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Drospirenone-only oral contraceptive: results from a multicenter noncomparative trial of efficacy, safety and tolerability☆,☆☆

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Abstract

Objectives: This study was performed to assess the contraceptive efficacy of the drospirenone (DRSP)-only pill and to provide information regarding its safety and cycle-control profile.
Study Design: This prospective, multicenter, noncomparative study was conducted at 41 European sites in healthy women at risk of pregnancy, aged 18 to 45 years. The study medication was DRSP 4.0 mg daily for 24 days followed by a placebo for 4 days (DRSP 4 mg 24/4, Exeltis, Spain) for thirteen 28-day treatment cycles. The primary efficacy endpoint was the overall Pearl Index (PI). Bleeding patterns, changes in vital signs and changes in laboratory values were also analyzed.
Results: A total of 713 participants with 7638 DRSP treatment cycles were analyzed. The overall PI was 0.51 (95% confidence interval, 0.1053–1.4922). The proportion of participants with any bleeding decreased from 72.7% in Cycle 1 to 40% in Cycle 6 and 32.1% in Cycle 13. Unscheduled bleeding decreased from 49.1% in Cycle 1 to 27.8% in Cycle 6 and to 22.8% in Cycle 13. Prolonged bleeding was reported by 6.5% during Cycles 2 to 4 decreasing to 4.2% during Cycles 11 to 13. There were no reports of deep vein thrombosis, pulmonary embolism or hyperkalemia. No relevant changes were observed for laboratory parameters, body weight, body mass index, blood pressure or heart rate. Study drug acceptability was considered as "excellent/good" by over 82% of subjects.
Conclusion: This new DRSP-only oral contraceptive provides clinical contraceptive efficacy similar to that of the currently marketed Combination estrogen plus progestin Oral Contraceptive, with a good safety profile, and favorable cycle control.
Implications: A novel 4-mg DRSP-only pill taken daily for 24 days followed by a placebo for 4 days demonstrated contraceptive efficacy similar to that of currently marketed Combination estrogen plus progestin Oral Contraceptive, with a good safety profile, and favorable cycle control.

Keywords: Drospirenone; Contraception; Progestin-only pill; Efficacy; Safety; Cycle control

1. Introduction

Approximately 100 million women worldwide currently use an oral contraceptive containing an estrogen plus a progestin (COCs) [1]. COCs' use is associated with an increased risk of a venous thromboembolism (VTE) and cardiovascular disease [2,3].

The World Health Organization has documented that progestin-only pills (POPs) do not increase the risk of VTE, stroke and myocardial infarction [4]. This safety advantage should result in more practitioners prescribing a POP to a larger number of eligible women.

Traditional POPs are taken daily and have been associated with poor cycle control and stringent missed-pill rules, such as a 3-h time window for next pill intake [5–8]. Desogestrel 75 mcg was an improvement over traditional POPs with a more generous missed-pill window (12 h), but Desogestrel 75 mcg's bleeding profile remains a significant barrier to more widespread use [5].

A novel drospirenone (DRSP)-only pill was developed to improve compliance and side effects. DRSP is a unique progestin derived from spironolactone with antimineralocorticoid and

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antiandrogenic properties [9]. The 4 mg dose of DRSP was selected after completion of pharmacokinetic and pharmacodynamic (PK/PD) studies. Multiple-dose exposure of DRSP 4 mg demonstrated a lower exposure of DRSP compared to 3-mg/20-mg ethinyl estradiol (EE) (Yaz®) (data on file, Exeltis), and additional testing with DRSP 4 mg demonstrated inhibition of ovulation with DRSP 4 mg similar to that of desogestrel 75 mcg during two 28-day cycles [10].

The regimen for this new oral contraceptive was DRSP daily for 24 days followed by a placebo for 4 days. This schedule was chosen as it was thought that a break in the intake regimen might improve cycle control if a progestogen withdrawal bleed is induced, which is then a scheduled bleed.

The aim of the current study was to assess the contraceptive efficacy of the DRSP-only pill and to provide information regarding its safety and cycle-control profile.

