ORIGINAL ARTICLE

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The effects of vilaprisan on the pharmacodynamics and pharmacokinetics of a combined oral contraceptive—A randomized controlled trial

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Aims: The primary objective was to explore whether the suppression of ovarian activity induced by a combined oral contraceptive (COC) is influenced by the simultaneous intake of the selective progesterone receptor modulator (SPRM) vilaprisan (VPR).

Methods: In this exploratory randomized, double-blind, parallel-group study, 71 healthy premenopausal women were randomized (1:1) to receive either 2 mg/d VPR or placebo for 3 months. Concomitantly, a COC (0.15 mg levonorgestrel, 0.03 mg ethinyloestradiol) was administered in a cyclic regimen. Ovarian activity (Hoogland score based on follicle size and hormone concentrations), cervical function (Insler score), bleeding pattern and endometrial thickness/histology were assessed before treatment, in treatment cycle 3 and during follow-up.

Results: The known COC-driven suppression of ovarian activity was mildly affected by VPR. COC+VPR group: 22, 0 and 6% of the subjects had Hoogland scores of 4 (active follicle-like structures), 5 or 6 (ovulation). COC+placebo group: 14% of the subjects had a score of 4 and none a score of 5 or 6 (Bayesian analysis for Hoogland score = 4, median difference in response rate: 7.5%; 90% credible interval [−8.5; 23.5%]). COC effects on cervical function were moderately affected (mucus more sperm permeable under COC+VPR). COC withdrawal bleeding, in contrast, was absent in 81% of the subjects receiving COC+VPR *vs* 0% receiving COC+placebo.

Conclusion: The SPRM VPR interfered with the pharmacodynamic effects of the COC. Therefore, full contraceptive effectiveness cannot be assumed without final judgement by a Pearl index study. Women on SPRMs should be advised to use non-hormonal contraception methods.

KEYWORDS

combined oral contraceptive, interaction, selective progesterone receptor modulator

1 | INTRODUCTION

Selective progesterone receptor modulators (SPRMs) are highly effective in the treatment of uterine fibroids.[1–3] Since many women suffering from symptomatic uterine fibroids are of reproductive age, they are typically faced with the difficult question of which method of contraception to use. SPRMs themselves, although known to have contraceptive properties,[4,5] cannot be recommended as contraceptives. Currently, there are no approved SPRM-based contraceptives for regular use and no published Pearl index studies with SPRMs. From a mechanistic point of view, hormonal contraceptives, which are among the most popular options currently, can probably not be recommended either. As the progestin component of hormonal contraceptives acts on the **progesterone receptor** as an agonist,[6] a pharmacodynamic (PD) interaction with SPRMs that act predominantly antagonistic on the progesterone receptor in many tissues[7] must be assumed. Such an interaction might diminish the contraceptive's efficacy. However, no such data are currently available and, in view of the complex interfaces in the hypothalamic–pituitary–ovarian axis and the potential tissue-specific PD effects of steroid receptor modulators on different endocrine systems, it seems necessary to take a closer look at this interaction potential.

Thus, in alignment with the health authorities, we decided to investigate the respective interaction potential as part of the clinical development programme for vilaprisan (VPR), a promising and thoroughly studied new SPRM,[2,5,7–12] which is being developed for the treatment of uterine fibroids. A standard combined oral contraceptive (COC) containing the progestin levonorgestrel (LNG) in combination with ethinyloestradiol (EO) was chosen as the *interaction partner*, because of the large market share of LNG/EO-containing COCs.[13]

The primary objective of our study was to assess whether the suppression of ovarian activity caused by the COC is influenced by the simultaneous intake of VPR. In addition, the impact of VPR coadministration on the cervical function, the endometrial thickness and histology, the bleeding pattern, and on the pharmacokinetics (PK) of EO and LNG was studied.

2 | METHODS

The study was conducted at 2 study sites in Berlin, Germany, dinox GmbH Female Health Research and CRS Clinical Research Services Berlin GmbH, between July 2017 and August 2018 (last subject, last visit). It was approved by the independent ethics committee at the Landesamt für Gesundheit und Soziales, Berlin, Germany. All participants provided written informed consent before enrolment. The study was completed as planned.

2.1 | Design and treatment

This was an exploratory randomized, double-blind, parallel-group study, which comprised 4 phases: screening, pretreatment cycle,

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**What is already known about the subject**

- Selective progesterone receptor modulators (SPRM) are approved for the treatment of uterine fibroids in women of reproductive age, i.e. women possibly wanting to use hormonal contraceptives.
- A pharmacodynamic interaction between SPRMs with their antagonistic activity at the progesterone receptor and the contraceptives' progestin components with their agonistic activity is anticipated.

What this study adds

- The SPRM vilaprisan counteracts pharmacodynamic effects of a combined oral contraceptive (COC).
- The strongest impact is on the uterus with complete blocking of the typical COC-induced withdrawal bleeding. COC-effects on cervical function and ovarian activity are impacted less distinctively.
- Full contraceptive effectiveness cannot be assumed when COCs are taken with SPRMs.

