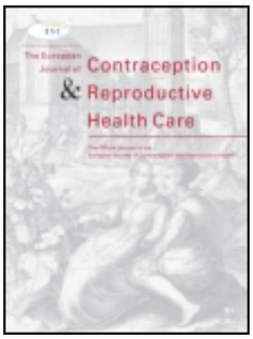

The European Journal of Contraception & Reproductive Health Care

ISSN: 1362-5187 (Print) 1473-0782 (Online) Journal homepage: informahealthcare.com/journals/iejc20

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To cite this article: Robin Kroll, Larry Seidman, Nancy Ricciotti, Brandon Howard & Herman Weiss (2015) A phase 1, multicentre, open-label study to evaluate ovarian follicular activity and hormone levels with an extended-regimen combined oral contraceptive with low-dose ethinyl estradiol supplementation, The European Journal of Contraception & Reproductive Health Care, 20:4, 249-258, DOI: 10.3109/13625187.2014.979282

To link to this article: https://doi.org/10.3109/13625187.2014.979282

The European Journal of Contraception and Reproductive Health Care, 2015; 20: 249–258

A phase 1, multicentre, open-label study to evaluate ovarian follicular activity and hormone levels with an extended-regimen combined oral contraceptive with low-dose ethinyl estradiol supplementation

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ABSTRACT

Objectives To evaluate the effect on ovarian follicular activity of the 91-day extended-regimen combined oral contraceptive (COC), consisting of 84 days of levonorgestrel (LNG)/ethinylestradiol (EE) 150 μg/30 μg tablets plus seven days of EE 10 μg tablets in place of placebo.

Methods This was a phase 1, open-label study. Ovarian follicular activity was classified via the Hoogland and Skouby method. Safety and tolerability as well as return to ovulation were assessed.

Results Of the 35 subjects included in the efficacy analysis, luteinized, unruptured follicles, or ovulation were detected in 0 of 35 cycles during the first 28-day interval; 1 of 35 cycles (2.9%) in the second 28-day interval; and 2 of 35 cycles (5.7%) in the final 35-day interval. The ovarian activity rate over the entire 91-day treatment period was 2.9%. There was a low incidence of treatment-emergent adverse events. Ovulation returned in most subjects (77.1%, 27/35) within 32 days following the last dose of COC.

Conclusions The 91-day extended-regimen COC with low-dose EE supplementation was found to be effective in suppressing ovarian activity and inhibiting ovulation and was well tolerated. Return to ovulation was rapid, occurring within approximately one month after discontinuation of COC.

KEYWORDS extended-regimen; combined oral contraceptive; ovarian activity; ovulation inhibition

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DOI: 10.3109/13625187.2014.979282

INTRODUCTION

Approximately 104 million women worldwide use combined oral contraceptives (COCs)[1]. Among the various reversible contraceptive methods available, COCs rank first in many major world regions including Africa, North and Latin America, Oceania, and Europe[1]. COCs have undergone significant evolution since their introduction in the early 1960s, with improved safety resulting from decreased doses of oestrogen, as well as an ever increasing variety of oestrogen/progestin combinations and regimen types[2,3]. Many COC regimens are based on a traditional 28-day cycle, although more recently, extended regimens have become available. Some examples of COC regimens used in various countries worldwide include the following: 21 active combination tablets (monophasic or multiphasic) followed by seven days placebo or no tablet; 24 active combination tablets followed by four placebo tablets; 21 days active combination tablets followed by two days placebo and five days of oestrogen-only tablets; and 84 active combination tablets (monophasic or multiphasic) followed by seven days placebo or oestrogen-only tablets.

Although COCs as a group are effective in preventing pregnancy, the traditional seven-day hormone-free interval (HFI) that is present in some regimens has been associated with reduced ovarian suppression that might yield less than optimal contraceptive efficacy[4,5]. Studies suggest that shortening or eliminating the seven-day HFI might decrease residual ovarian activity and enhance ovarian suppression[5–9]. In addition, the seven-day HFI has been associated with hormone withdrawal symptoms, such as headache, pelvic pain and cramping, and breast tenderness, that could affect satisfaction leading to discontinuation and unintended pregnancy[10,11]. Extending the duration of administration of an active combination tablet, or eliminating the HFI, might decrease hormonal withdrawal symptoms and improve women's compliance[12–14].

