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Original Research Article

Multicenter, open-label trial to assess the safety and tolerability of drospirenone 4.0 mg over 6 cycles in female adolescents, with a 7-cycle extension phase ☆,☆☆

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ABSTRACT

Objective: To assess the safety, tolerability and bleeding patterns of drospirenone 4.0 mg.
Study design: A multicenter, open-label, safety trial in sexually-active adolescents aged 12–17 years for six 28-day treatment cycles (Core Phase) and an optional 7–13 cycle extension with administration of drospirenone 4.0 mg in a regimen of 24 active/4 placebo tablets.
Results: We enrolled 111 subjects, and after eight failed Screening and one withdrew consent, 102 remained evaluable; 89 (87.3%) completed the Core Phase. Overall, treatment with drospirenone 4.0 mg was well tolerated. Possibly-related TEAEs were reported for 23 subjects (22.5% of the 102 evaluable); two serious adverse events were reported during the Extension Phase (pharyngitis and joint dislocation), neither related to treatment. The number of subjects reporting dysmenorrhea decreased from 47 prior to Screening, to 14 at the end of Cycle 6, to 8 at the end of Cycle 13. Assessments of vital signs and gynecological and physical examinations were unremarkable.

We observed a trend towards less bleeding and/or spotting over the first cycles with the use of drospirenone: the proportion of subjects with both scheduled and unscheduled bleeding and spotting decreased, while the proportion with absence of bleeding or spotting increased. Only five subjects (4.9% of 102 evaluable) prematurely terminated the trial due to irregular bleeding.

At the end of 6 months, 85.3% rated the tolerability of drospirenone as "excellent" or "good".
Conclusions: The results indicate that 4.0 mg drospirenone over 13 treatment cycles was well tolerated, safe and acceptable for the majority of adolescents.
Implications: Drospirenone 4.0 mg oral pills provide a well-tolerated, safe and acceptable contraceptive choice for adolescents.

1. Introduction

Approximately 100 million women worldwide use a combined oral contraceptive, containing an estrogen plus a progestogen (COC) [1]. Although COC use is associated with an increased absolute risk of venous embolism (3 to 10 per 10,000 women/year, compared to 0.8 per 10,000 women/year for pre-menopausal non-users of COCs [2]) and increased adjusted risk for cardiovascular disease (odds ratios up to 2.13 and 2.48 for stroke and MI, respectively, compared to non- or never-users of COCs [2]), the estrogen-free, mid-dosed progestogen-only pills (POPs), are not [2–4].

POPs are taken daily and have been associated with poor cycle control and stringent missed pill rules, such as a 3-to-12-hour time

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window for taking the next pill [5–7]. Adhering to such a strict intake regimen requires a high level of discipline, and delays of more than 3 to 12 hours occur frequently, reducing contraceptive reliability [7–9]. Moreover, POPs rely mostly on cervical mucus changes, and many do not reliably suppress ovulation [10]. Failure rates in typical use are essentially the same, however, for COCs and POPs [11].

A new 4.0 mg formulation of the progestogen, drospirenone, having a regimen of 24 active tablets followed by 4 placebo tablets, was designed to reduce unscheduled bleeding while providing effective ovarian suppression [12]. In combination with ethinyl estradiol (EE) and 17ß-estradiol (E2), drospirenone has been extensively studied in the preclinical and clinical setting. Drospirenone 3 mg, in combination with EE 30 μg or 20 μg, from 21 days to 24 days, is registered for use in the prevention of pregnancy as an oral contraceptive (e.g., Yasmin®, Yasminelle®, YAZ®).

In a prospective, multicenter, non-comparative study in healthy women ages 18 to 45 from 41 European sites, Archer and colleagues found that drospirenone 4.0 mg provided clinical contraceptive efficacy comparable to that of currently-marketed COCs, along with a good safety profile and favorable cycle control [6]. These findings distinguish this new estrogen-free pill from traditional POPs by allowing the same "safety window" or flexibility in intake as COCs, while maintaining contraceptive reliability [8,12,13].

In a pivotal, multicenter, randomized comparative study in nearly 1200 healthy women, Kubba et al reported a better bleeding profile for drospirenone 4.0 mg compared to desogestrel 0.075 mg over 9 cycles, potentially leading to improved tolerability and acceptance [13].

