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Contraceptive efficacy and safety of a low-dose oral contraceptive, (0.03 mg ethinyl oestradiol and 2 mg chlormadinone acetate) Belara®, over three medication cycles

J. Spona[†], N. Binder[‡], K. Höschen[‡] and W. Feichtinger[§]

[†]Vitalogic, Vienna, Austria; [‡]Grünenthal GmbH, Aachen, Germany; and [§]Institute for Sterility Treatment, Vienna, Austria

ABSTRACT

Objective To describe the modulation of ovarian function during three medication cycles with 0.03 mg ethinyl oestradiol (EE) and 2 mg chlormadinone acetate (CMA), leading to inhibition of conception in healthy women.

Methods Phase II, single-centre, open, non-controlled trial. The main outcome measure was inhibition of ovarian activity, assessed by frequent monitoring of the presence, size and persistence of follicle-like structures using ultrasonography. Secondary parameters included: cervical reaction score (CRS-probability of fertilization), endometrial thickness (probability of nidation), and serum levels of the sex hormones oestradiol, progesterone, luteinizing hormone and follicle stimulating hormone. Safety was primarily assessed by monitoring the occurrence of adverse events.

Results Thirty-three subjects were eligible for the trial and were included in the efficacy assessment (per protocol analysis, PPA). All subjects ovulated during the pretreatment cycle, but none during the three medication cycles. Follicular growth was profoundly suppressed during the medication phase, with residual ovarian activity occurring in only 12/83 (14.5%) treatment cycles. The CRS was negative during each medication cycle and endometrial thickness was suppressed on each medication day, with median values of 4.0–6.0 mm. EE/CMA was well tolerated, with few adverse events reported; most were typically cycle-related and included headache, breast discomfort, nausea and vomiting.

Conclusion During the administration of EE/CMA follicular development, cervical reaction and endometrial thickness are profoundly suppressed, resulting in unfavourable conditions for fertilization, implantation and, thus, pregnancy.

KEY WORDS Contraception, Ovarian activity, Ethinyl oestradiol/chlormadinone acetate, Belara®, Cycle stability, Efficacy, Safety

Correspondence: Professor Dr J. Spona, Czerningasse 10, 1020 Wien, Austria. Tel: 0043 (1) 877 91530. Fax: 0043 (1) 877 91539. E-mail: juergen.spona@vitalogic.at

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INTRODUCTION

Steroid drugs with contraceptive properties have been available for several decades, but are still subject to improvement[1]. One of the most important changes has been the gradual lowering of steroid dosage in commercially available contraceptives, aiming at a reduction of adverse effects[2]. Reduced-dose contraceptive pills still largely achieve the goal of suppression of pituitary-ovarian activity, with few unwanted pregnancies and minimal side effects.

Previous trials have used pituitary-ovarian inhibition to assess the suppressive potential of contraceptive drugs[1,3,4]. According to van Heusden and Fauser[4], however, many of these trials allowed for major underreporting of residual ovarian activity due to infrequent (once per cycle) or conditional monitoring (when a follicle >12 mm appeared). Consequently, they provide incomplete and/or incomparable results of potential ovarian activity.

Considerable efforts have been made to assess additional indices, and several grading systems have been reported[1,5]. A modified grading system according to Hoogland and Skouby[5] was applied to the current trial. It combines the ultrasonic examination of the follicles with the determination of hormone levels, in order to differentiate various levels of ovarian activity.

Belara® is a low-dose, combined, oral contraceptive (OC) containing 0.03 mg ethinyl oestradiol (EE) and 2 mg chlormadinone acetate (CMA). The dose of 2 mg CMA is known to inhibit ovulation, whilst the 0.03 mg EE ensures satisfactory cycle control with minimal oestrogen-related side effects[6,7]. CMA is a derivative of progesterone; it exhibits antiandrogenic properties[8], without significant mineralocorticoid and anti-mineralocorticoid actions[9].

The aim of the current trial was to monitor the effects of EE/CMA on ovarian function, including the hormonal and morphological changes that will lead to reliable contraception. Follicle size, sex hormone levels, cervical reaction and endometrial thickness were measured frequently (every other day) and grading was performed every cycle, according to the methodology used by Hoogland and Skouby[5]. In this trial, a grading scheme was used, as reported by Spona *et al.* in previous trials[10–12]. This helped to determine a comprehensive picture of the potential for pregnancy whilst taking EE/CMA.