Compared to 28-day regimens, extended-regimen COCs reduce the number of scheduled bleeding episodes and reduce or eliminate the HFI, while providing a similar efficacy and safety profile[15–18]. The extended-regimen COC with low-dose ethinylestradiol (EE) supplementation provides 84 days of active levonorgestrel (LNG)/EE 150 μg/30 μg tablets followed by seven days of EE 10 μg tablets in place of placebo, and is currently approved in the United States and Canada. A previously reported clinical study demonstrated the safety and efficacy of this extended-regimen COC[15,16]. In addition, a comparative study of three different COC treatment regimens found the extended-regimen COC to be associated with decreased levels of follicle stimulating hormone (FSH) and estradiol, as well as decreased number of developing follicles, after the seven-day EE interval compared to regimens with a standard seven-day HFI[19]. However, the impact of the extended-regimen COC with low-dose EE supplementation on ovarian activity, and on return to fertility after discontinuation, have not yet been fully evaluated.

The aim of this study was to fully characterise the effects of the 91-day extended-regimen COC with low-dose EE supplementation on ovarian activity and ovulation inhibition using the Hoogland and Skouby grading system[20], and to document return of ovulation after discontinuation of the regimen.

METHODS

Study design

This was a phase 1, open-label, non-comparative study conducted in the United States between 1 May 2009 and 30 December 2009 at two clinical sites: Women's Clinical Research Center in Seattle, Washington, and Philadelphia Clinical Research, LLC, in Philadelphia, Pennsylvania. The institutional review board, Copernicus Group IRB, reviewed and approved the study protocol, informed consent, and other relevant study documents.

Subjects were healthy women, 18 to 34 years old, who were non-pregnant and non-lactating with a body mass index of ≥ 18 kg/m^2 and < 30 kg/m^2 and a weight of < 200 lbs (< 90.7 kg). Main exclusion criteria were: (i) history or presence of any condition which contraindicated the use of COCs; (ii) within 6 months postpartum or post-abortion at the screening visit, and (iii) current smoker. Subjects were observed over an approximately 21-week period that included an approximately 1-month pre-treatment control cycle, a 91-day treatment cycle, and an approximately 1-month post-treatment cycle (Figure 1). Treatment consisted of a 91-day cycle of the extended-regimen COC, which included 84 days of active LNG/EE 150 μg/30 μg combination tablets followed by seven

