sided type I error 2.5, 80% power, and a 2:1 treatment allocation rate), a sample size of 531 in the DRSP group and 266 in the DSG group was required. A sample size of 443 women in the DRSP group and 222 in the DSG group was needed to prove superiority under the same assumptions. Considering the possibility of a drop-out rate of 20%, 857 DRSP- and 333 DSG-treated women were to be enrolled in the clinical trial.

Randomization and blinding

Randomization was performed using a validated system that automates the random assignment of treatment groups to randomization numbers. The randomization scheme was completed in a 5:2 ratio using blocking methodology via a center-based randomization method. The randomization data were kept strictly confidential, accessible only at the time of unblinding. The DRSP-only group received the test product (DRSP 4.0 mg) in blister A plus reference placebo in blister B. The DSG group received the test placebo in blister A plus reference product (DSG 0.075 mg) in blister B.

Safety analysis

Safety analyses were performed for the Safety Set. Safety assessments were to be summarized by treatment groups by means of the default summary statistics. All treatment-emergent adverse events (TEAEs) were summarized by calculating the number and percentage of women with adverse events by preferred term and system organ class. TEAEs were also summarized by severity and relationship to treatment. The number and percentage of women with serious adverse events and TEAEs leading to premature discontinuation were provided.

Statistics

The discontinuation rate statistic was performed on the Full Analysis Set bleeding data and was summarized by treatment groups using summary statistics. A chi-square test was applied to compare rates in both treatment groups. AUC estimates were calculated for both analyzed discontinuation rates (overall and bleeding related).

Results

Study population

A total of 1213 women were randomized to DRSP (872 women) or DSG (341 women), and 1190 received the allocated treatments (858 DRSP and 332 DSG, see Figure 1). Of 1190 treated women, 253 (21.2%) women terminated prematurely: 170 women (19.8%) in the DRSP group and 83 women (24.9%) in the DSG group (see Figure 1 and Table 1).

Analysis of adverse events

Overall, 15.7% of women in the DRSP group and 18.7% of women in the DSG group experienced TEAEs classified as at least possibly related to the study treatment. The most frequently reported TEAEs assessed as possibly related to the trial treatment were vaginal bleeding (3.1% in the DRSP group and 6.0% in the DSG group, $p < .05$), acne (3.0% DRSP and 5.1% DSG), and weight increased (2.2% DRSP and 1.8% DSG).

The frequency of individual TEAEs assessed as severe was low. Four of them were related to vaginal bleeding (two women per treatment group, i.e. 0.2% in the DRSP group and 0.6% in the DSG group) and two women (0.2%) in the DRSP and one

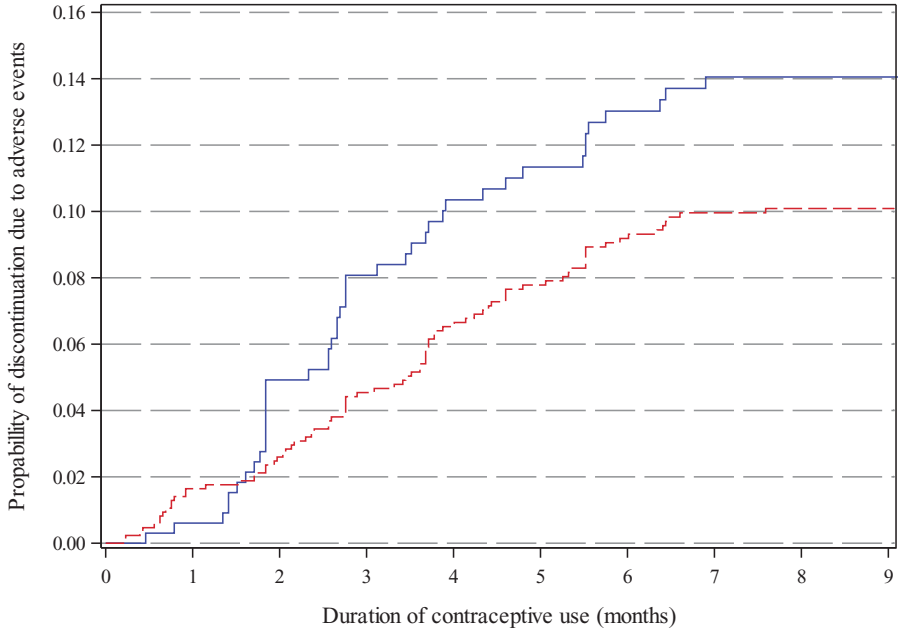
Table 1. Baseline characteristics.