MATERIALS AND METHODS

Trial design and setting

This was a single-centre, open, non-controlled phase II trial performed at the Institute for Sterility Treatment, Vienna, Austria, between 20th November 2002 and 11th July 2003. The trial was designed to evaluate the contraceptive efficacy (ovulation inhibition) and safety of a new combination pill (EE/CMA/Belara®) in healthy women with no known infertility.

The trial was subdivided into six stages: a pretreatment cycle (screening phase), three medication cycles, a post-treatment cycle (days 1–28 after medication cycle 3) and a final examination (on day 29 after completion of medication cycle 3). If the pretreatment cycle was ovulatory, the subject was entered into the medication phase of the trial.

The trial was performed in accordance with Good Clinical Practice (GCP), the Declaration of Helsinki, and was approved, with two amendments, by the Human Ethics Committee of the participating centre. The trial complied with European Medicines Agency (EMEA) guidelines for the investigation of oral contraceptives in women. All participants had given their written informed consent.

Trial population

Healthy, non-smoking (aged 18–35 years) or smoking (aged 18–30 years) women were recruited into the trial. Additional inclusion criteria were: a negative pregnancy test, no wish to become pregnant (during the next six cycles), normal laboratory values (with respect to haematology, coagulation, chemistry and sex hormone levels), a body mass index ≤ 30 and a normal cervical cytology.

Eligible women were required to have a regular ovulatory cycle (24–35 days) during screening, an interval of at least 1 month without hormonal or intrauterine contraception before treatment and a normal ultrasonographic appearance of the endometrium.

Subjects were excluded if they were nursing mothers, had a history of severe allergic disease, epilepsy, psychiatric illness, alcohol or drug/medication dependency, or had a chronic disease or diet that might affect the pharmacokinetics of the test medication. Women were also excluded if they had a history

of menstrual disorders or abnormalities, severe migraine, chronic diseases, or were taking other hormonal contraceptives or concomitant medications with known drug interactions.

All eligible subjects were examined by the investigator. Assessments included: demographic data, medical history and menstrual history (last 3 months), previous and concomitant medication, physical examination including a gynaecological examination, laboratory investigations and a pregnancy test. All participants could withdraw or be withdrawn from the trial at any time.

Trial treatment

Starting on the first day of their next menstrual bleeding, eligible women were required during three 28-day cycles to take one Belara® pill (Grünenthal GmbH, Aachen, Germany) orally at the same time every day (preferably in the evening) for 21 consecutive days, followed by a pill-free interval of 7 days.

Assessments

All women, assigned to the per protocol analysis (PPA), who completed the trial, were taken into account for assessment of efficacy of the OC. Due to the exploratory nature of the trial, there was no primary endpoint. The main endpoint was the inhibition of ovarian activity assessed by the presence, size and persistence of follicle-like structures (FLS) using an ultrasonic examination of the ovaries. Grading was conducted according to a modified Hoogland and Skouby score[10–12] (Table 1). The Hoogland–Skouby score was determined for each cycle.

Secondary variables measured included: changes in endometrial thickness assessed by transvaginal ultrasound as an indication of ovulation[13,14], the amount and consistency of the cervical mucus (cervical reaction score, CRS) to assess the potential of fertilization[15,16] and the decrease in serum levels of sex hormones (oestradiol, luteinizing hormone [LH], follicle stimulating hormone [FSH], and progesterone).

The CRS was calculated by performing cervical smears and taking four variables into account, either quantitatively or qualitatively: the amount of mucus, the Spinnbarkeit, its capacity to crystallize on a glass slide thereby producing the pattern of a fern leaf ('fern test'), and the width of the external cervical os[15]. Results were classified as either negative (score 1–3), slight (score 4–6), moderate (score 7–9) or full cervical reaction (score 10–12; Table 2).

Efficacy assessments were conducted on the even days during each 28-day medication cycle and the post-treatment cycle, corresponding to 14 assessments per cycle. Ovarian activity was graded per cycle making use of the modified Hoogland and Skouby score.

Safety of the treatment with the trial medication was assessed by observing changes in vital signs, gynaecological status (in particular, with regard to the occurrence of intermenstrual bleeding) and cervical cytology, and the self-reporting of adverse events or bleeding disturbances in a diary. The occurrence of pregnancy was not considered an adverse event unless a congenital anomaly arose as a result.