2. Materials and methods

This prospective, multicenter, noncomparative Phase III study was performed to demonstrate the efficacy and safety of DRSP-only oral contraceptive (DRSP 4-mg tablets for 24 days+placebo for 4 days). Participants who forgot one tablet were allowed to take two tablets at the same time on the day after, without back-up contraception when the delay was no longer than 24 h.

The study was conducted at 41 centers located in Czech Republic, Germany, Hungary, Poland and Romania between July 11, 2011 and March 18, 2013. The protocol was designed and conducted according to the laws, regulations and administrative provisions relating to the implementation of good clinical practice in the conduct of clinical trials on medical products in human use. Institutional review board approval was obtained for all study sites in accordance with the declaration of Helsinki and its updates. Participants were counseled, and they signed the written informed consent before entering the study.

Healthy women at risk of pregnancy, aged 18 to 45 years, agreeing to use the study contraceptive as their only birth control method for at least 13 cycles were included in the study. Subjects with blood pressure above 140 for systolic blood pressure (SBP) and 90 for diastolic blood pressure (DBP) or with any abnormal findings that precluded participation in the study of a hormonal contraceptive were excluded. There were no weight or body mass index (BMI) restrictions, nor any restriction regarding tobacco use or personal or familial cardiovascular disease history, except for the Czech Republic subjects.

This study consisted of thirteen 28-day treatment cycles followed by a 10–28-day follow-up period. After the screening visit, eligible women were enrolled and instructed to take one active DRSP 4-mg tablet for 24 days followed by four placebo tablets for 4 days. Serum or urine pregnancy tests, assessment of vital signs and of general safety laboratory parameters, review of concomitant medications and adverse events were performed during follow-up visits. In addition, the subjects were asked to fill in an electronic diary (pill intake time, additional contraception, occurrence and intensity of bleeding or spotting, sexual intercourse), starting at the screening visit.

The primary efficacy endpoint was the overall Pearl Index (PI). PI after correction for additional contraception for sexual activity status and cumulative pregnancy rate were secondary efficacy parameters. Pregnancy was confirmed by quantitative serum human Chorionic Gonadotropin (hCG) test.

Evaluation of bleeding and spotting was based on the subject's daily diary. Definitions regarding bleeding patterns are presented in Table 1.

Safety assessment was based on adverse event reports using MedDRA definitions and changes in vital signs or laboratory data during the course of the study.

Acceptability was assessed by the subject and by the investigator using general questions regarding drug tolerability and subject well-being. Each used a rating of excellent, good, moderate or poor.

The number of subjects to be included was set at 700. This number was calculated in order to provide at least 400 women with 13 treatment cycles.

The primary efficacy endpoint was the PI, defined as the number of contraceptive failures per 100 women–years of exposure. It was calculated as follows: 100 * total number of pregnancy * 13 divided by the total number of 28-day medication cycles. Overall PI included all pregnancies which occurred during the study. For the calculation of the PI after correction for back-up contraception and sexual activity status, all medication cycles in which back-up contraception was used or without intercourse were considered as not evaluable and were not included.

Bleeding patterns, changes in vital signs and changes in laboratory values were summarized using descriptive statistics [mean, median, standard deviation (SD), minimum and maximum values].

Table 1
Definitions for unscheduled and scheduled endometrial bleeding and spotting.

Term	Definition
Bleeding	Bleeding that required the use of sanitary protection
Spotting	Blood loss that did not require new use of any type of sanitary protection
Scheduled	Bleeding or spotting that occurred during hormone-free intervals (Days 25–28 ± 1). Up to 8 consecutive bleeding/spotting days were considered scheduled bleeding days
Bleeding day	
Unscheduled bleeding/spotting day	Any bleeding/spotting that occurred while taking active hormones (Days 2–23), except days that were classified as scheduled bleeding days
Episode of bleeding/spotting	Bleeding/Spotting bounded on either end by 2 days of no bleeding or spotting
Amenorrhea	No bleeding or spotting during the reference period
Prolonged bleeding episode	More than 14 days of bleeding/spotting
Bleeding intensity	Rated as slight, moderate or heavy

3. Results

A total of 713 participants received the study medication. Their mean age was 28.7 years, ranging from 18 to 46 years, with a majority of the women (79.8%) under the age of 35. At entry, 15.4% of subjects had at least one VTE risk, and 25.5% subjects were smokers (Table 2).