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treatment phase and follow-up (Figure 1). In total, 71 healthy premenopausal women were randomly assigned to 1 of 2 treatment groups following a computerized randomization procedure using 1:1 allocation and random block sizes of 4. Subjects in both groups received a marketed COC containing 0.15 mg LNG + 0.03 mg EO/d (Microgynon 30, Bayer AG, Germany) for 3 28-day cycles (LNG+EO on Day 1–21, corresponding placebo on Day 22–28). After the third treatment cycle (TC), a 7-day placebo extension period followed, resulting in a total treatment duration of 91 days. In 1 group, the COC tablet was administered together with a tablet containing 2 mg VPR (Bayer AG, Germany; COC+VPR group), in the other group, the COC tablet was given with a placebo tablet of the same appearance as the VPR tablet (COC+placebo group) on each day of the 91-day treatment phase. All medications were supplied by Bayer AG, Germany. The 2-mg dose of VPR, which has been identified in Phase 2 as the optimum dose for treating uterine fibroids,[10,12] is the dose used in Phase 3 studies as well.

Study drug intake started on the first or second day of menstrual bleeding after the pretreatment cycle. Assessments were performed until the second menstrual bleeding after the last study drug intake. The extra 7-day placebo period after TC3 allowed a comparison of VPR plasma concentrations with and without concomitant intake of the COC (end of LNG/EO intake in TC3 *vs* end of placebo intake on day 90 ± 1).
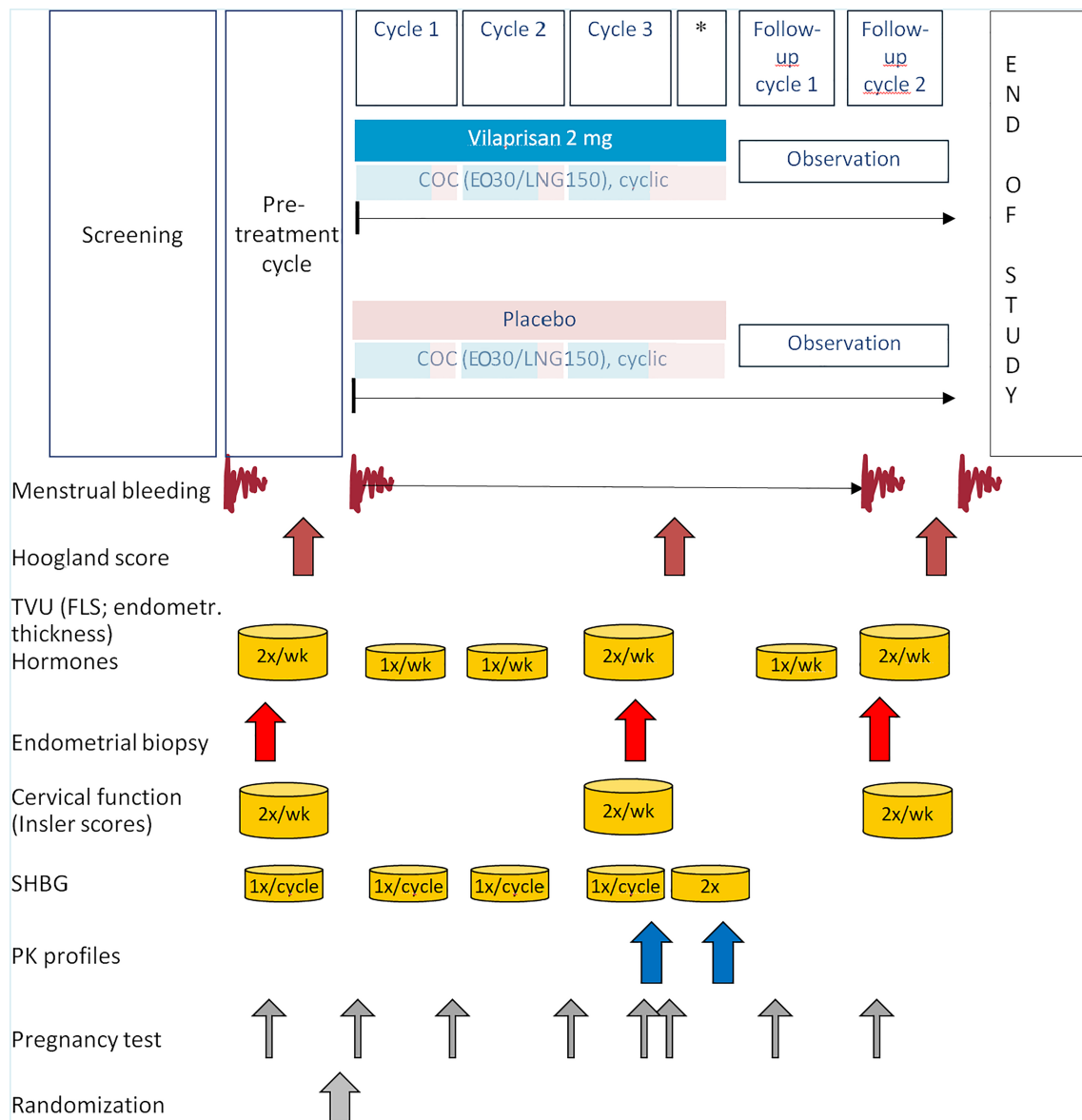
FIGURE 1   Design of the study. * placebo extension of cycle 3; COC, combined oral contraceptive; FLS, follicle-like structures; EO30, ethinyloestradiol 0.03 mg/d; LNG150, levonorgestrel 0.15 mg/d; PK, pharmacokinetic; SHBG, sex hormone-binding globulin; TVU, transvaginal ultrasound. The COC was given for three 28-day cycles (LNG/EO on days 1 through 21; corresponding placebo on days 22 through 28). After the third treatment cycle, a 7-day placebo extension period followed, resulting in a total treatment duration of 91 days. Safety monitoring included the continuous assessment of adverse events and concomitant medications plus standard clinical laboratory tests and vital signs approximately once per cycle