Due in part to its 30-hour half-life, drospirenone 4.0 mg obviates the need to adhere to the strict intake regimen required for other POPs. This is an important advantage that may incentivize use in many women, particularly adolescents, who are likely to be less compliant and have more periodic delays or skipped doses than adults (adolescents frequently miss doses for a full day or longer) [14]. Drospirenone's antiandrogenic properties, moreover, may provide additional benefits to adolescents in the control of acne [15–17].

Teenagers, moreover, are more likely than adult women to use hormonal contraceptives for purposes other than birth control [18]. Even among 15–19-year olds who have never had sex, 8% use the pill [18], most commonly for menstrual pain (54%), menstrual regulation (33%) and acne (30%) [18]. These statistics are not surprising, since menstrual-related disorders and irregular menses are particularly common during adolescence, with 70–91% of female teenagers reporting painful periods, [19–21] and approximately 25% experiencing marked menstrual disturbances [19].

Despite their widespread use in teenagers, the vast majority of hormonal contraceptives have not been studied adequately in adolescents [22], with few industry-sponsored trials enrolling subjects younger than 18 years of age. Trials that have included adolescents typically exclude those younger than 16 [22]. This lack of testing has resulted in a dearth of data for multiple hormonal contraceptive agents that are commonly used in the clinical care of adolescent females [22].

In view of the paucity of data in this important patient population, the objective of this open-label trial was to assess the safety and tolerability of drospirenone 4.0 mg in adolescents, including bleeding pattern.

The primary endpoints were: (1) treatment-emergent adverse events (TEAEs); (2) vital signs; (3) clinical laboratory parameters; (4) vaginal bleeding pattern (subject diaries); and (5) drospirenone acceptability.

There were no secondary endpoints.

2. Methods

This was a multicenter, open-label, safety trial in female adolescents (EudraCT number: 2013-005234-37). A Core Phase consisted of a Screening Visit, investigational product dispensation visit, and six 28-day treatment cycles, with five on-site visits and a follow-up visit 10–14 days after the last product intake. An Optional Extension Phase contained treatment cycles 7–13 and four visits (two on-site and two telephone interviews). The duration of treatment totaled 364 days.

At the Screening Visit, we performed informed consent and standard screening procedures, and instructed subjects to take one tablet per day. During the medication cycle, the subjects took 24 active tablets (each containing 4.0 mg drospirenone) followed by 4 placebo tablets. The subjects filled in a paper diary daily for the documentation of vaginal bleeding pattern and intake of a tablet from the blister for each medication cycle (amount, date and time) during Cycles 1–13 (please refer to definitions for bleeding and spotting below Fig. 2).

2.1. Inclusion/exclusion criteria

This trial included female adolescents requesting an OC, who were 12–17 years of age; postmenarchial for at least six months; and with at least four regular menstrual cycles during the six months before Screening. Contraindications to participation in this study included any conditions or medications that could interfere with menstrual cycling or reduce cycling levels of the investigational drug or would typically constitute contraindications to use of estrogen-containing OCs. The inclusion/exclusion criteria are displayed in Supplementary Table 1; we excluded subjects for ANY ONE of the reasons shown.

2.2. Determination of sample size

The sample size calculation was not based on statistical considerations, and was therefore not powered to detect bleeding differences. We planned to screen about 130 subjects to have approximately 100 in the safety set (all subjects who took at least one 4.0 mg dose of drospirenone).

2.3. Data management, tabulations, and statistical analyses

We analyzed safety and tolerability variables for the safety set (n = 102), and vaginal bleeding pattern data over 13 cycles for the per-protocol set (all subjects who were included in the safety set and did not present any major protocol deviation, n = 87). All AE data were listed.

We calculated descriptive statistics for the main Baseline and outcome variables, and used default summary statistics to analyze vaginal bleeding pattern data for the study population (n = 102) and the core per-protocol set (all subjects who were included in the safety set who did not present any major protocol deviation during the core phase of the trial, n = 93). We also used default summary statistics to analyze missed tablets or entries for subjects with and without unscheduled bleeding and/or spotting. We did not replace subjects who prematurely discontinued the trial. For categorical data, where appropriate, we presented the number of missing values in a "missing" category. We provided missing data, including (partial) missing dates or times, in the study listings.

2.4. Study ethics

The Independent Ethics Committee approved the protocol, protocol amendments, including subject information sheets for

adolescents and their parents/legal representatives, assent and Informed Consent Forms (ICFs). Due to the vulnerability of adolescents and the absence of marketing authorization for drospirenone, an Independent Data Monitoring Committee was constituted.