Statistical analysis

As the trial was designed to be descriptive, no formal sample size was planned. It was estimated that 65 subjects should be screened in order to enter 36

Table 1 Grading of ovarian activity according to the modified Hoogland and Skouby[5] score

Grading of residual ovarian activity	*FLS diameter (mm)*	*Oestradiol (nmol/L)*	*Progesterone (nmol/L)*
1 No activity	≤10	–	–
2 Potential activity	10 < FLS ≤ 13	–	–
3 Non-active FLS	>13	≤0.1	–
4 Active FLS	>13	>0.1	≤5
5 LUF	>13, persistent	>0.1	>5
6 Ovulation	>13, ruptured	>0.1	>5

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

Table 2 Cervical score according to Insler *et al.*[15]

Index	*Finding*	*Points*
Amount of mucus	None	0
	Scant; a small amount of mucus can be drawn from the cervical canal	1
	Dribble; a glistening drop of mucus seen in the external os; mucus easily drawn	2
	Cascade; abundant mucus pouring out of external os	3
Spinnbarkeit	None	0
	Slight; uninterrupted mucus thread may be drawn approximately one-quarter of the distance between the external os and the vulva	1
	Moderate; uninterrupted mucus thread may be drawn about halfway between the external os and the vulva	2
	Pronounced; uninterrupted mucus thread may be drawn for the whole distance between the external os and vulva	3
Ferning	None; amorphous	0
	Linear; fine linear ferning seen in a few spots; no side branching	1
	Partial; good ferning with side branches in parts of the slide linear ferning or amorphous mucus in other parts	2
	Complete; full ferning of the whole preparation	3
Cervix	Closed; mucosa pale pink; external os hardly admits a small applicator	0
	Partially open; mucosa pink; the cervical canal easily penetrable by an applicator	2
	Gaping; mucosa hyperaemic; external os patulous	3

Cervical score, sum (points for all four indices).

subjects into the medication phase. All analyses were exploratory and no confirmatory tests were performed.

RESULTS

Subjects

A consort diagram of the women screened is shown in Figure 1. Of the 65 subjects screened, 40 (61.5%) were eligible for inclusion. Of these, 33 subjects (82.5%) were included in the efficacy assessment as per protocol. Baseline demographics and characteristics are shown in Table 3. The mean age of the women was 26.0 years, 19 subjects (57.6%) were non-smokers. All women reported regular menstrual cycles (mean length 28.2 days) during the previous three months and 26 subjects (78.8%) had applied contraceptive measures prior to the pre-treatment phase.

Contraceptive efficacy

The results concerning ovarian activity are shown in Table 4. All 33 subjects in the PPA ovulated during the pre-treatment phase (grade 6). During the treatment phase, in which a total of 83 medication cycles were monitored, EE/CMA inhibited ovulation in every subject in the PPA. One breakthrough ovulation occurred in a subject in the full analysis set following episodes of vomiting and diarrhoea. The majority of cycles (59/83; 71.1%) had a Hoogland and Skouby grade 1, indicating no ovarian activity, with the highest incidence of pronounced ovarian suppression in medication cycle 1 (27/30, 90.0%). Residual ovarian activity during treatment was also low at 14.5% (12/83; grade 2). Again, ovarian suppression was greatest during the first medication cycle, with only 6.7% (2/30) showing residual ovarian activity (grade 2) compared with 25% (7/28) and 12% (3/25) in medication cycles 2 and 3, respectively.

The formation of an active FLS (grade 4) was observed in 11 (13.3%) of a total of 83 medication cycles and a luteinized unruptured follicle >13 mm (LUF grade 5) was seen in 1/83 (1.2%) of medication cycles. Ovulation returned to normal (grade 6) in 26/32 (81.3%) of subjects during the post-treatment phase.