Of the 713 participants, 27.8% prematurely terminated the study treatment, primarily due to adverse events (12.3%) or consent withdrawal (10.4%) (Fig. 1).

The mean treatment duration was 304.1 ± 107.9 days, and the median duration was 364.0 days ranging from 1 to 393 days.

A total of 713 participants with 7638 DRSP treatment cycles were analyzed in the full analysis set population. During these cycles, three participants, all below 35 years of age, became pregnant in Cycle 2, Cycle 3 and Cycle 13, respectively.

The overall PI was 0.51 [95% confidence interval (CI), 0.1053–1.4922] (Table 3). The overall PI after correction for additional contraception and sexual activity status, as well as PI according to age range, are presented in Table 3. The 13-cycle cumulative pregnancy rate was 0.50% (95% CI, 0–1.07%) for all participants and 0.64% (95% CI, 1–1.37%) for participants≤35 years of age.

Table 2
Participant demographics at baseline.

	Statistic	DRSP (*N*=713)
Age (years)	Mean (SD)	28.7 (7.1)
Age group		
≤35 years	*n* (%)	569 (79.8%)
>35 years	*n* (%)	144 (20.2%)
Ethnicity		
Caucasian	*n* (%)	710 (99.6%)
BMI [kg/m^2]	Mean (SD)	23.0 (3.8)
	Min/Max	16/38
BMI group		
<30 kg/m^2	*n* (%)	672 (94.2%)
≥30 kg/m^2	*n* (%)	41 (5.8%)
BP group		
SBP < 130 mmHg and DBP < 85 mmHg	*n* (%)	571 (80.1%)
SBP≥130 mmHg or DBP≥85 mmHg	*n* (%)	142 (19.9%)
Smoking status		
Nonsmoker	*n* (%)	493 (69.1%)
Current smoker	*n* (%)	182 (25.5%)
Ex-smoker	*n* (%)	38 (5.3%)
VTE risk factor		
Presence of at least one risk factor	*n* (%)	110 (15.4%)
Previous delivery		
Yes	*n* (%)	305 (42.8%)
Regular menstrual bleeding during the last 6 cycles		
Yes	*n* (%)	680 (95.4%)
Prior treatment with sex hormones and modulators of the genital system		
Yes	*n* (%)	455 (63.8%)

N: Number of participants in specified analysis set; *n*: number of participants with available data; %: percentage based on *N*; VTE: venous thromboembolism.

The proportion of participants with any bleeding decreased from 72.7% in Cycle 1 to 40% in Cycle 6 and 32.1% in Cycle 13.

Scheduled bleeding during the hormone-free interval was reported by 47.9% of the women in Cycle 1 decreasing to 36.8% in Cycle 6 and 24.4% in Cycle 13 (Fig. 2).

Unscheduled bleeding decreased from 49.1% in Cycle 1 to 27.8% in Cycle 6 and to 22.8% in Cycle 13 (Fig. 3). The mean number of unscheduled bleeding days decreased from 1.9 in Cycle 1 to 0.9 in Cycle 6 and 0.7 in Cycle 13.

Overall, bleeding duration decreased over time (Cycle 1: 2.9 days, Cycle 6: 1.3 days and Cycle 13: 1 day), and more than 90% of bleeding days were classified as slight or moderate.

Prolonged bleeding was reported by 6.5% of the participants during Cycles 2 to 4 decreasing to 4.2% during Cycles 11 to 13. The incidence of participants without bleeding episode increased from 14.4% during Cycles 2 to 4 to 26.6% during Cycles 11 to 13.

Spotting was reported by 87.1% of participants in Cycle 1 decreasing to 62.7% in Cycle 6 and to 44.7% in Cycle 13. Unscheduled spotting decreased from 69.6% in Cycle 1 to 48.3% in Cycle 6 and to 35.1% in Cycle 13. The mean number of unscheduled spotting days decreased from 3.4 in Cycle 1 to 1.7 days in Cycle 6 and to 1.2 days in Cycle 13.