2.2 | Study population

Healthy premenopausal women, aged 18–35 years, nonsmokers, with a body mass index ≥18 and ≤30 kg/m² presenting an ovulation in the pretreatment cycle were eligible for treatment. The use of additional, nonhormonal contraception was obligatory during the study, i.e. male condom, cap, diaphragm or sponge, each in combination with spermicide; not required in case of bilateral fallopian tube blockage of the subject or vasectomy of the partner(s). Key exclusion criteria included any clinically relevant abnormal findings in the pretreatment examinations (physical and gynaecological examination, blood and urine laboratory tests, vital signs, endometrial biopsy) and any contraindication

for the intake of VPR or the COC, e.g. indications of an increased risk of venous or arterial thromboembolism.

2.3 | PD and safety investigations

Primary endpoint was the assessment of ovarian activity using the Hoogland scoring system,[14] which combines follicle size and oestradiol (O2) and progesterone serum concentrations. Transvaginal ultrasound to measure the size of follicles and follicle-like structures (FLS) as well as blood sampling for analyses of serum hormone concentrations, i.e. O2, progesterone, luteinizing hormone (LH) and

follicle-stimulating hormone (FSH), and sex hormone-binding globulin (SHBG) were performed at the time points specified in Figure 1. The largest FLS in either ovary as well as the concentrations of O2 and progesterone were determined and resulted in a Hoogland score (1 = no activity; 6 = ovulation) for the respective cycle.

Cervical function was assessed using the Insler score,[15] which includes the evaluation of the appearance of the external cervical *os* and the quantity, spinnbarkeit (spinnability) and ferning of the cervical mucus.

The evaluation of the bleeding pattern was based on the subject's daily self-assessment of their maximum bleeding intensity on a 5-point scale (none, spotting, light, normal, heavy). Induced amenorrhoea was defined as "bleeding intensity was 'none' on all treatment days, excluding the initial bleeding at treatment start and the day of and the three days after the endometrial biopsy".

Endometrial thickness was measured during transvaginal ultrasound investigations. An endometrial biopsy using Pipelle de Cornier sampling was performed on Day 9 of the pretreatment cycle, on Day 21 of TC3, and on Day 9 of follow-up cycle 2. Samples were assessed in a blinded fashion by 3 expert pathologists, who worked independently of each other. After a general assessment of the sample for pathological findings using standard histopathology criteria, i.e. *atrophic, inactive, proliferative, disordered proliferative, secretory, menstrual, endometritis* and *other* according to Blaustein's Pathology of the Female Genital Tract,[16] the samples were evaluated for progesterone receptor modulator-associated endometrial changes (PAECs), the occurrence of which after treatment with SPRMs has been reported by Mutter *et al.*[17]

Safety monitoring included the continuous assessment of adverse events and concomitant medications as well as standard clinical laboratory tests and vital signs, approximately once per cycle. Urine pregnancy tests were carried out before, during and after treatment.

2.4 | PK investigations

Blood samples for PK analyses of LNG, EO and VPR were taken on 1 day at the end of TC3 (Day 16 ± 5 of TC3), predose and 1, 2, 3, 4, 8 and 12 hours postdose (PK profile 1). Additional samples for PK analyses of VPR were taken in COC+VPR group at the end of the extended placebo period (Day 90 ± 1; PK profile 2). Bioanalytical measurements (LNG, EO and VPR) were carried out at InVentive Health Clinique (now Syneos Health), Einstein, Québec, Canada. Liquid chromatography–tandem mass spectrometry detection methods, which were validated according to the relevant European Medicines Agency and US Food and Drug Administration guidelines,[18,19] were used to determine VPR, LNG and EO in plasma (details in Supplement 1). The maximum plasma concentration after multiple dosing ($C_{max,md}$) was obtained directly from the concentration data. The area under the plasma concentration-time curve after multiple dosing in the dosing interval ($AUC(0-24)_{md}$) was calculated by the mixed linear/logarithmic trapezoidal rule.