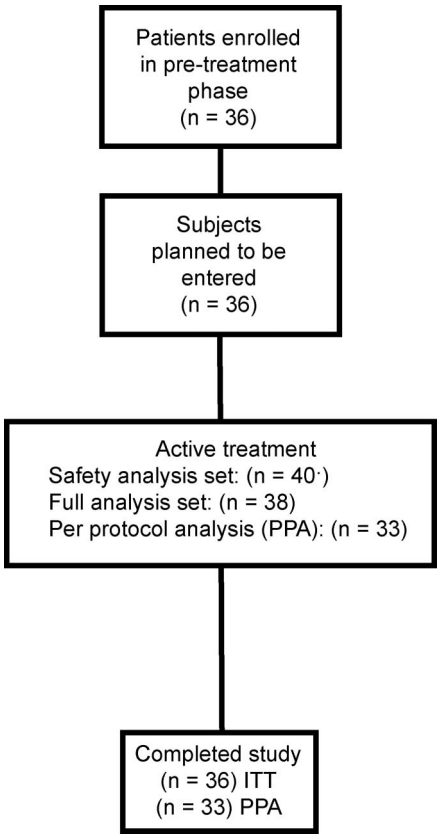

Figure 1 Consort diagram of the volunteers recruited. Five of them were excluded from the PPA (one with less than 1 month wash-out period without hormonal contraception, two with irregular menstrual cycle and two with data sets omitted from one or more medication cycles). Four participants were withdrawn prior to study completion (one due to an adverse event, one lost to follow-up and two for reasons not stated by them); two of these four participants are also represented in the PPA exclusion figures (participants 8 and 25). Two participants were excluded from the FAS as not all their medication cycles were amenable to analysis. FAS: full analysis set. *four additional subjects entered during screening

The changes in FLS size, cervical score and endometrial thickness are shown in Figure 2. The cervical reaction score (indicating the likelihood of fertilization) was negative (score 1–3) during treatment, reflecting cervical hostility and, thus, unfavourable conditions for fertilization.

The endometrium was thin on each medication cycle day, with median values of 4.0–6.0 mm, indicating that the potential for nidation was also suppressed, The median maximum values of the endometrial thickness under treatment (7.0 mm, as compared with 13.0 mm in pre- and post-treatments phases) also showed that there was no pathological stimulation of the endometrium during the trial.

During pretreatment, oestradiol and progesterone levels were typical of an ovulatory cycle. During treatment, the sex hormone levels were generally suppressed. Median levels of oestradiol on days 1–21 were low (about 15 pg/mL), but they increased slightly during the pill-free interval. Levels of LH and FSH also rose during the pill-free interval. Progesterone was completely suppressed (median <1.2 ng/mL) during the medication phase of the trial.

Table 3 Subject baseline demographics and characteristics

Features	*n = 33*
Mean age (years) (range)	26 (19–35)
Mean BMI (kg/m^2) (range)	21.5 (18.0–28.7)
Number of smokers (%)	
Non smoker	19 (57.6)
Smoker	10 (30.3)
Ex-smoker	4 (12.1)
Number using contraception (%) during last 3 months	26 (78.8)
Number with a regular menstrual cycle	33 (100)
Mean cycle length (days) (range)	28.2 (25–34)
Number reporting complaint during last 3 months (%)	14 (42.4)

Contraceptive safety

Over the entire trial, 35/40 (87.5%) participants (safety population) reported adverse events. During the pretreatment phase, 11/40 (27.5%) subjects reported an adverse event, most commonly one that was typically cycle-related, such as headache, vomiting or breast discomfort which affected 7.5, 7.5 and 5.0% of the women, respectively. A breakdown of adverse events is shown in Table 5.

The incidence of adverse events rose during the medication phase with 34/40 (85%) participants recording adverse events. Again, the most common adverse events were cycle-related, with 16/40 (40%) subjects reporting headache, 9/40 (22.5%) vomiting, 8/40 (20.0%) nausea and 7/40 (17.5%) breast

Table 4 Absolute and relative frequencies of residual ovarian activity assessed by (grades 1–6)

Time	*Grade*		*n (%)*
Pretreatment cycle ($n=33$)	1	No activity	0 (0)
	2	Potential activity	0 (0)
	3	Non-active FLS	0 (0)
	4	Active FLS	0 (0)
	5	LUF	0 (0)
	6	Ovulation	33 (100)
Medication cycle 1 ($n=30$)	1	No activity	27 (90.0)
	2	Potential activity	2 (6.7)
	3	Non-active FLS	0 (0)
	4	Active FLS	1 (3.3)
	5	LUF	0 (0)
	6	Ovulation	0 (0)
Medication cycle 2 ($n=28$)	1	No activity	16 (57.1)
	2	Potential activity	7 (25)
	3	Non-active FLS	0 (0)
	4	Active FLS	4 (14.3)
	5	LUF	1 (3.6)
	6	Ovulation	0 (0)
Medication cycle 3 ($n=25$)	1	No activity	16 (64.0)
	2	Potential activity	3 (12.0)
	3	Non-active FLS	0 (0)
	4	Active FLS	6 (24.0)
	5	LUF	0 (0)
	6	Ovulation	0 (0)
Post-treatment cycle ($n=32$)	0	Insufficient data/drop-out	1 (3.1)
	1	No activity	1 (3.1)
	2	Potential activity	1 (3.1)
	3	Non-active FLS	1 (3.1)
	4	Active FLS	0 (0)
	5	LUF	2 (6.3)
	6	Ovulation	26 (81.3)
All medication cycles ($n=83$)	1	No activity	59 (71.1)
	2	Potential activity	12 (14.5)
	3	Non-active FLS	0 (0)
	4	Active FLS	11 (13.3)
	5	LUF	1 (1.2)
	6	Ovulation	0 (0)