There were no reports of deep vein thrombosis, pulmonary embolism or hyperkalemia. The most frequent individual treatment emergent adverse events (TEAEs) are presented in Table 3. At least one possibly DRSP-related TEAE was reported by 150 participants (21.0%). The most frequent individual TEAEs, assessed as possibly related, were acne (5.5%), metrorrhagia (1.7%), headache (1.5%) and decreased libido (1.4%) (Table 3). The vast majority of TEAEs were classified as mild or moderate. An increase in the thyroid stimulating hormone (TSH) levels was found in 15 participants (2.1%) (Table 4). Severe TEAEs were reported for 25 participants (3.5%). No serious adverse events were reported during the course of the study.

Overall, 88 (12.3%) participants prematurely terminated the trial due to adverse event. The most frequent TEAEs leading to withdrawal were acne (2.9%), metrorrhagia (1.7%) and irregular menstruation (1.3%). The majority of these TEAEs were assessed as at least possibly related to study treatment.

No relevant changes were observed over time with regard to laboratory parameters, body weight or BMI, blood pressure or heart rate. A median weight decrease of 1 kg was observed in obese participants who had an initial BMI≥30 kg/m^2. A median decrease of 8 mmHg for SBP and 5 mmHg for DBP was observed in 137/142 participants who were found to have an initial SBP≥130 mmHg or DBP≥85 mmHg. Based on gynaecological and transvaginal ultrasonography examination, only 2 clinically significant findings were demonstrated: 1 ovarian cyst and 1 salpingo–oophoritis. A shift from normal cervical cytology at screening to abnormal (ASC-US, CIN1 or CIN2) at the last visit was reported for a total of 14/713 women.

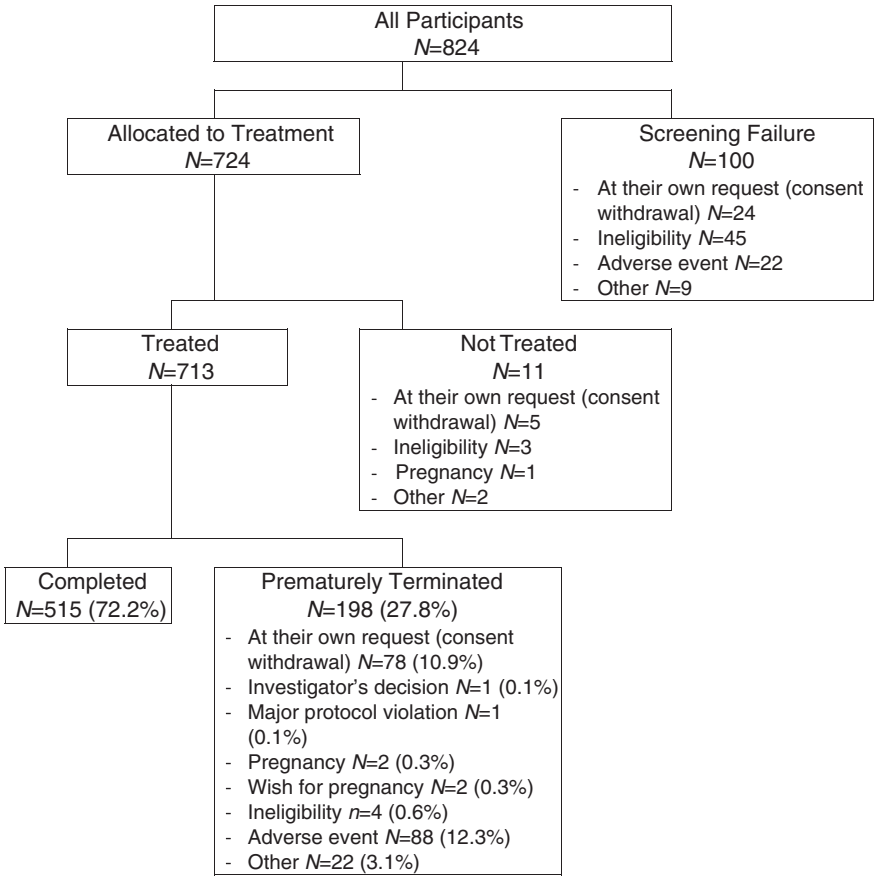

Fig. 1. Flow chart of participants disposition.