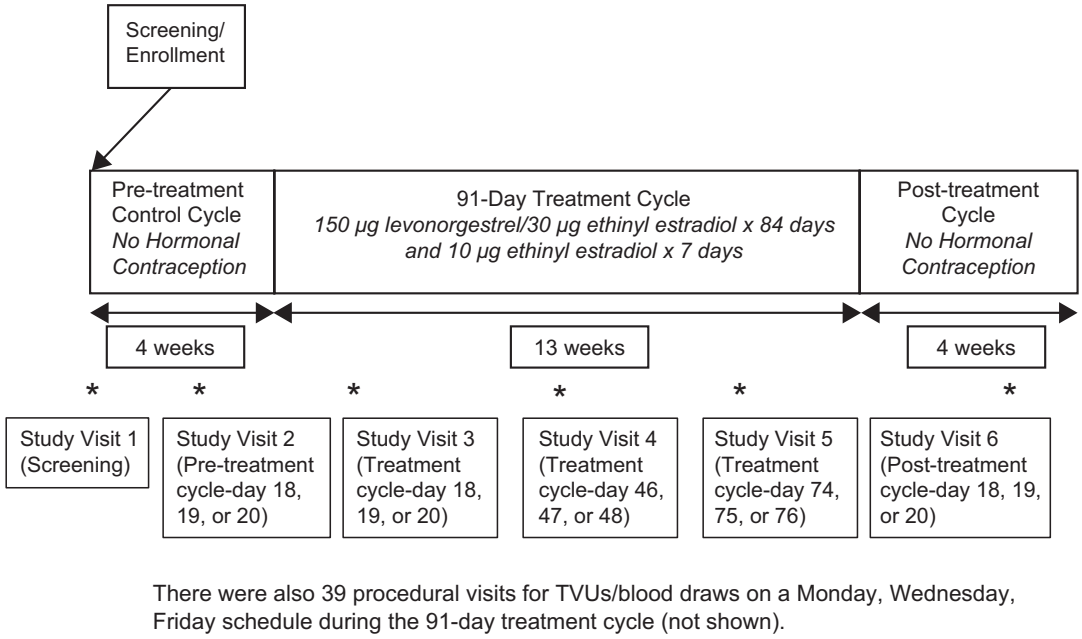

Figure 1 Study flow diagram (TVU, transvaginal ultrasound).

days of EE 10 µg tablets (Seasonique®, Teva Branded Pharmaceutical Products R&D, Inc.).

Subjects who met eligibility criteria at the screening visit completed the pre-treatment control cycle, during which time they used no hormonal contraceptives. On cycle-day 18, 19, or 20 of the pre-treatment cycle, baseline serum hormone concentrations of 17β-estradiol (E2), progesterone (PGN), FSH, and luteinizing hormone (LH) were obtained. Spontaneous ovulation, as assessed by PGN levels only (≥15.9 nmol/L or 5 ng/mL), was confirmed before beginning treatment with the extended-regimen COC. Subjects who did not have a serum PGN level ≥15.9 nmol/L during this control cycle were terminated from the study and replaced.

During the 91-day treatment cycle, all subjects began the extended-regimen COC on the first Sunday of or after start of their spontaneous menses and took one tablet daily for 13 consecutive weeks. Transvaginal ultrasound (TVUs) and serum hormone concentrations were obtained in a total of 39 procedural visits during the treatment cycle following a Monday, Wednesday, and Friday schedule. Subjects were instructed to record tablet-taking in paper diaries on a daily basis. In addition to the procedural visits, at three times during the treatment cycle vital signs, adverse events, study drug compliance, and other parameters were assessed.

The post-treatment cycle began on the day following a subject's last dose of the extended-regimen COC. A final study visit was conducted at cycle-day 18, 19, or 20 of the post-treatment cycle during which serum hormone concentrations were obtained and study supplies were collected including the study diary.

Three cohorts were defined for the analyses of safety and efficacy. The safety cohort consisted of all subjects who took at least one dose of study drug. The intent-to-treat (ITT) cohort included all treated subjects who had at least one baseline and one post-baseline TVU/blood draw during procedural visits. The efficacy cohort was comprised of all subjects in the ITT cohort with the exception of subjects excluded for the following reasons: completed <84 days of treatment; missed two consecutive, or more than two total, extended-regimen COC tablets; missed two consecutive TVUs/blood draws during the first 84 days of treatment; or missed more than three total tests during the first 84 days of treatment.

Primary analysis

The primary objective was the evaluation of ovarian follicular development, which was assessed using measurements of follicle size by TVU and by serum hormone concentrations of PGN and E2, and classified

by the method of Hoogland and Skouby[20]. In order to monitor the progression of ovarian activity over the course of the treatment cycle and to compare ovarian activity rates to those previously reported for conventional 28-day cyclic COCs, the 91-day treatment cycle was converted into three cycle-based intervals; the first 28 days of COC treatment, the second 28 days of COC treatment, and the final 35 days of treatment, which included 28 days of COC followed by seven days of low-dose EE supplementation. A Hoogland and Skouby grade was assigned each Monday, Wednesday, and Friday of the treatment period when the follicle size and serum hormone levels were measured. The maximum Hoogland and Skouby grades over each of the three 28- to 35-day cycle-based intervals as well as the combined total were calculated and summarised. Each subject was assigned a grade ranging from 0 to 5 (Table 1)[20]. For this study, ovarian activity rate was defined as the proportion of cycles with a Hoogland and Skouby grade of 4 (luteinized unruptured follicle) or 5 (ovulation with follicle rupture) and was calculated as: Ovarian activity rate (%) = (Number of cycles graded 4 or 5/Total number of cycles) $\times$ 100. The ovarian activity rate was presented as a point estimate with 2-sided 90% confidence intervals (CI).