We conducted the trial in accordance with the Declaration of Helsinki (1996) as well as with the valid national laws of the participating countries, with the International Conference on Harmonization Harmonized Tripartite Guideline for Good Clinical Practice (E6), and with the Commission Directives 2001/20/EC, 2005/28/EC and 2001/83/EC.

2.5. Subject information and consent

We received assent forms signed by adolescents and ICFs signed by subjects' parents/legal representatives, where applicable, according to national legislation, for all subjects prior to the start of any trial-related procedures. We documented collection of assent forms and ICFs on the Case Report Form (CRF).

3. Results

3.1. Subject disposition and demographics

This one-year study enrolled 111 patients at nine centers in Germany (4), Finland (1), Sweden (1) and Ukraine (3). Supplementary Table 2 contains the list of study locations. The first subject entered the trial on 22 May 2014 and the last subject completed the trial on 19 September 2016. Fig. 1 displays the disposition of subjects: eight failed Screening and one withdrew consent. Of the 102 evaluable subjects in the safety set, 89 (87.3%) completed the Core Phase and 74 (72.5%) completed the Extension Phase. Subject demographics are presented in Table 1.

3.2. Safety and tolerability results

Table 2 summarizes adverse events.

Overall, 65 subjects (63.7%) experienced 215 TEAEs. At least possibly-related TEAEs were reported for 23 subjects (22.5%). The