2.5 | Statistics

The primary variables were the number of subjects with ovulation (Hoogland score = 6) or risk of ovulation (Hoogland score = 5; luteinized unruptured follicle) and the number of subjects with an active FLS (Hoogland score = 4) in TC3. These numbers were summarized by treatment using frequency tables. For the evaluation of the differences in response rate between both treatments, an exploratory Bayesian analysis was carried out using noninformative prior information. The same approach was used to evaluate the number of subjects with induced amenorrhoea during the treatment phase.

For the evaluation of the PK drug–drug-interaction with VPR as the potential perpetrator and LNG and EO as the victim drugs, an analysis of variance was performed for $AUC(0-24)_{md}$ and $C_{max,md}$ of LNG and EO to compare the 2 treatments. Point estimates, 90% confidence intervals (CI) and 95% prediction intervals for the ratio COC+VPR/COC+placebo were derived by inverse log-transformation of the least square mean differences.

The PK drug–drug interaction with the COC as the potential perpetrator and VPR as the victim drug was assessed by comparing the PK parameters $AUC(0-24)_{md}$ and $C_{max,md}$ of VPR obtained on PK profile days 1 and 2 in subjects receiving COC+VPR (intraindividual comparison).

The sample size was selected to compare the response rate for the Hoogland score = 4 in TC3 between COC+placebo and COC+VPR. Response rates for subjects with Hoogland score = 4 were around 35% in historical studies with a lower-dosed COC.[20,21] Assuming similar rates, point estimates in the range of 35 ± 20% were anticipated for *n* = 24 subjects. The precision of the rate estimates was assessed by 90% Clopper–Pearson CIs with an expected width ≤35%. Therefore, 24 subjects per treatment arm were considered appropriate to assess relevant changes in Hoogland scores. Taking drop-outs and subjects invalid for the primary analysis into account, up to 80 subjects were planned to be randomized. Statistical analyses were done using the software SAS release 9.2 (SAS Institute Inc., Cary, NC, USA).

2.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

3 | RESULTS

3.1 | Study subjects and analysis sets

In total, 139 premenopausal women were screened for this study. Of these, 71 healthy women were randomized to 1 of the 2 treatment groups and treated with at least 1 dose of the assigned study medication (36 subjects in COC+placebo group, 35 subjects in COC+VPR

group: safety analysis set; Figure 2). The data of 8 subjects were excluded from the PK and PD analyses due to early discontinuation of treatment. In addition, 2 subjects were excluded from the PD analysis due to intake of prohibited medication, i.e. hormones for emergency contraception.

The demographic and baseline clinical characteristics were well balanced with no notable differences between groups (Tables 1–3). The subjects were aged between 18 and 35 years and mostly Caucasian.

3.2 | PD

In both treatment groups, ovarian activity as assessed on the basis of FLS diameters and hormone concentrations was mildly influenced in the treatment phase compared to the respective pretreatment cycle (Table 2). The mean maximum FLS diameters as well as the mean average and maximum hormone concentrations were generally lower in the treatment phase than before and after treatment. In TC3, follicles did not grow to diameters >13 mm (Hoogland scores of 1 or 2) in 86% and 72% of the subjects from the COC+placebo and COC+VPR group, respectively (Table 4). However, larger FLS with O2 values >27.2 pg/mL (Hoogland score = 4, active FLS) were observed in 14 and 22% of the subjects from the COC+placebo and COC+VPR group, respectively, and an ovulation (Hoogland score = 6) was observed in 2 subjects (6%) from the COC+VPR group. Large follicles followed by rupture and increased progesterone values had already
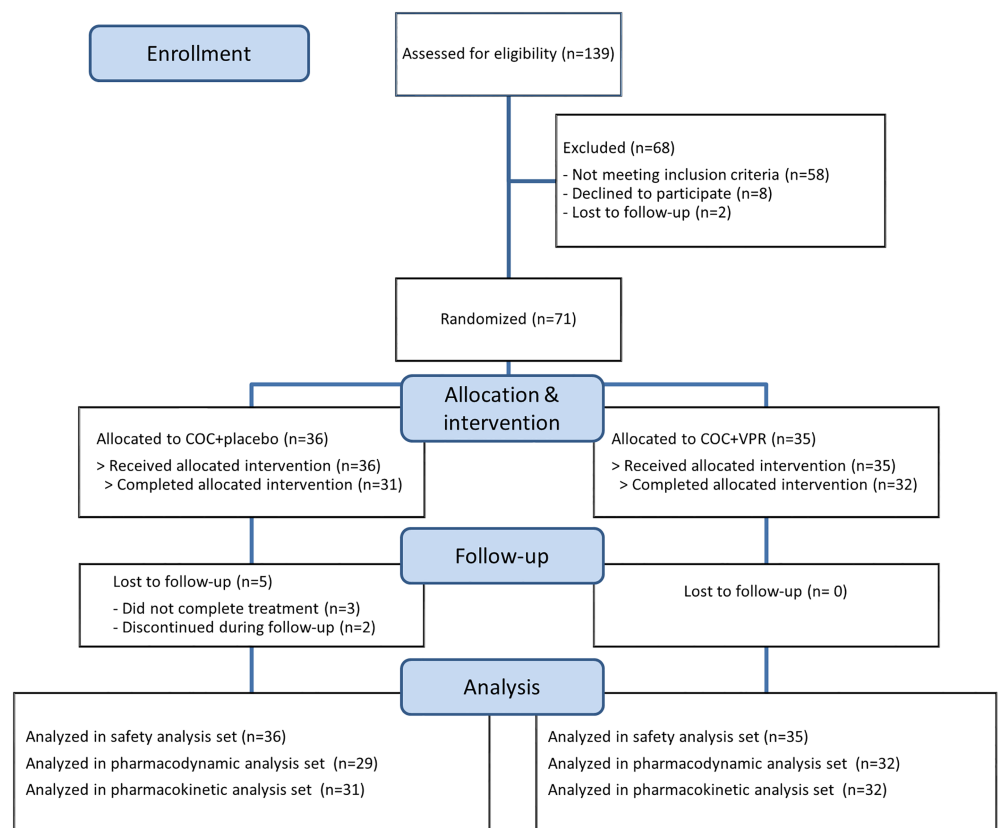
TABLE 1 Baseline demographic data (safety analysis set, $n = 71$)