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

discomfort. Common cold was reported by 9/40 (22.5%) women, indicating the seasonal nature of the trial. Most adverse events during the medication phase were classified as mild (71.1%), with 24.0% being of moderate and 5.0% of severe intensity. There were no serious adverse events related to the trial medication. In general, the incidence of adverse events decreased over the three medication cycles.

Four women did not complete the trial. Of these, one withdrew from the trial during the medication phase due to an adverse event (a local reaction from frequent blood sampling) and three (7.5%) withdrew in medication cycle 3, for reasons they did not mention. One of the latter was lost to follow-up. During the post-treatment phase, the incidence of adverse events was lower than that observed during pre-treatment, with 8/36 (22.2%) women (safety population), who completed the trial, reporting adverse events. One case of acute appendicitis was the only serious adverse event during the post-treatment phase; it was considered to be unrelated to the trial medication.

No other clinical or laboratory abnormalities were observed during the trial. All pregnancy tests were negative and there were no pathological changes in the cervix.

During pretreatment, 4/33 (12.1%) of the women (PPA) reported intermenstrual bleeding. As expected, the incidence of intermenstrual bleeding increased during treatment. It was highest in medication cycle 1, with 12/30 (40%) women reporting intermenstrual bleeding. Intermenstrual bleeding declined during the next two medication cycles, with the incidence in cycle 3 (16%) being similar to pretreatment (12.1%). Spotting and breakthrough bleeding occurred in similar numbers of women during each cycle.

Single cycles were occasionally omitted from the full analysis set due to missing FLS values or sex hormone measurements leading to unreliable grading according to Hoogland and Skouby[5]. Similarly, single cycles were omitted from the per protocol set if more than one pill per medication cycle was missed, diarrhoea or vomiting had occurred, or antibiotics were taken (all of which diminish the efficacy of OCs).

DISCUSSION AND CONCLUSION

This single-centre, open, non-controlled, phase II trial was designed to evaluate the contraceptive efficacy (ovulation inhibition) and safety of a modern low-dose combination pill (EE/CMA) in women with no known infertility.