In addition to measuring serum PGN and E2 levels for the Hoogland and Skouby grading calculations, serum concentrations of LH and FSH were measured as another means of assessing ovarian activity.

Secondary analyses

Return of ovulatory capacity after treatment with the extended-regimen COC was assessed at the final study visit (cycle-day 18, 19, or 20 of the post-treatment cycle). Serum PGN level only (a concentration of $\geq$15.9 nmol/L) was used to indicate that ovulation had occurred. If a PGN value $\geq$15.9 nmol/L was not reached at the final study visit, then serum PGN concentrations were repeated up to 6 times in total on a Monday, Wednesday, and Friday schedule (up to 12 days after the initial assessment) until a value of $\geq$15.9 nmol/L was reached. The 2-sided 95% CIs for the return to ovulation were calculated using the exact Clopper-Pearson method.

Tolerability and safety were assessed by adverse events (AEs) reported by subjects or identified by the investigator at each study visit and by summarising measurements of vital signs and results of clinical laboratory tests obtained at screening and at designated time points throughout the study.

Compliance with study drug use was assessed by tablet counts at scheduled study visits and by subject-reported tablet-taking in the diaries.

RESULTS

A total of 83 subjects were screened and 62 were enrolled. Forty-five subjects received at least one dose

Table 1 Ovarian Activity Grading System.[20]

		Follicle-like structure	*Hormones*	
Grading of ovarian activity		*Size mm*	*Estradiol nmol/L*	*Progesterone nmol/L*
0	No activity	$\leq$10		
1	Potential activity	>10		
2	Non-active FLS	>13	$\leq$0.1	
3	Active FLS	>13	>0.1	$\leq$5
4	LUF	>13, persisting	>0.1	>5
5	"Ovulation"	>13, ruptured*	>0.1	>5

FLS, follicle-like structure; LUF, luteinized unruptured follicle.

Adapted from Hoogland HJ and Skouby SO, Ultrasound evaluation of ovarian activity under oral contraceptive. *Contraception* 1993;47:583–90, adapted with permission from the Association of Reproductive Health Professionals and the Society of Family Planning.

*Grade 5 was distinguished from Grade 4 by follicle rupture, defined as the disappearance of the follicle or a decrease in maximum follicular diameter by 50% within 2 to 4 days.

of the extended-regimen COC and were included in the safety cohort. Of the 45 subjects in the safety cohort, a total of 43 (95.6%) were included in the ITT cohort and 35 (77.8%) were included in the efficacy cohort. Demographic characteristics for the ITT and efficacy cohorts were similar (Table 2).

The maximum Hoogland and Skouby grades over each of the three 28- to 35-day cycle-based intervals and the combined total are shown in Table 3. In the efficacy cohort, ovulation (grade 5) was detected in 0 out of 35 cycles during the first 28-day interval; 1 out of 35 cycles (2.9%) in the second 28-day interval; and 2 out of 35 cycles (5.7%) in the final 35-day interval. No cycles were identified as grade 4 indicating a luteinized unruptured follicle. Overall, the ovarian activity rate for the entire 91-day cycle was 2.9% (3 out of 105 cycles), and ovulation was inhibited in 97.1% of cycles (102 out of 105 cycles). Similar results were demonstrated when the Hoogland and Skouby grading system was applied to cycles evaluated in the ITT cohort (ovarian activity rate 2.4%; ovulation inhibition 97.6%).