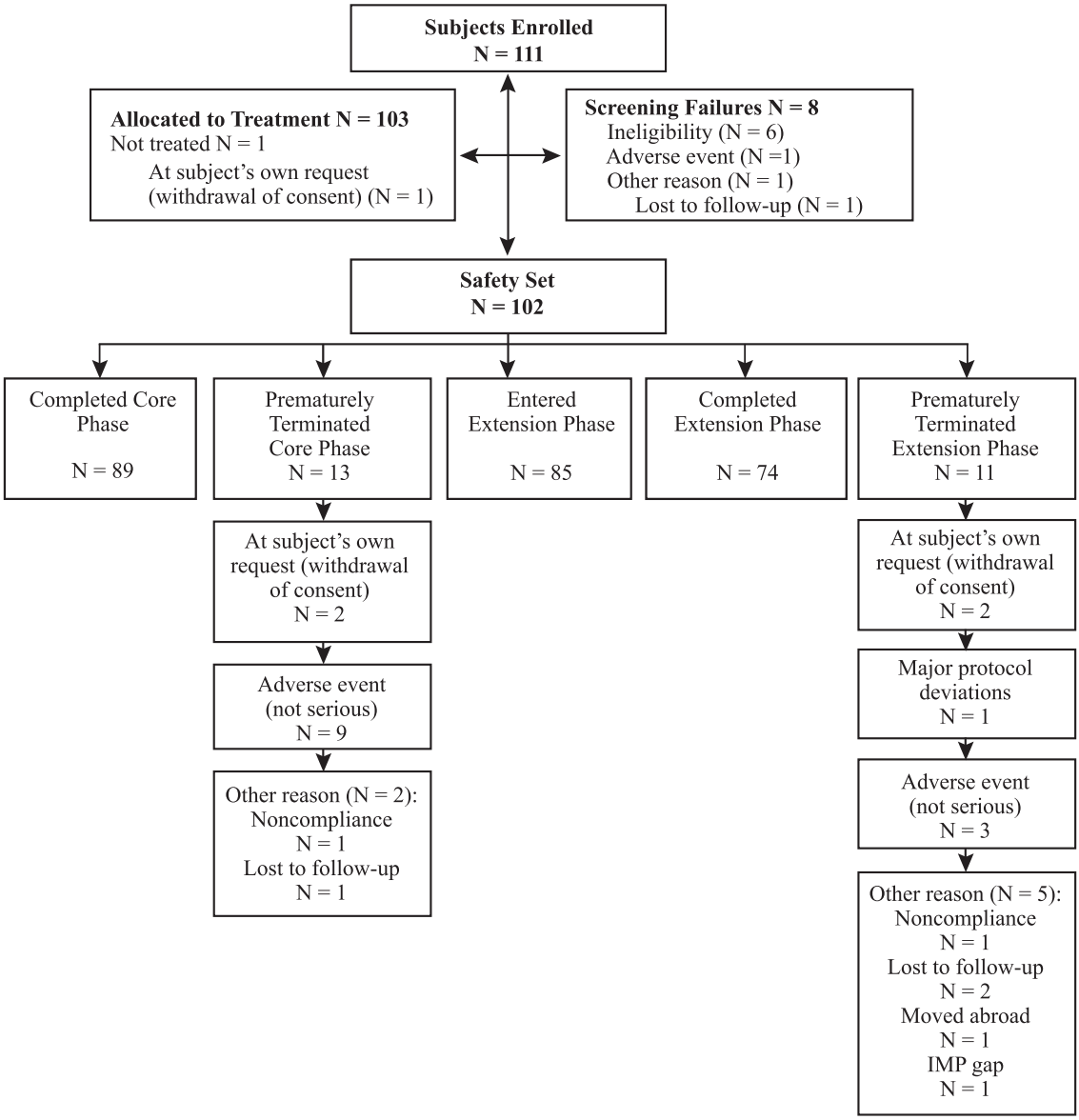

Fig. 1. Flow chart of subjects disposition with reasons for withdrawal: core phase and extension phase of multicenter clinical trial of drospirenone 4.0 mg in female adolescents. Core elements of the study protocol can be found under the study's EudraCT number at the EU Clinical Trials Register.

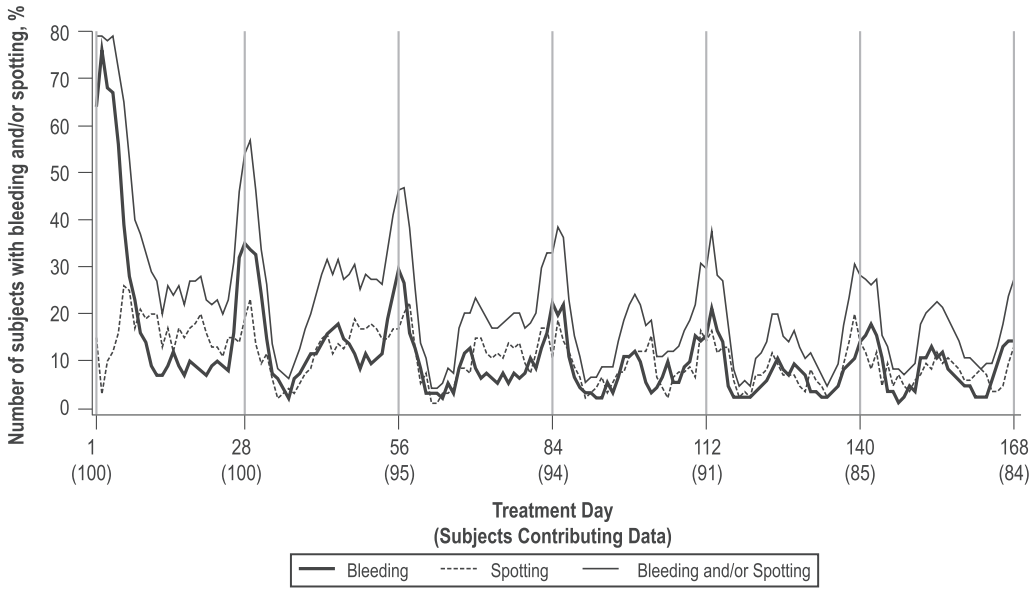

Fig. 2. Number and percent of subjects with bleeding, spotting and bleeding and/or spotting by treatment day, core phase – cycles 1–6 of multicenter clinical trial of drospirenone 4.0 mg in female adolescents. Safety Set. Bleeding was defined as evidence of blood loss that requires the use of sanitary protection with a tampon, pad or pantyliner. Spotting was defined as evidence of minimal blood loss that does not require new use of any type of sanitary protection, including pantyliners. Scheduled bleeding was defined as any bleeding or spotting that occurs during hormone free intervals (defined as Days 25–28 ± 1). Up to 8 consecutive bleeding/spotting days are considered as scheduled bleeding days. Any bleeding or spotting that occurs during cycle Days (1–8)* of the first treatment cycle and lasts up to 8 consecutive bleeding/spotting days is also considered as scheduled bleeding days. Unscheduled bleeding was defined as any bleeding/spotting that occurs while taking active hormones (Days 2–23), excluding days which are classified as scheduled bleeding days. Each subject was instructed to fill in her vaginal bleeding data. *Days (1–8) refers to bleeding which starts on Cycle 1 Days 1–7, but the end day can be Day 8.

Table 1
Subject demographics with status of hormonal contraceptive use in multicenter clinical trial of drospirenone 4.0 mg in female adolescents. Safety Set.