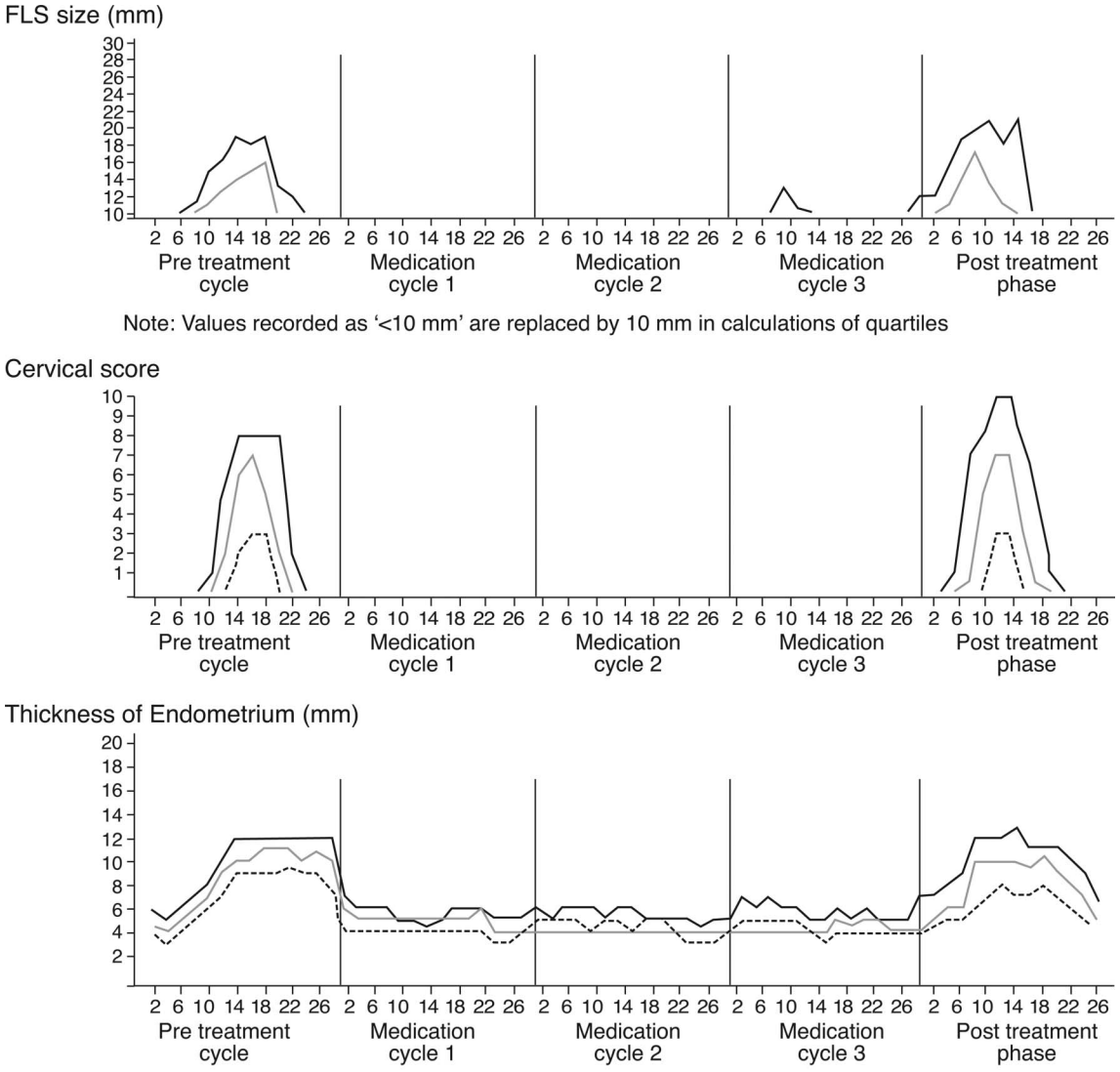

Figure 2 Size of follicle-like structure, cervical score and endometrial thickness

In total, 40/65 (61.5%) women were screened, received trial medication and were eligible for the safety analysis. Of these, 33 (82.5%) were eligible for the analysis of efficacy as per protocol. The demographics of the subjects were those of a healthy female population and thus corresponded to those of potential users.

The current trial used the grading of ovarian activity according to Hoogland and Skouby[5], which was reviewed and modified by Spona[10–12]. This combines the ultrasonic examination of follicles and the determination of hormone levels to differentiate levels of ovarian activity. Follicle size, sex hormone levels, cervical reaction and endometrial thickness were measured every other day, and grading was performed for each cycle. This ensured that comprehensive information regarding residual ovarian activity was obtained. Secondary assessments (changes of cervical reaction and endometrial thickness) helped to thoroughly assess the potential for pregnancy.

EE/CMA suppressed ovarian activity to a major degree, as reflected by only 14.5% of the cycles

Table 5 Number (%) of women with adverse events [95% confidence intervals (CIs)]