Table 3
Efficacy results — PI (full analysis set).

	Statistic	DPSR (*N*=713)
Overall PI		
Pregnancy	*n* (%)	3 (0.4%)
Total number of exposure cycles	*N*	7638
Overall PI	%	0.5106
95% CI for PI	Lower limit/ upper limit	0.1053/ 1.4922
PI after correction for additional contraception and sexual activity status		
Pregnancy	*n* (%)	3 (0.4%)
Total number of cycles with sexual activity and without additional contraception	*N*	7191
Overall PI after correction for additional contraception and sexual activity status	%	0.5423
95% CI for PI	Lower limit/ upper limit	0.1118/ 1.5850
PI according to subject age		
≤35 years	*n* (%)	*N*=569
Pregnancy	*N*	3 (0.5%)
Total number of exposure cycles	%	5530
Overall PI		0.7052
95% CI for PI	Lower limit/ upper limit	0.1454/ 2.0610

N: Number of subjects in full analysis set; *n*: number of subjects/cycle with data available; %: percentage based on *N*.

Study drug acceptability was considered as "excellent" or "good" by over 82% of participants and investigators at the last visit.

4. Discussion

This new DRSP-only oral contraceptive had an overall PI of 0.50, which is comparable to the COC 24/4 with 20-mcg EE and 3-mg DRSP [11].

The novel DRSP 4-mg tablet taken for 24 days followed by 4 days of placebo (24/4) was chosen in order to induce scheduled withdrawal bleeding and reduce unscheduled bleeding in contrast to other POPs with a continuous regimen. The 24/4 cycle regimen resulted in a reduction of unscheduled bleeding over time, and the mean number of unscheduled bleeding days decreased accordingly. In addition, more than 90% of bleeding days were classified as slight or moderate.

Few participants discontinued the study due to irregular bleeding (4.2%). This compares favorably to the discontinuation rate with continuous use of desogestrel 75 mcg (22.5%) and levonorgestrel (18%) [5].

The rate of AE was low during this study, and no cardiovascular events were reported even though 25.5% of

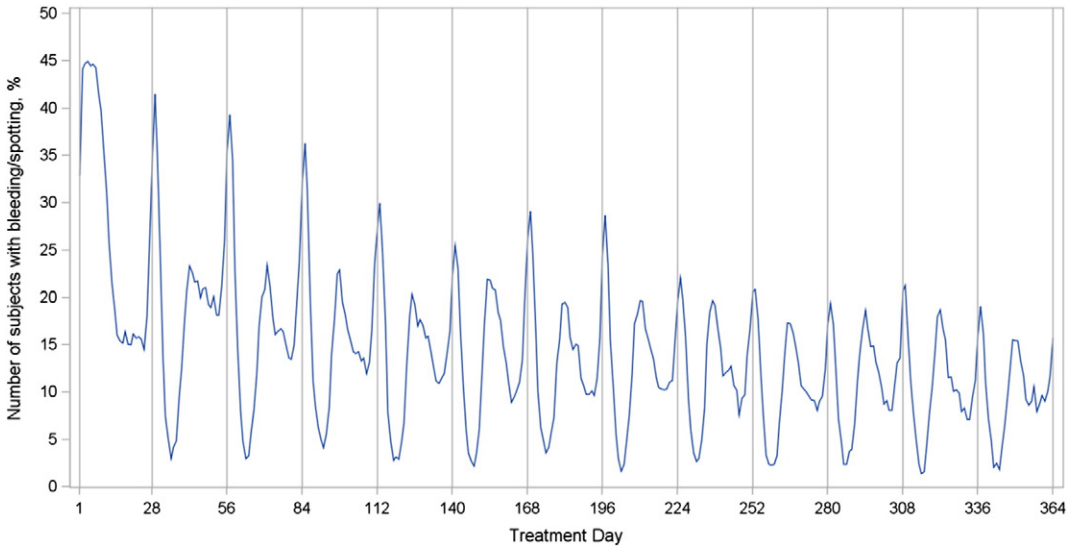

Fig. 2. Number of participants with bleeding and/or spotting.

participants with at least one cardiovascular risk factor were included in this trial. In addition, there was no significant increase in weight, while obese participants were found to have a loss of approximately 1.0 kg. These data compare favorably to a recent publication that described a small increase of weight with other POPs [12].