Following treatment with the extended-regimen COC, all subjects demonstrated serum levels of PGN, E2, LH, and FSH that were lower than pre-treatment levels, and these lower concentrations were generally maintained over the course of the treatment period. In the case of PGN levels, they remained consistently low during the treatment period except for a spike that occurred around treatment days 69 to 72 (cycle-based interval 3) due to the two cycles that exhibited a Hoogland and Skouby grade 5 during that interval (Figure 2). Mean serum PGN levels over the treatment period ranged from 1.8 nmol/L to 3.1 nmol/L (excluding the ovulation spike around days 69 to 72) compared with a mean of 29.7 nmol/L in the pre-treatment

Table 2 Demographics and other baseline characteristics.

Parameter	*ITT cohort (n = 43)*	*Efficacy cohort (n = 35)*
Race, *n* (%)		
African American	6 (14.0%)	6 (17.1%)
Asian	2 (4.7%)	2 (5.7%)
Caucasian	32 (74.4%)	25 (71.4%)
Other	3 (7.0%)	2 (5.7%)
Age, mean (SD), y	26.96 (3.90)	27.60 (3.75)
BMI, mean (SD), kg/m^2	23.14 (3.25)	23.39 (3.14)
Systolic blood pressure, mean (SD), mm Hg	104.05 (9.96)	104.97 (10.25)
Diastolic blood pressure, mean (SD), mm Hg	65.16 (5.92)	65.43 (6.28)
Heart rate, mean (SD), beats/min	69.79 (8.01)	70.26 (8.34)

BMI, body mass index; ITT, intent to treat; SD, standard deviation.

Table 3 Ovarian activity rates (cycle level) for the 91-day treatment cycle converted into three cycle-based intervals of 28 to 35 days: Efficacy cohort.

*Ovarian Activity Grade**	*Interval 1 (28 days) [35 subject cycles]*		*Interval 2 (28 days) [35 subject cycles]*		*Interval 3 (35 days) [35 subject cycles]*		*Total (91 days) [105 subject cycles]*	
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*
0 – No activity	20	57.14	31	88.57	31	88.57	82	78.10
1 – Potential activity	6	17.14	1	2.86	1	2.86	8	7.62
2 – Non-active FLS	0	0.00	2	5.71	1	2.86	3	2.86
3 – Active FLS	9	25.71	0	0.00	0	0.00	9	8.57
4 – LUF	0	0.00	0	0.00	0	0.00	0	0.00
5 – Ovulation	0	0.00	1	2.86	2	5.71	3‡	2.86
Ovarian activity rate†	0	0.00	1	2.86	2	5.71	3‡	2.86
90% CI		0.00, 8.2		0.15, 12.85		1.02, 16.92		0.78, 7.22

n, number of subject cycles; CI, confidence interval; FLS, follicle-like structure; LUF, luteinized unruptured follicle.
*Only the most significant ovarian activity grade was used for subject cycles in each cycle-based interval.
†Includes subjects who experienced LUF (grade 4) and ovulation (grade 5).
‡One subject demonstrated a grade 5 score in cycle-based intervals 2 and 3.

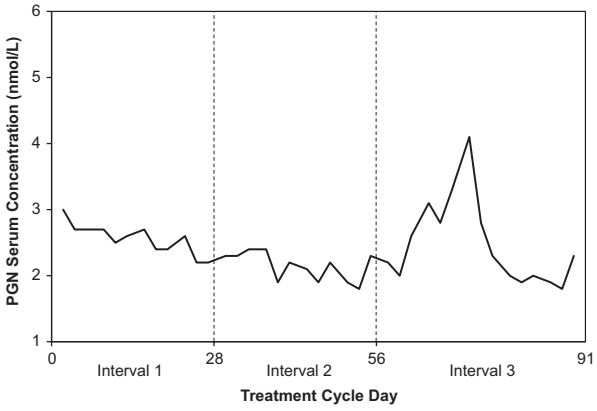

Figure 2 Mean serum progesterone (PGN) levels during 91-day treatment period.

control cycle. Mean E2 levels ranged from 0.15 to 0.03 nmol/L over the entire treatment period compared to 0.42 nmol/L in the pre-treatment control cycle (Figure 3). Starting from slightly elevated concentrations during the initial phase of treatment (cycle-based interval 1), both LH and FSH were markedly suppressed compared to mean pre-treatment control cycle values (5.38 U/L and 3.82 U/L, respectively), except during the last few days of the treatment cycle when the FSH level appeared to increase (Figure 4). The increase in the FSH level corresponds approximately to when the EE dose changed from 30 to 10 μg.