Event	*Pretreatment n = 40 (%)*	*Medication phase n = 40 (%)*	*Post-treatment n = 36 (%)*
Reporting at least one event	11 (27.5) [95% CI, 14.60–43.89]	34 (85) [95% CI, 70.16–94.29]	8 (22.2) [95% CI, 10.12–39.15]
Serious adverse events	0 (0) [95% CI, 0.07–14.53]	0 (0)	1 (2.8)*
Adverse events leading to withdrawal	0 (0)	1 (2.5)** [95% CI, 0.06–13.16]	0 (0)
Most common adverse events (>three subjects)			
Headache	3 (7.5) [95% CI, 1.57–20.39]	16 (40.0) [95% CI, 24.86–56.67]	3 (8.3) [95% CI, 1.75–22.47]
Dizziness	1 (2.5) [95% CI, 0.06–13.16]	4 (10.0) [95% CI, 2.79–23.66]	0 (0)
Nausea	1 (2.5) [95% CI, 0.06–13.16]	8 (20.0) [95% CI, 9.05–35.65]	0 (0)
Vomiting	3 (7.5) [95% CI, 1.57–20.39]	9 (22.5) [95% CI, 10.84–38.45]	0 (0)
Fatigue	1 (2.5) [95% CI, 0.06–13.16]	4 (10.0) [95% CI, 2.79–23.66]	1 (2.8) [95% CI, 0.07–14.53]
Breast discomfort	2 (5.0) [95% CI, 0.61–16.92]	7 (17.5) [95% CI, 7.34–32.78]	0 (0)
Dysmenorrhoea	0 (0) [95% CI, 1.57–20.39]	3 (7.5) [95% CI, 0.07–14.53]	1 (2.8)
Common cold	1 (2.5) [95% CI, 0.06–13.16]	9 (22.5) [95% CI, 10.84–38.45]	0 (0)
Naso-pharyngitis	0 (0)	3 (7.5) [95% CI, 1.57–20.39]	0 (0)

*Acute appendicitis, not related to the trial medication.
**Injection site reaction due to frequent blood sampling.

showing any residual ovarian activity during treatment (grade 4–5). The formation of a LUF only occurred in 1/83 (1.2%) medication cycles and no ovulation was observed (PPA). One breakthrough ovulation following vomiting and diarrhoea was detected in the full analysis set; this finding led to the exclusion of this subject's data sets and thus her exclusion from PPA. However, her cervical reaction time and endometrial thickness were suppressed to such a degree that conception and nidation were unlikely to have taken place.

During pretreatment, oestradiol and progesterone levels were typical of an ovulatory cycle. During treatment, levels of oestradiol were low during days 1–21 of the cycle, reflecting suppression of the pituitary axis, but they increased slightly during the pill-free interval. Levels of LH and FSH also increased during the pill-free interval. Progesterone was completely suppressed during the medication phase, indicating an absence of ovulation. The marked effect of EE/CMA can be explained by the high binding affinity of CMA to progesterone receptors, which is approximately 30% greater than that of progesterone[6].

As expected, ovarian suppression was greatest during the first medication cycle. This is most likely due to the fact that medication intake during the first cycle is taken on the first day of menstrual bleeding when ovarian, hormonal, cervical and endometrial processes are down-regulated to their lowest level. In contrast, during subsequent medication cycles, the pill-free interval of 7 days duration allowed some rebound in follicular and endometrial growth and an increase in oestradiol to occur. Levels of LH and FSH also increased during the pill-free interval.

The results of this trial compare favourably with those of trials of other OCs, during which much higher residual ovarian activity (up to 50%) has been reported[3,10]. Our data also compare favourably with those of previous reports on the efficacy and safety of EE/CMA[17–19] and post-marketing surveillance trials[20]. For example, in a multicentre, phase III trial during which 1655 women took EE/CMA for a total of 22337 cycles, contraceptive efficacy was outstanding (adjusted Pearl index of 0.27) and it was associated with great cycle stability, and beneficial anti-androgenic effects on both hair and skin[19].

Overall, EE/CMA had a favourable safety profile and was well tolerated. Most side effects were cycle-related, and included headache, nausea, vomiting and breast discomfort. There were no serious adverse events attributed to the trial medication. The adverse events that affected our patients were of the same type as the widely accepted complaints characterizing the use of OCs; due to the smaller number of participants, the frequency of side effects in this study was higher than previously reported[21,22]. The safety profile of EE/CMA is most likely related to its almost complete absence of mineralocorticoid and anti-mineralocorticoid effects, and its lack of interference with hepatic metabolism[9].

In line with previous observations[8], body weight was not affected. The frequency of intermenstrual bleeding was low and, during the third medication cycle, it was similar to that during the pretreatment phase. These results are encouraging, because inadequate cycle control and increase in body weight are common reasons for discontinuation of hormonal contraception.

In summary, EE/CMA is a well-tolerated and highly effective OC, with little or no interference with cycle stability. All these factors should increase compliance. With a profoundly suppressed follicular development, negative cervical reaction and endometrial thinning, pregnancy during treatment EE/CMA seems extremely unlikely. EE/CMA also displays an anti-androgenic activity[8,17–19], which may benefit users with seborrhoea and moderate acne.

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Conflict of Interest Statement Two of the authors are employed by Grunenthal GmbH, which manufactures the oral contraceptive assessed in the present study.

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