There was a decrease in blood pressure in participants whose baseline values were SBP > 130 and DSP > 85 mm Hg. The effect of DRSP on blood pressure has been demonstrated in a double-blind, randomized, placebo-controlled study (12-week) with 3-mg DRSP/1-mg E2 in postmenopausal women with hypertension (systolic, 140 to 159 and/or diastolic, 90 to 99 mmHg)., The blood pressure was reduced on DRSP/E2 (clinic BP, −14.1/−7.9 for DRSP vs. −7.1/−4.3 mmHg for placebo, ($p < 0.0001$) [13]. This finding is probably due to the antimineral-corticoid properties of DRSP.

The limitations on these findings include the noncomparative design of the protocol [14] and the fact that cycle-control and drug adherence assessments were based on participants' diaries. It is well known that discrepancies exist between subject self-reporting of adherence and actual adherence [15].

An increase in TSH level was observed in 2.1% of the participants and was considered not clinically relevant by the investigators.

In conclusion, this new DRSP-only contraceptive provides clinical contraceptive efficacy similar to that of currently marketed COCs, with a good safety profile, and

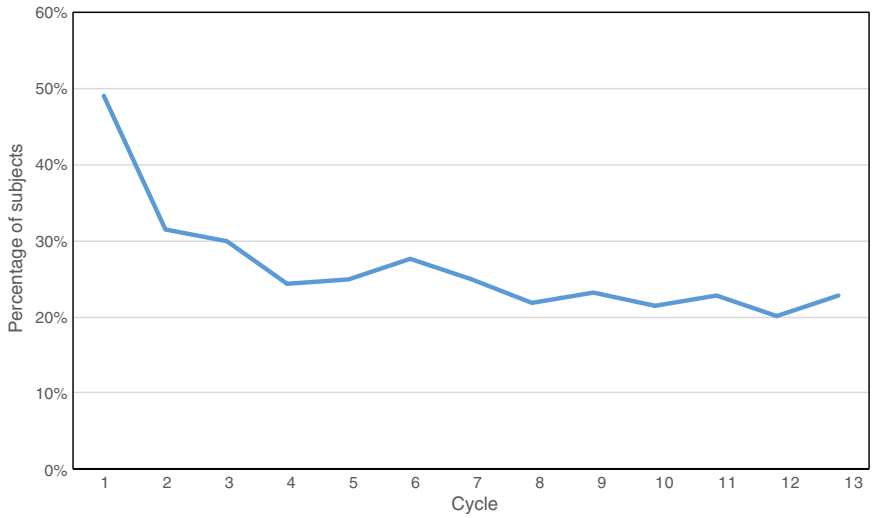

Fig. 3. Percentage of participants with unscheduled bleeding by cycle.

Table 4
Incidence of most frequent (≥2%) TEAEs by preferred term.

	DRSP (*N*=713)	
	n	%
Acne	45	6,3
Headache	32	4.5
Nasopharyngitis	22	3.1
Cystitis	21	2.9
Metrorrhagia	19	2.7
Tonsillitis	19	2.7
Menstruation irregular	15	2.1
Blood TSH increased	15	2.1
Cervical dysplasia	14	2.0

favorable cycle control, thus providing an appropriate contraceptive option for a much broader group of women than the group for whom previous POPs were recommended.

Declaration of interest

David F. Archer, MD, is a consultant to AbbVie Laboratories, Agile Therapeutics, Bayer Healthcare, Endoceutics, Exeltis (CHEMO), Shionogi, TEVA and TherapeuticsMD; he received Industry Research Support for Research from AbbVie, Bayer Healthcare, Endoceutics and TherapeuticsMD; Pharmaceutical Stock Holdings: Agile Therapeutics Stock Options.

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Dominique Drouin is an employee of Exeltis.

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