	Statistic	DRSP (N = 858)	DSG (N = 332)
Age (years)	Mean (SD)	28.9 (7.1)	28.9 (7.1)
Age group			
≤35 years	*n* (%)	682 (79.5)	259 (78.0)
>35 years	*n* (%)	176 (20.5)	73 (22.0)
Ethnicity			
Caucasian	*n* (%)	856 (99.8)	331 (99.7)
BMI (kg/m^2)	Mean (SD)	22.96 (3.537)	22.82 (3.905)
	Min/max	16.6/41.0	15.9/38.0
BMI group			
<30 kg/m^2	*n* (%)	828 (96.5)	316 (95.2)
≥30 kg/m^2	*n* (%)	30 (3.5)	16 (4.8)
Blood pressure group			
SBP <130 and DBP <85 mmHg	*n* (%)	727 (84.7)	290 (87.3)
SBP ≥130 and DBP ≥85 mmHg	*n* (%)	131 (15.3)	42 (12.7)
Subject status			
Switcher	*n* (%)		
Direct switcher	*n* (%)	628 (73.2)	259 (78.0)
Indirect switcher	*n* (%)	39 (4.5)	14 (4.2)
Starter	*n* (%)	191 (22.3)	59 (17.8)
Unknown	*n* (%)	–	–
VTE risk factors			
Presence of at least one risk factor	*n* (%)	142 (16.5)	59 (17.8)
Previous delivery			
Yes	*n* (%)	395 (46.0)	150 (45.2)
Regular menstrual bleeding during the last 6 cycles			
Yes	*n* (%)	786 (91.6)	305 (91.9)
Prior treatment with sex hormones and modulators of the genital system			
Yes	*n* (%)	469 (54.7)	195 (58.7)

Table 2. Incidence of TEAEs leading to premature discontinuation.

Preferred term	DRSP ($N = 858$) *n* (%)	DSG ($N = 332$) *n* (%)	Total ($N = 1190$) *n* (%)
Subjects with at least one TEAE leading to premature discontinuation	82 (9.6)	44 (13.3)	126 (10.6)
Abnormal uterine bleeding	27 (3.5)	22 (6.9)	49 (4.2)
Acne	9 (1.0)	9 (2.7)	18 (1.5)
Weight increased	8 (0.9)	3 (0.9)	11 (0.9)
Libido decreased	5 (0.6)	2 (0.6)	7 (0.6)
Headache	2 (0.2)	2 (0.6)	4 (0.3)
Alopecia	2 (0.2)	1 (0.3)	3 (0.3)
Mood swings	3 (0.3)	0	3 (0.3)
Abdominal pain	2 (0.2)	0	2 (0.2)
Depressed mood	2 (0.2)	0	2 (0.2)
Depression	1 (0.1)	1 (0.3)	2 (0.2)
Gamma-glutamyltransferase increased	2 (0.2)	0	2 (0.2)
Nausea	2 (0.2)	0	2 (0.2)
Rash	2 (0.2)	0	2 (0.2)
Abdominal pain lower	1 (0.1)	0	1 (0.1)
Abdominal pain upper	1 (0.1)	0	1 (0.1)
Affective disorder	1 (0.1)	0	1 (0.1)
Alanine aminotransferase increased	1 (0.1)	0	1 (0.1)
Blood thyroid stimulating hormone increased	1 (0.1)	0	1 (0.1)
Constipation	1 (0.1)	0	1 (0.1)
Contact lens intolerance	1 (0.1)	0	1 (0.1)
Dysmenorrhea	1 (0.1)	0	1 (0.1)
Feeling abnormal	0	1 (0.3)	1 (0.1)
Generalized edema	0	1 (0.3)	1 (0.1)
Hot flush	1 (0.1)	0	1 (0.1)
Hyperhidrosis	1 (0.1)	0	1 (0.1)
Hyperthyroidism	1 (0.1)	0	1 (0.1)
Hypertrichosis	0	1 (0.3)	1 (0.1)
Malaise	1 (0.1)	0	1 (0.1)
Premenstrual syndrome	1 (0.1)	0	1 (0.1)
Respiratory tract infection	1 (0.1)	0	1 (0.1)
Skin disorder	0	1 (0.3)	1 (0.1)
Vertigo	1 (0.1)	0	1 (0.1)

DRSP: drospirenone; DSG: desogestrel; TEAE: treatment-emergent adverse event.



Arm	Treatment duration (months)	AUC
DSG	9	0.8566588
DRSP	9	0.583116

Figure 2. Probability of discontinuation due to adverse events. Kaplan–Meier's curve. DSG: desogestrel; DRSP: drospirenone; AUC: area under the curve.

Table 3. TEAEs related to bleeding disorders in total and by relatedness, severity, and discontinuation.