		Drospirenone 4.0 mg (*N* = 102)
Age (years)[a]	*n*	102
	Mean (SD)	16.1 (0.89)
	Median	16.0
	Min/Max	14/17
Race [*n* (%)]	White	99 (97.1)
	Black	–
	Asian	–
	Other	3 (2.9)
	Missing	–
Current level of education [*n* (%)]	No school diploma	2 (2.0)
	Short-course secondary school	4 (3.9)
	Intermediate secondary school	33 (32.4)
	High school	49 (48.0)
	University student	6 (5.9)
	Other	8 (7.8)
	Missing	-
Number of starters[b]	*n* (%)	72 (70.6)
Number of direct switchers[c]	*n* (%)	25 (24.5)
Number of indirect switchers[d]	*n* (%)	5 (4.9)

N: Number of subjects in safety set. %: Percentage based on *N*.
n: Number of subjects with data available. SD: Standard deviation.
[a] Age was derived from imputed date of birth and subject's signed assent form.
[b] Starter is defined as first administration of a hormonal contraceptive or at least 4-month break after the administration of another hormonal contraceptive.
[c] Direct switcher is defined as no break in administration from another hormonal contraceptive to drospirenone 4.0 mg.
[d] Indirect switcher is defined as more than 2 days, and less than 4-month break in administration from another hormonal contraceptive to drospirenone 4.0 mg.

Table 2
Summary of adverse events, treatment-emergent adverse events, and serious adverse events: number of subjects and events in multicenter clinical trial of drospirenone 4.0 mg in female adolescents. Safety set.

	Drospirenone 4.0 mg (*N* = 102)	
	Number of subjects *n* (%)	Number of events #
Subjects with at least one AE	72 (70.6)	236
Subjects with at least one TEAE	65 (63.7)	215
Subjects with at least one related TEAE[a]	23	(22.5) 42
Subjects with at least one severe TEAE	11 (10.8)	19
Subjects with at least one SAE	2 (2.0)	2
Subjects with at least one TESAE	2 (2.0)	2
Subjects with at least one related TESAE	–	–
Subjects with at least one TEAE leading to discontinuation	11 (10.8)	11
Subjects with at least one TEAE of special interest	–	–
Subjects with at least one TEAE based on abnormal bleeding	6 (5.9)	6
Subjects who died	–	–

AE, adverse event; mg, milligrams; SAE, serious adverse event; TEAE, treatment emergent adverse event.
N: Number of subjects in safety set %: Percentage based on *N*.
n: Number of subjects with data available #: Number of events.
[a] Related TEAEs include those assessed as "possibly related" or "related" and the events with missing relationship assessment.

most frequently reported events were reproductive, breast, and psychiatric disorders (altered moods, mood swings, or depression), and the vast majority of TEAEs were mild or moderate. There were no deaths or TEAEs of special interest (deep vein thrombosis, pulmonary embolism and hyperkalemia) reported.

Of the 102 evaluable subjects, two (2.0%) experienced pharyngitis and joint dislocation, both assessed as serious, requiring hospitalization, but unrelated to drospirenone 4.0 mg. The most frequent TEAE leading to withdrawal was irregular bleeding (4.9%). No pregnancies occurred during the trial.

Of the subjects who reported dysmenorrhea prior to the start of the trial, the number reporting it decreased progressively through-

Table 3
Improvement of dysmenorrhea (percent of subjects reporting dysmenorrhea by severity during each cycle) in multicenter clinical trial of drospirenone 4.0 mg in female adolescents.

	No	Yes *N* = 47 (46.1% of all)			Missing
		Mild	Moderate	Severe	
Visit 1a (Screening)		29.8%	48.9%	21.3%	0.0%
Visit 6/EDV (End of Cycle 6)	66.0%	19.1%	6.4%	4.3%	4.3%
Visit 8/EDV (End of Cycle13)	57.4%	10.6%	2.1%	4.3%	25.5%

EDV = early discontinuation visit.
Of the 102 subjects in the safety set, 55 (53.9%) reported no dysmenorrhea within the last 6 cycles prior to Screening Visit 1a.
All other percentages are based on the 47 subjects who did report suffering from dysmenorrhea prior to Screening.

out the study (Table 3), as did the number of subjects using pain medication for dysmenorrhea, from 24 (51.1%) to 6 (12.8%) to 1 (2.1%), at the end of Cycles 1, 6, and 13, respectively.