	COC+VPR ($n = 35$)	COC+placebo ($n = 36$)
Age (y) arithmetic mean ± standard deviation	28.0 ± 4.5	29.1 ± 4.4
Ethnic origin, n (%)		
Asian	1 (3)	--
Black or African American	2 (6)	1 (3)
Caucasian	30 (86)	35 (98)
Multiple	2 (6)	--
Body mass index, kg/m², arithmetic mean ± standard deviation	23.3 ± 2.83	23.4 ± 2.99

COC, combined oral contraceptive; VPR, vilaprisan

been observed in both subjects in TC2. Both subjects showed drug exposure levels and a time-dependent increase in SHBG concentrations (SHBG induction by EO) that suggested regular intake of the COC. The Bayesian analysis using noninformative prior showed median differences in response rates of 5.2 and 7.5% for Hoogland scores ≥5 and = 4, respectively. However, these differences are of no statistical relevance as the corresponding 90% credible intervals include zero (Table 4).

As expected under treatment with a COC, serum FSH concentrations decreased from the beginning of each treatment cycle until Day


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┌─────────────┐    ┌────────────────────────────────┐
│ Enrollment  │    │ Assessed for eligibility (n=139)│
└─────────────┘    └────────────────────────────────┘
                              │
                              │   ┌──────────────────────────────────────┐
                              │   │ Excluded (n=68)                      │
                              │   │ - Not meeting inclusion criteria (n=58)│
                              │   │ - Declined to participate (n=8)      │
                              │   │ - Lost to follow-up (n=2)            │
                              │   └──────────────────────────────────────┘
                       ┌──────────────────┐
                       │ Randomized (n=71)│
                       └──────────────────┘
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Allocation & intervention

Allocated to COC+placebo (n=36)
> Received allocated intervention (n=36)
> Completed allocated intervention (n=31)

Allocated to COC+VPR (n=35)
> Received allocated intervention (n=35)
> Completed allocated intervention (n=32)

Follow-up

Lost to follow-up (n=5)
- Did not complete treatment (n=3)
- Discontinued during follow-up (n=2)

Lost to follow-up (n= 0)

Analysis

Analyzed in safety analysis set (n=36)
Analyzed in pharmacodynamic analysis set (n=29)
Analyzed in pharmacokinetic analysis set (n=31)

Analyzed in safety analysis set (n=35)
Analyzed in pharmacodynamic analysis set (n=32)
Analyzed in pharmacokinetic analysis set (n=32)

FIGURE 2 Disposition of subjects. COC, combined oral contraceptive; VPR, vilaprisan

TABLE 2 Follicle-like structures and hormone concentrations before, during and after treatment (pharmacodynamic analysis set, $n = 61$)