Ovulation returned in 27 of 35 subjects (77.1%) in the efficacy cohort within 32 days after the last dose of extended-regimen COC (Table 4). Similar results were seen in the ITT cohort.

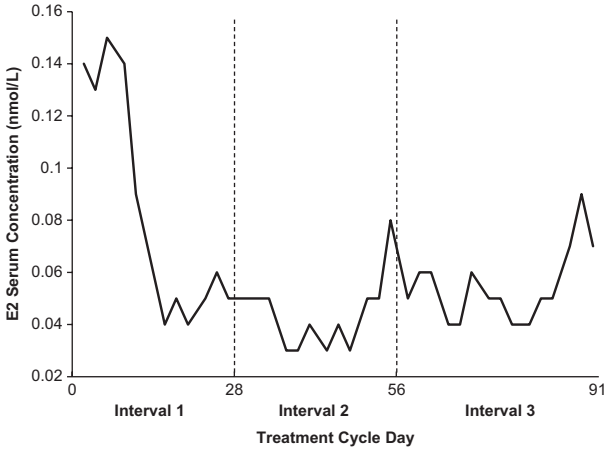

Figure 3 Mean serum 17β-estradiol (E2) levels during 91-day treatment period.

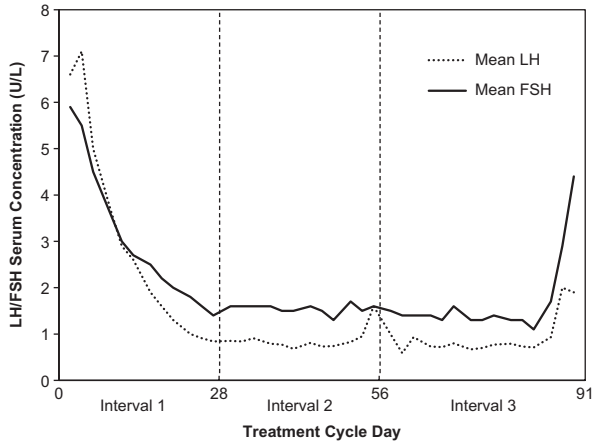

Figure 4 Mean serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels during 91-day treatment period.

Treatment-emergent AEs (TEAEs) were reported by 31 of the 45 subjects (68.9%) in the safety cohort. The most frequently occurring TEAEs were headache (28.9%; 13/45), upper respiratory tract infection (13.3%; 6/45), and acne (8.9%; 4/45). TEAEs that were considered at least possibly related to study treatment by the investigator were reported by 19 of the 45 subjects (42.2%). Of the TEAEs considered to be treatment-related by the investigator, the most common were headache (26.7%; 12/45) and acne (8.9%; 4/45). With the exception of dysmenorrhoea (6.7%; 3/45), no other treatment-related AEs occurred in >5% of subjects. Two AEs led to discontinuation (severe headache and elevated liver function tests), both of which were considered to be possibly related to the study drug by the investigator. There were no serious AEs or subject deaths.

Minimal changes in vital signs during the course of the study were observed. No subjects were observed to have systolic BP of ≥140 mm Hg and/or diastolic BP of ≥90 mm Hg at any time during the study. No weight changes of greater than ±10% from baseline were observed. Mean compliance rates for the ITT and efficacy cohorts were identical (>99.9%).

DISCUSSION

Findings and interpretation

Extended-regimen COCs allow for fewer scheduled bleeding episodes (preferred by some women), as

Table 4 Proportion of subjects who returned to ovulation during the post-treatment cycle.