Assessments of vital signs and gynecological and physical examinations were unremarkable. Absolute median changes from Baseline at endpoint were minimal: body weight, +1.0 kg (min/max: −10/7); body mass index (BMI), +0.30 kg/m^2 (min/max: −3.9/2.4); systolic and diastolic blood pressure, 0.0 mmHg; and heart rate, +2.4 bpm (min/max: −15/28). Based on individual blood pressure or heart rate changes, no TEAEs were reported.

Hematology and most biochemistry parameters and thyroid-stimulating hormone (TSH) remained within the reference ranges of all relevant age groups at all assessments. Overall, abnormal values of hemoglobin, erythrocytes, hematocrit, creatine kinase (CK) N-acetylcysteine (NAC)-activated and TSH that were assessed as being clinically significant were reported for three subjects.

3.3. Vaginal bleeding pattern analysis results

We observed a trend towards less bleeding and/or spotting over the first cycles with use of drospirenone. The proportion of subjects who started bleeding or spotting on Cycle Day [25–28] ± 1 decreased from 50.0% in Cycle 1 to 38.1% in Cycle 6 (Fig. 2), while the proportion of subjects with no bleeding or spotting increased, from 18.9% in Cycle 2 to 30.8% during Cycle 4.

The bleeding patterns reported during the first six cycles continued in the Extension Phase of the study (Fig. 3). The median overall number of bleeding and/or spotting days decreased from 14.0 in Cycles 2–4 to 11.0 in Cycles 11–13. The median number of scheduled bleeding and/or spotting days decreased from 4.0 in Cycles 2–4 to 0.0 in Cycles 11–13. In contrast, the median number of unscheduled days fluctuated between 5.0 and 6.0 during Cycles 2–4, reaching a maximum of 8.0 during Cycles 11–13.

The number of subjects reporting absence of bleeding or spotting increased with treatment duration.

We also examined bleeding patterns for a number of important subgroups (Supplementary Tables 3–6):

Throughout the study, the percentage of women with *no* scheduled/unscheduled bleeding or spotting generally *increased*, as did the percentage with *no* scheduled spotting/bleeding but unscheduled spotting/bleeding.

In contrast, the percentage of women with scheduled spotting/bleeding and unscheduled spotting/bleeding generally *decreased*, as did the percentage with only scheduled spotting/bleeding.

As presented in Supplementary Table 7, the median number of unscheduled spotting/bleeding days was minimal, ranging from 1.0 in 53 subjects at Screening to 0.0 in 40 subjects (Cycle 6), 0.0 in 39 subjects (Cycle 8), and 3.0 in 35 subjects (Cycle 13). Throughout the study, approximately half of the episodes were spotting only. The median number of scheduled spotting/bleeding days

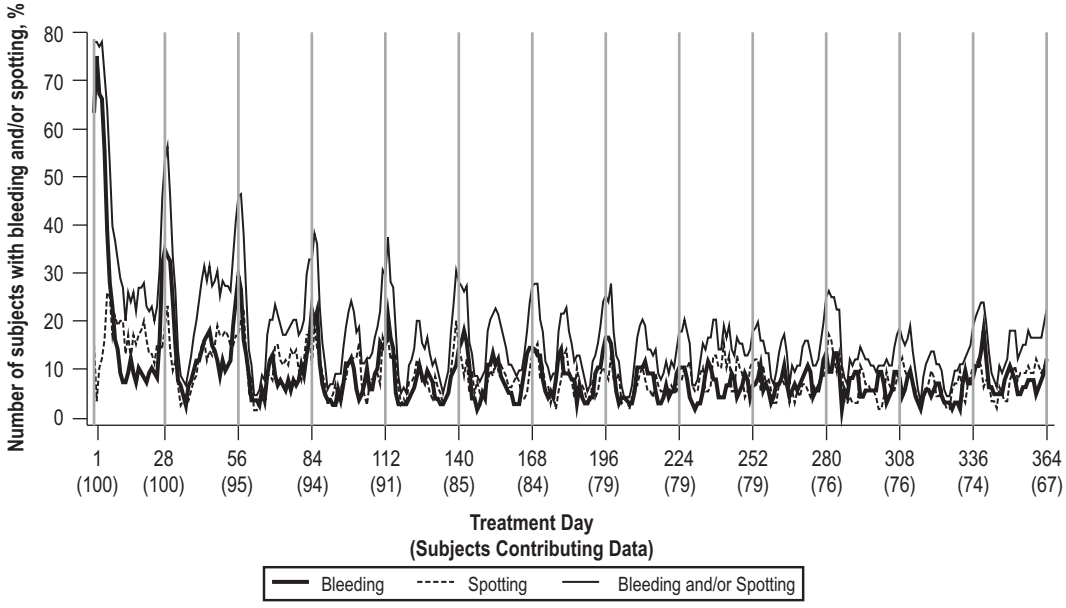

Fig. 3. Number and percent of subjects with bleeding, spotting and bleeding and/or spotting by treatment day, core and extension phases – cycles 1–13 of multicenter clinical trial of drospirenone 4.0 mg in female adolescents. Safety Set.