Time	Treatment group	FLS, mm maximum diameter	FSH, IU/L C_{max}	FSH, IU/L C_{av}	LH, IU/L C_{max}	LH, IU/L C_{av}	O2, pg/mL C_{max}	O2, pg/mL C_{av}	P, µg/L C_{max}
Pre- treatment cycle	COC+VPR	18.8 ± 2.9	10.4 ± 4.0	6.2 ± 1.6	30.7 ± 22.5	11.9 ± 4.4	257.1 ± 94.5	128.2 ± 43.6	14.2 ± 6.9
	COC+placebo	19.4 ± 3.2	9.5 ± 3.4	5.9 ± 1.4	30.8 ± 24.2	12.3 ± 6.0	284.7 ± 93.2	138.7 ± 45.8	12.6 ± 6.2
Treatment phase	COC+VPR	14.0 ± 6.8	10.1 ± 3.6	4.2 ± 1.2	15.3 ± 7.5	6.6 ± 2.9	126.3 ± 141.3	31.5 ± 32.4	1.4 ± 3.9
	COC+placebo	12.6 ± 6.6	8.9 ± 3.2	3.6 ± 1.4	8.9 ± 3.9	3.5 ± 2.0	95.6 ± 116.2	26.3 ± 24.9	0.4 ± 0.2
Follow-up cycle 2	COC+VPR	20.0 ± 7.2	10.2 ± 3.3	5.4 ± 1.0	27.7 ± 22.4	9.0 ± 3.3	294.6 ± 132.6	134.9 ± 48.5	16.8 ± 8.0
	COC+placebo	20.5 ± 9.3	9.2 ± 3.2	5.1 ± 0.9	33.5 ± 20.8	10.7 ± 4.2	302.9 ± 153.4	136.1 ± 61.2	14.7 ± 6.5

C_{av}, average concentration in serum; C_{max}, observed maximum concentration in serum; COC, combined oral contraceptive; O2, oestradiol; FLS, follicle-like structure; FSH, follicle-stimulating hormone; LH, luteinizing hormone; P, progesterone. VPR, vilaprisan.

Values are arithmetic means and standard deviations.

The diameter of the largest follicle-like structure was defined as the calculated mean of the longitudinal and transversal diameters (measured by transvaginal ultrasound) of the largest FLS in each ovary. Based on these values, the maximum FLS diameter observed during each study period was described.

TABLE 3 Cervical function (Insler score) before treatment and in treatment cycle 3 (pharmacodynamic analysis set, $n = 61$)

Time	Cervical score rating (Insler score)	COC+VPR ($n = 32$) % (n)	COC+placebo ($n = 29$) % (n)
Pre-treatment cycle	Negative (0–3)	0	0
	Slight (4–6)	6% (2)	10% (3)
	Moderate (7–9)	25% (8)	17% (5)
	Full (10–12)	69% (22)	72% (21)
Treatment cycle 3	Negative (0–3)	9% (3)	21% (6)
	Slight (4–6)	6% (2)	41% (12)
	Moderate (7–9)	44% (14)	31% (9)
	Full (10–12)	41% (13)	7% (2)

COC, combined oral contraceptive; VPR, vilaprisan.

Values are % (number of subjects). The Insler score is based on the evaluation of the appearance of the external cervical os and the quantity, spinnbarkeit (spinnability), and ferning of the cervical mucus.[5,15] The sum of the scores for these four parameters (possible values: 0 – 12) is categorized as *negative* (0 – 3), *slight* (4 – 6), *moderate* (7 – 9) and *full* (10 – 12).

21 (last dose of LNG+EO) in both groups (Supplement 2). Comparing the 2 treatment groups, a slightly less reduction was seen in the COC+VPR group (Table 2). In both groups, the mean average FSH values (C_{av}) increased again in follow-up period 2.

Whereas an explicit increase of the serum LH concentrations was observed around Day 15 in the pretreatment cycle (LH surge), LH concentrations were clearly suppressed in both groups during the treatment phase with slightly lower C_{max} and C_{av} of LH in the COC+placebo than in the COC+VPR group (Table 2). This was also reflected in the number of subjects who had at least once a LH value >10 U/L (pretreatment/follow-up cycle: 92%, treatment phase: COC+placebo: 34%, COC+VPR: 66%).

In accordance with the observed suppression of the follicle growth, average and maximum O2 concentrations in serum were decreased in both groups during the treatment phase (Table 2). Considering the large standard deviations, there were no apparent differences in the mean maximum O2 and mean average O2 values between the 2 groups.

Serum progesterone concentrations were also clearly decreased in both treatment groups during the treatment phase (Table 2). Whereas in the pretreatment cycle all subjects had at least 1 value above 1.57 µg/L indicating luteinization of the follicle or ovulation, this was the case for only 3 subjects in TC2 and 2 subjects in TC3 (all from the COC+VPR group). Whereas 2 of these subjects showed an ovulation in TC2 and TC3, in 1 subject the progesterone value was only slightly increased at a single time point during TC2. Ultrasound results on follicle sizes and hormone values of this subject did not clearly show an ovulatory cycle.

In the pretreatment cycle, nearly all subjects (>90%) had a cervical score rating of *moderate* or *full*, indicative of the cervical mucus being permeable for sperm (Table 3). In the COC+VPR group, this

TABLE 4 Ovarian activity (Hoogland score) in treatment cycle 3 (pharmacodynamic analysis set, *n* = 61)