	DRSP ($N = 858$)				DSG ($N = 332$)			
	Total *n* (%)	Related *n* (%)	Severe *n* (%)	Discontinuation *n* (%)	Total *n* (%)	Related *n* (%)	Severe *n* (%)	Discontinuation *n* (%)
Abnormal uterine bleeding	40 (4.6)	35 (4)	3 (0.3)	27 (3.2)	31 (9.3)	27 (8.1)	2 (0.6)	22 (6.6)
Dysmenorrhea	8 (0.9)	5 (0.6)	1 (0.1)	1 (0.1)	2 (0.6)	1 (0.3)	1 (0.3)	0
Total	48 (5.5)	40 (4.6)	4 (0.4)	28 (3.3)	33 (9.9)	28 (8.4)	3 (0.9)	22 (6.6)

DRSP: drospirenone; DSG: desogestrel; TEAE: treatment-emergent adverse event.

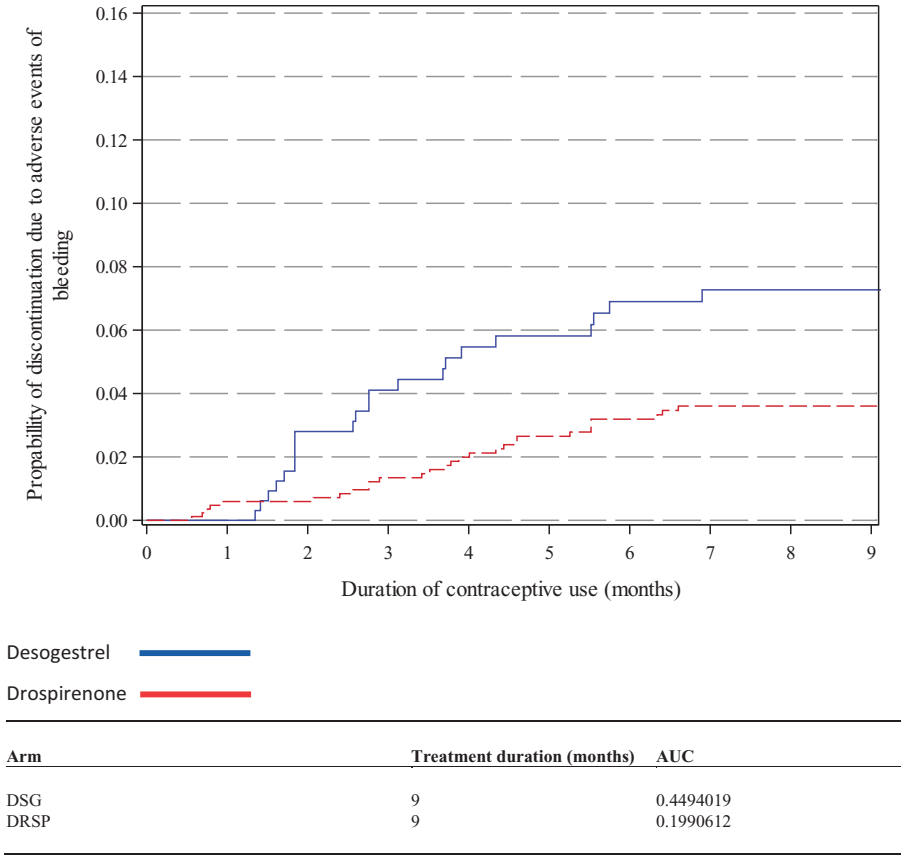


Figure 3. Probability of discontinuation due to adverse events of bleeding. Kaplan–Meier's curve. DSG: desogestrel; DRSP: drospirenone; AUC: area under the curve.

(0.3%) in the DSG group experience acne and libido decrease, respectively. Headache was reported by two women (0.2%) in the DRSP group. All other severe TEAEs each occurred only in one woman.

Adverse events leading to study discontinuation

Overall, 82 (9.6%) women in the DRSP group and 44 (13.3%) women in the DSG group experienced TEAEs leading to study discontinuation (see Table 2). The most common individual TEAEs leading to withdrawal were vaginal bleeding (2.6% in the DRSP group vs. 5.4% in the DSG group) and acne (1.0% in the DRSP group vs. 2.7% in the DSG group).

Using the Kaplan–Meier curve estimates and the area under the curve (AUC) for the overall adverse events as a discontinuation reason, the difference between DRSP and DSG was 32.0% in favor of DRSP, with AUC estimates of 0.583 for DRSP and 0.857 for DSG (see Figure 2). The discontinuation rate was 10% for the DRSP group and 14% for the DSG group ($p < .005$).