Table 4
Drospirenone 4.0 mg acceptability ratings based on subject questionnaires completed at each time point in multicenter clinical trial of drospirenone 4.0 mg in female adolescents: number and percent of subjects responding at each ranking level to 6 questions.

	Drospirenone 4.0 mg (N = 102)			
	Visit 2 *n* (%)	Visit 6/EDV *n* (%)	Visit 8/EDV *n* (%)	Endpoint* *n* (%)
How did the subject tolerate the intake of the trial medication?				
Excellent	49 (48.0)	50 (49.0)	42 (41.2)	48 (47.1)
Good	50 (49.0)	37 (36.3)	31 (30.4)	36 (35.3)
Moderate	3 (2.9)	13 (12.7)	9 (8.8)	16 (15.7)
Bad	–	–	–	–
No answer	–	–	–	–
Missing	–	2 (2.0)	20 (19.6)	2 (2.0)
Do you believe that the treatment has had an effect on your body weight?				
Greatly improved		3 (2.9)	3 (2.9)	3 (2.9)
Improved		9 (8.8)	7 (6.9)	8 (7.8)
Not changed		78 (76.5)	67 (65.7)	79 (77.5)
Worsened		10 (9.8)	5 (4.9)	10 (9.8)
Greatly worsened		–	–	–
Missing		2 (2.0)	20 (19.6)	2 (2.0)
Do you believe that the treatment has had an effect on your body fat?				
Greatly improved		2 (2.0)	1 (1.0)	1 (1.0)
Improved		5 (4.9)	10 (9.8)	11 (10.8)
Not changed		89 (87.3)	68 (66.7)	83 (81.4)
Worsened		4 (3.9)	3 (2.9)	5 (4.9)
Greatly worsened		–	–	–
Missing		2 (2.0)	20 (19.6)	2 (2.0)
Do you believe that the treatment has had an effect on predictability of your vaginal bleeding during the cycle?				
Greatly improved		14 (13.7)	11 (10.8)	13 (12.7)
Improved		46 (45.1)	44 (43.1)	49 (48.0)
Not changed		15 (14.7)	14 (13.7)	18 (17.6)
Worsened		23 (22.5)	11 (10.8)	18 (17.6)
Greatly worsened		2 (2.0)	1 (1.0)	2 (2.0)
Missing		2 (2.0)	21 (20.6)	2 (2.0)
Do you believe that the treatment has had an effect on the volume of your vaginal bleeding during the cycle?				
Greatly improved		23 (22.5)	25 (24.5)	30 (29.4)
Improved		58 (56.9)	38 (37.3)	47 (46.1)
Not changed		15 (14.7)	15 (14.7)	18 (17.6)
Worsened		4 (3.9)	3 (2.9)	5 (4.9)
Greatly worsened		–	–	–
Missing		2 (2.0)	21 (20.6)	2 (2.0)
Do you believe that the treatment has had an effect on the duration of your vaginal bleeding during the cycle?				
Greatly improved		21 (20.6)	22 (21.6)	26 (25.5)
Improved		53 (52.0)	39 (38.2)	45 (44.1)
Not changed		17 (16.7)	16 (15.7)	20 (19.6)
Worsened		8 (7.8)	3 (2.9)	7 (6.9)
Greatly worsened		1 (1.0)	1 (1.0)	2 (2.0)
Missing		2 (2.0)	21(20.6)	2 (2.0)

* Assessment at endpoint is the last individual assessment, at end of cycle 6, 13 or at early discontinuation.

was also minimal, ranging from 7.0 in 48 subjects at Screening to 0.0 in 33, 24, and 19 subjects at Cycles 6, 8, and 13 respectively.

The percentage of women with *persistent* unscheduled spotting or bleeding decreased from 5.0% (5 subjects) at Screening to 0.0% from Cycle 3 to the end of the study (Supplementary Table 8).

