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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