In total, 48 (5.5%) women in the DRSP group and 33 (9.9%) in the DSG group experienced bleeding-related TEAEs (see Table 3). Most of the bleeding-related TEAEs were mild or moderate, whereas four (0.4%) women with DRSP and three (0.9%) women with DSG experienced TEAEs of severe intensity. A total of 28 (3.3%) women in the DRSP group and 22 (6.6%) women in the DSG group discontinued the trial due to bleeding-related TEAEs ($p < .005$).

Using the Kaplan–Meier curve estimates and the AUC for bleeding as a discontinuation reason, the difference between DRSP and DSG was 55.7% in favor of DRSP, with AUC estimates of 0.199 for the DRSP group and 0.449 for the DSG group (see Figure 3). The discontinuation rate was 3.7% for the DRSP group and 7.3% for the DSG group.

Discussion

Increasing satisfaction with contraception is essential to help women feel comfortable with the method and continue its use. The most common reason for stopping a contraceptive method completely due to dissatisfaction is the bleeding profile. As described by Hooper [15], the side-effect profile of a contraceptive is another important determinant governing selection, as

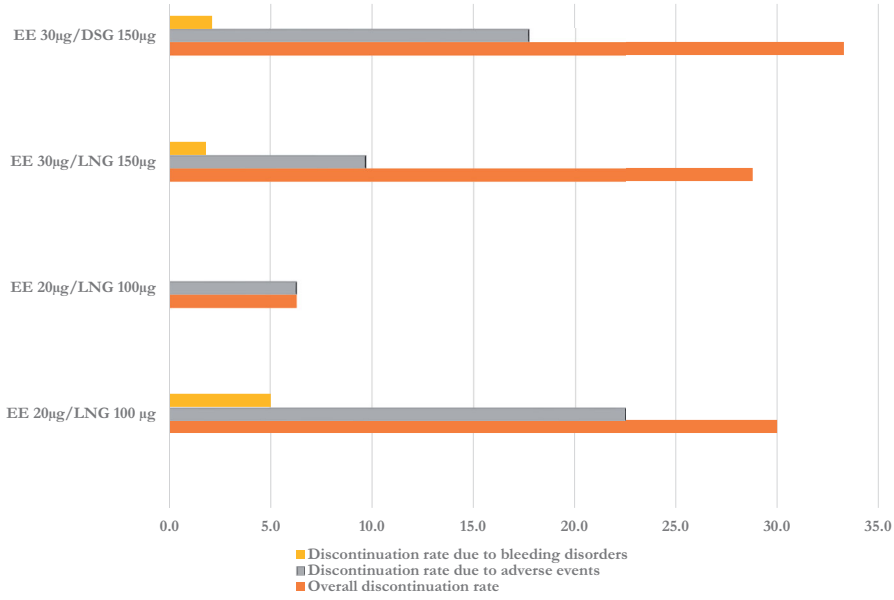


Figure 4. Discontinuation rates in different clinical trias due to adverse events and bleeding disorders of using COC's with 20 and 30 µg ethinylestradiol. Modified from Edelman et al. [20].

this may negatively influence compliance and persistence with the prescribed regimen [16–19].

Our approach to investigate the discontinuation rates due to bleeding is also in accordance with the findings by Hooper [15] who could show that women (especially those in the older age groups) are willing to compromise between effects on the menstrual cycle and other contraceptive attributes when selecting the method that is right for them. More than 40% of participants of the above-mentioned survey indicated that they would consider using a highly effective contraceptive even if it might cause bleeding irregularities, and over 50% documented their wish to accept irregular bleeding if they could have fewer or no periods over the time. Nevertheless, the reasons given for asking for a switch from one hormonal contraceptive to another indicate that bleeding/spotting issues and other contraceptive-related side effects remain a potential barrier to the continuance of the use of such methods [15].

The trend of using estrogen-free contraceptives, despite the possible occurrence of bleeding irregularities, is also triggered by an improved cardiovascular safety of POPs even in comparison to the use of low-dose second-generation COCs [6].

It is worth noting that the discontinuation rates for DRSP as a POP in this study are comparable to reported discontinuation rates of COCs containing 20 and 30 µg ethinylestradiol (findings of the study of Edelman are presented in Figure 4) [20]. This indicates that the new generation of estrogen-free contraceptives does not expose women to a significantly higher probability of discontinuation when compared to COCs.

Adding to this general consideration, associated factors like overweight/obesity, age >35, and smoking result in additive cardiovascular risks [21]. Therefore, the use of estrogen-free formulations like the DRSP-only pill will gain a higher relevance.

Hence, the improvement in the acceptability of the bleeding profile of the new POP with DRSP alone will help to increase the use of POPs in all groups of women.

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Disclosure statement

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ORCID

Pedro-Antonio Regidor http://orcid.org/0000-0002-9551-2847

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