Hoogland Score	Ovarian activity	Description	COC+VPR (n = 32) % (N)	COC+placebo (n = 29) % (N)	Median difference in response rate (90% credible interval)
1	No activity	FLS ≤10 mm	41% (13)	55% (16)	
2	Potential activity	FLS >10 and ≤13 mm	31% (10)	31% (9)	
3	Non-active FLS	FLS >13 mm E2 ≤27.2 pg/mL	0	0	
4	Active FLS	FLS >13 mm E2 >27.2 pg/mL P ≤1.57 µg/L	22% (7)	14% (4)	7.49 % (-8.49%; 23.47%)
5	Luteinized unruptured follicle	FLS >13 mm, persisting E2 >27.2 pg/mL P >1.57 µg/L	0	0	5.22% (-3.24%; 15.56%)
6	Ovulation	FLS >13 mm, ruptured E2 >27.2 pg/mL P >1.57 µg/L	6% (2)	0	

COC, combined oral contraceptive; FLS, follicle-like structure; O2, oestradiol, 27.2 pg/mL = 0.1 nmol/L; P, progesterone, 1.57 µg/L = 5 nmol/L; VPR, vilaprisan. Values are % (number of subjects).

For the evaluation of the differences in response rates between both treatments, an exploratory Bayesian analysis was carried out using noninformative prior information.

percentage hardly changed during treatment. In the COC+placebo group, in contrast, the percentage of subjects with a rating of *moderate* or *full* decreased to 38% in TC3, i.e. the effect of the COC was clearly diminished by the addition of VPR.

Most subjects of the COC+placebo group had scheduled (withdrawal) bleedings starting during the COC-free intervals (Days 22–28 of each treatment cycle; Figure 3). In addition, spotting or unscheduled bleedings were documented for several subjects. The bleeding pattern observed in the COC+VPR group differed substantially from that in the COC+placebo group. Following the initial bleeding at the start of treatment, most of the subjects did not report any further bleeding during the treatment phase. The induced amenorrhoea rate was 81.3% (90% Clopper–Pearson CI: 66.3–91.5%) in the COC+VPR group and none in the COC+placebo group.

All biopsy samples taken during the study were diagnosed as *benign endometrium* by all 3 expert readers. Biopsy tissue collected at the end of treatment with COC+placebo was described mostly as *secretory endometrium* (96.6%). At the end of COC+VPR treatment, by contrast, 35.5% of the samples were assessed as *secretory*, 29.0% as *atrophic* and 19.4% as *inactive endometrium*. No majority decision was available for 16% of the samples from the COC+VPR group *vs* none for samples from the COC+placebo group. It is of special note that the readers frequently noted *fragmented specimen* and *disrupted architecture* in samples from the COC+VPR group. PAECs were seen in only 1 out of 28 (3.6%) evaluable samples taken in the COC+placebo group and in 8 out of 22 (36.4%) evaluable samples taken in the COC

+VPR group at the end of TC3. No PAECs were seen in samples taken before treatment or during follow-up.

Whereas endometrial thickness increased toward the end of the pretreatment cycle, values remained low during the treatment phase without a relevant difference between the 2 groups (Figure 4; COC+VPR: 8.8 ± 1.8 mm maximum endometrial thickness; COC+placebo: 8.6 ± 2.4 mm).

As expected during the intake of a COC containing EO,[22] mean SHBG concentrations increased from pretreatment values of about 60 nmol/L (Day 9) to mean values of about 100 nmol/L during treatment. After the last intake of LNG+EO on Day 77, values decreased again and reached the pretreatment level at the end of the treatment phase. No relevant differences between the 2 groups were observed.

Ovulatory cycles followed by menstrual bleeding returned quickly after the end of treatment in most subjects (90% in follow-up cycle 2) in both groups.