Bleeding patterns of women who discontinued the study early are displayed in Supplementary Fig. 1. The proportion of subjects who started bleeding or spotting on Cycle Day [25–28] ± 1 decreased from approximately 60% in Cycle 1 to 55% in Cycle 6.

Overall, five subjects (4.9%) prematurely terminated the trial due to irregular bleeding, and one subject due to amenorrhea. None of these TEAEs were severe.

The mean (SD) treatment duration was 312.3 (99.71) days. The median duration was 364.0 days, ranging from 27 to 384.

3.4. Acceptability of drospirenone 4.0 mg

Acceptability data confirm that the majority of subjects rated drospirenone 4.0 mg tolerability as "excellent" (49.0%) or "good" (36.3%) at the end of 6 months (Visit 6) (Table 4). At Visit 6, the majority also reported that treatment with drospirenone 4.0 mg positively affected the volume, duration, and predictability of vaginal bleeding. During our study, both unscheduled bleeding and scheduled bleeding decreased with use of drospirenone 4.0 mg.

4. Discussion

With 24 + 4 administration of drospirenone 4.0 mg over 13 treatment cycles to healthy adolescents, we observed the following: the percentage of subjects with both scheduled and unscheduled bleeding and spotting decreased; the number of bleeding/spotting days decreased; the percentage of subjects with absence of bleeding or spotting increased; and bleeding became lighter and shorter. These results, and the improved predictability of bleeding reported by the majority of subjects in our study, are consistent with the well-known pattern of unfavorable bleeding profiles during the early cycles of OC administration [23].

The incidence of premature trial terminations due to abnormal bleeding, the most common cause of contraceptive discontinuation in POPs users, was low: 4.9%. These results compare favorably with

discontinuation rates with continuous use of desogestrel 75 μg (22.5%) and levonorgestrel 30 μg (18%) in a large double-blind, randomized trial [24], and in the previous two Phase III clinical trials with drospirenone in adults [5,6].

Although no pregnancies were reported, it should be noted that condom contraception was recommended and the study population was relatively small. Treatment had a positive effect on dysmenorrhea, the incidence and intensity of which markedly decreased over time, as did the use of pain medication for dysmenorrhea.

Overall, treatment with drospirenone 4.0 mg was well-tolerated: two serious adverse events were reported during the Extension Phase, but were judged by the investigators to be not related to treatment with drospirenone. The vast majority of adverse events were mild to moderate, and only one in ten subjects discontinued prematurely due to TEAEs. No relevant safety findings were detected, based on gynecological or physical examination. 85.3% of subjects rated the tolerability of drospirenone as "excellent" or "good".

Because this novel drospirenone regimen: (1) induces scheduled withdrawal bleeding and reduces unscheduled bleeding in contrast to other POPs with a continuous regimen [12,13], (2) is well-tolerated, and (3) has a window for a forgotten dose of 24 hours, it is well-accepted by females between the ages of 12 and 17. This should result in practitioners prescribing a POP to a larger number of eligible women, particularly adolescents, in whom periodic delays and skipped doses may occur more frequently. In addition, women with absolute or relative contraindications for estrogens, and also other women currently using COCs, will be more amenable to use of a POP if unscheduled bleeding is reduced [12,25].

As the only oral contraceptive containing drospirenone alone as the active ingredient, drospirenone 4.0 mg empowers women with flexibility in options for birth control. While many OCs are available, drospirenone 4.0 mg is not paired with an estrogen-class molecule, and thus is not expected to increase cardiovascular risk. Further, it is both safe and effective for women, regardless of BMI [6,13,25] (particularly important, as obesity rates have continued to climb in recent decades) [26,27]. These benefits make drospirenone a viable first choice OC for many women, including adolescents.

Strengths of our study include the low drop-out rate and high compliance that speak to the tolerability of the regimen and its acceptance in adolescents, which has previously been shown to be at least comparable to that of competitor products [12,13,25]. This trial also extends the database of OC use in this insufficiently-studied population.

Although not designed to include a second cohort, the absence of a comparator regimen in our study precludes direct comparison of the results to those for other OCs. Another limitation is the comparatively small sample size that was not determined by statistical methods.

The results of this trial in adolescents indicate that the bleeding pattern changes induced by the use of drospirenone 4.0 mg in a regimen of 24 active tablets/4 placebo over 13 treatment cycles were acceptable for the majority of adolescents, and that drospirenone was well-tolerated and safe in this population.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.contraception.2020.02.004.

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