	Efficacy cohort (n = 35)			*ITT cohort (n = 43)*		
Ovulation status	*n*	*%*	*95% CI*[†]	*n*[‡]	*%*	*95% CI*
Returned to ovulation*	27	77.14	59.86, 89.58	33	78.57	63.19, 89.70
Did not ovulate	8	22.86	10.42, 40.14	9	21.43	10.30, 36.81

CI, confidence interval; ITT, intent to treat.

*If progesterone (PGN) ≥ 15.9 nmol/L was not obtained at final study visit (cycle-day 18, 19, or 20 of post-treatment cycle), then PGN concentrations were measured up to 6 times total on a Monday, Wednesday, Friday schedule until a value of ≥ 15.9 nmol/L was reached or a period of 12 days had elapsed since initial assessment.

[†]95% confidence interval is based on the exact Clopper-Pearson method.

[‡]One subject discontinued due to an adverse event.

well as an alteration of the HFI potentially leading to improved compliance and enhanced ovarian suppression[5–13,21–25]. In this phase 1 study, the 91-day extended-regimen COC with low-dose EE supplementation during the traditional HFI interval resulted in a low ovarian activity rate (Hoogland and Skouby grade of 4 [LUF]/5 [ovulation]) of 2.9% and inhibition of ovulation in 97.1% of cycles over the 91-day treatment cycle. The results of the current study also showed that treatment with the extended-regimen COC decreased the production of endogenous FSH and LH, thereby impairing follicular development and inhibiting ovulation.

Despite the level of ovarian suppression exhibited by the extended-regimen COC, ovulation resumed in most subjects (77.1%) within approximately one month following the discontinuation of treatment, as documented by serum PGN levels. These results are consistent with previous reports suggesting that return of fertility following cessation of extended-cycle or continuous-use COCs is similar to that observed with cyclic COCs[26–28].

The extended-regimen COC was found to be well tolerated in this study, with the most common treatment-related AEs being headache and acne. The low incidence of clinical and laboratory AEs observed are consistent with the known AE profiles associated with other COCs[17,18]. Although the examination of safety in this trial was limited by its short duration and small sample size, there were no unusual safety signals.

Strengths and weaknesses of the study

Strengths of the study include the rigorous schedule of study/procedural visits for blood draws, TVUs, and other procedures, totalling 45 visits over a 21-week period. The study design enabled a full characterization of ovarian activity using the well-established method of Hoogland and Skouby and, to our knowledge, represents the first such characterization of a 91-day extended-regimen COC. In addition to the E2 and PGN serum hormone levels obtained for the Hoogland and Skouby analysis, the analysis of FSH and LH levels during the treatment cycle and the analysis of PGN levels post-treatment further add to the study strengths.

Contraceptive efficacy of COCs is typically evaluated over the course of at least one year of use and is impacted considerably by the level of adherence to the regimen. Unintended pregnancy rates based on typical-use of COCs in the first year of use are estimated at 9% compared with an estimated 0.3% for perfect-use[29]. Weaknesses of the current study include the fact that it only followed subjects for 3 months while on study drug and adherence was assessed by tablet counts and subject-reported diaries rather than by biochemical methods such as serum LNG levels. Lack of confirmation of adherence introduces a level of uncertainty regarding the actual adherence rate. The current study also does not address additional contraceptive effects of oral contraceptives such as alterations in the cervical mucus and endometrium[30]. Other limitations of the study include the non-comparative design and exclusion of obese women. The effect of the Sunday start,

in which all subjects began the extended-regimen COC on the first Sunday of or after start of their spontaneous menses, on follicular development in the current study is not known.

Differences in results and conclusions in relation to other studies

Previous studies have used the Hoogland and Skouby method to characterise a variety of COCs based on a more traditional 28-day treatment cycle[7,31–35]. Although it is difficult to make comparisons because of differences in study design and treatment duration, the results presented here (ovarian activity rate of 2.9% during the entire 91-day treatment cycle and ovarian activity rates of 0%, 2.9%, and 5.7% during the cycle-based Intervals 1, 2, and 3, respectively) are generally similar to those of other studies. In one report by Endrikat *et al.*, a four-phasic estradiol valerate/dienogest COC regimen with two days of placebo was found to have an ovarian activity rate of 3.13% during the second 28-day treatment cycle[32]. In another study by Spona and colleagues, the ovarian activity rate of an ethinylestradiol/chlormadinone acetate COC regimen with a seven-day pill-free interval was found to be 1.2% over three 28-day treatment cycles[31]. The results presented here are also consistent with previous reports that used methods other than Hoogland and Skouby to demonstrate suppression of ovarian follicular activity with the addition of low-dose EE during the traditional seven-day HFI[8,9,19]. Further research is needed to more fully understand the impact of EE supplementation on ovarian activity with extended-regimen COCs.

As mentioned previously, the current study does not address all possible contraceptive effects of COCs. The efficacy profile of the 91-day extended-regimen COC with low-dose EE supplementation can be further supported in the pivotal phase 3 study[15]. Based on data from the phase 3 study, the United States Food and Drug Administration labelling for the extended-regimen COC reports a Pearl Index of 1.34 using the 14-day rule, based on seven pregnancies that occurred after COC initiation and no more than 14 days after the last dose of combination medication in women aged 18 to 35, excluding cycles in which another contraceptive method was used[36]. A reanalysis (unpublished) yielded a European-based (i.e., 2-day rule) overall Pearl Index of 0.76 (upper two-sided 95% confidence limit using the Bootstrap method 1.76) based on three pregnancies that occurred after COC initiation and no more than two days after the last dose of combination medication in women aged 18 to 35, excluding cycles in which another contraceptive method was used.

Relevance of the findings: Implications for clinicians and policy makers

When the results of the current study are taken in conjunction with the phase 3 study, the data support the efficacy and tolerability of the 91-day extended-regimen COC with EE supplementation. The regimen has been approved in the United States since 2006, with subsequent widespread use. As of June 2014, the European Medicines Agency's Committee for Medicinal Products for Human Use has recommended the granting of marketing authorization for the extended-regimen COC in France, Austria, Belgium, Germany, Italy, Poland, Romania, Slovakia, and Slovenia.

Unanswered questions and future research

As additional extended-regimen COCs become available, a more detailed understanding of their impact on ovarian activity will be possible. Future studies could examine the impact on ovarian activity over multiple treatment cycles or include comparisons of ovarian activity rates between extended-regimen COCs of different formulations. As noted above, future research could also continue to explore the impact of EE supplementation on ovarian activity with extended-regimen COCs.

CONCLUSIONS

Overall in this phase 1 study, the 91-day extended-regimen COC with low-dose EE supplementation demonstrated ovarian suppression as indicated by generally low Hoogland and Skouby grades and corresponding low ovarian activity rates. The regimen was well-tolerated, and demonstrated rapid return to ovulation within the first month after discontinuation of the regimen.

ACKNOWLEDGEMENTS

The authors thank Rebecca Miles, PhD, of MedVal Scientific Information Services, LLC, for providing medical writing and editorial assistance. This manuscript was prepared according to the International Society for Medical Publication Professionals' Good Publication Practice for Communicating Company-Sponsored Medical Research: the GPP2 Guidelines.

Declaration of interest: This study was sponsored by Teva Branded Pharmaceutical Products R & D, Inc. AMC Global Central Laboratory, Rochester, New York was contracted for routine central laboratory activity. The study drug, extended-regimen COC with low-dose EE supplementation, was supplied by Teva Branded Pharmaceutical Products R & D, Inc. Funding to support the preparation of this manuscript was provided to MedVal Scientific Information Services, LLC, Skillman, New Jersey by Teva Women's Health, Inc.

Robin Kroll has served as a consultant/advisor and clinical study investigator for Teva. Larry Seidman has served as a consultant/advisor and clinical study investigator for Teva. Nancy Ricciotti is an employee of Teva Branded Pharmaceutical Products, R & D, Inc. Brandon Howard and Herman Weiss are employees of Teva Global Medical Affairs.

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