3.3 | PK

Coadministration of VPR had no effect on the exposure of EO or LNG (total and unbound; AUC (0–24)md, Cmax,md; Table 5). The exposure of VPR, in contrast, was slightly increased when the drug was administered concurrently with the EO/LNG-containing COC, but without clinical relevance.
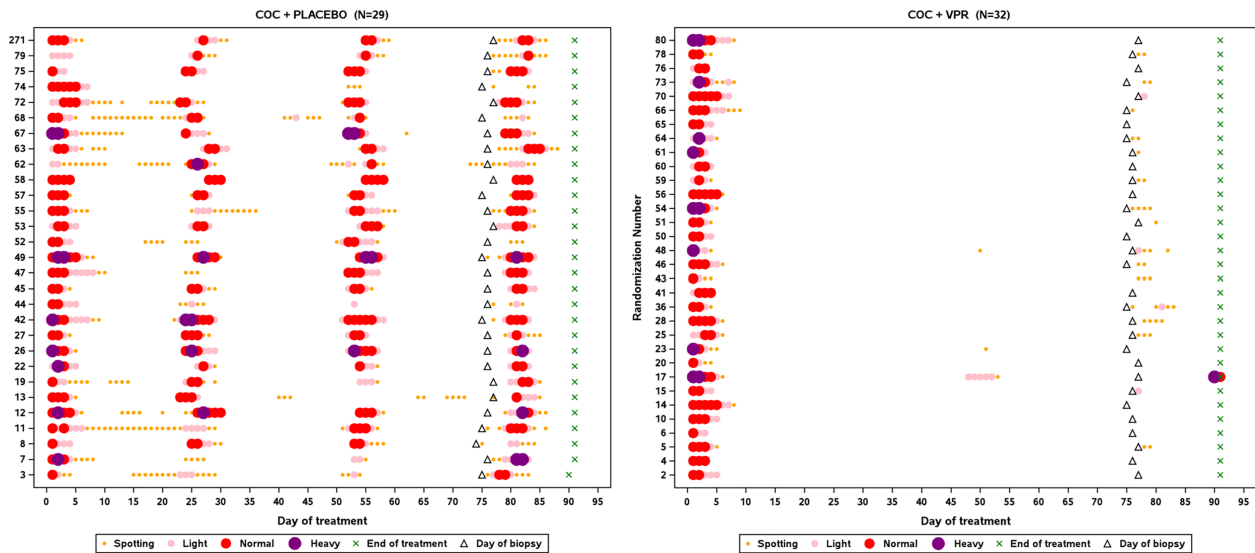
FIGURE 3 Bleeding intensity during treatment: Individual data (pharmacodynamic analysis set, *n* = 61). COC, combined oral contraceptive; VPR, vilaprisan. Bleeding intensity = *none* on all treatment days, excluding the initial bleeding at treatment start and the day of and the 3 days after the endometrial biopsy, was defined as *induced amenorrhoea*
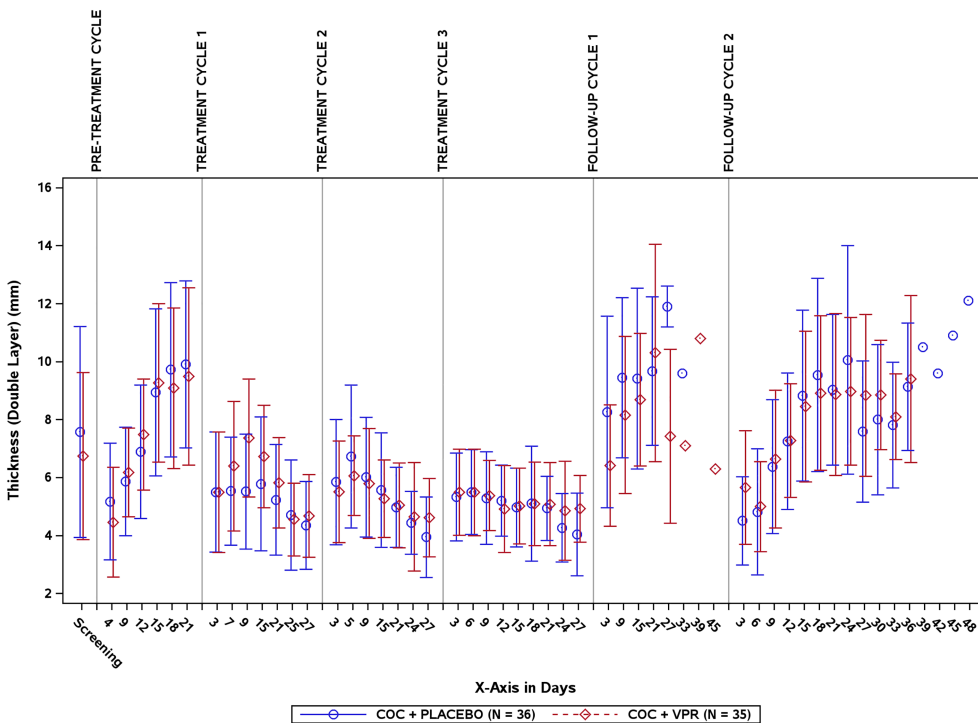
FIGURE 4 Endometrial thickness before, during and after treatment (safety analysis set, *n* = 71), COC, combined oral contraceptive; VPR, vilaprisan. Symbols represent arithmetic means, whiskers the corresponding standard deviation. The standard deviation was not calculated if the sample size was too small

3.4 | Safety

All 71 treated women had at least 1 treatment-emergent adverse event (TEAE), mainly of mild intensity. One serious TEAE occurred during study drug intake (COC+VPR: severe dizziness, hospitalization reported) and led to premature termination of study participation. Five days after the end of study drug intake, the event was recovered as reported by the subject (no hospital discharge report available). In addition, 3 subjects discontinued the study drug intake prematurely due to TEAEs (COC+VPR: mild alopecia; COC+placebo: moderately increased liver enzyme values; mild mood swings and simultaneously moderate pelvic pain).

The number of subjects affected was similar in the 2 treatment groups for most TEAEs. The most commonly reported TEAEs (affecting ≥20% of the total study population) were nasopharyngitis, postprocedural hemorrhage (uterine bleeding after endometrial biopsy), headache, pelvic pain, and endometrial and cervix disorders. With respect to the safety monitoring of the uterus during the ultrasound investigation, the investigators were specifically advised to document findings using predefined categories, which were based on

TABLE 5 Exposure of LNG, EO and VPR and analysis of drug–drug interactions (pharmacokinetic analysis set, $n = 63$)

Analyte	Parameter	Unit	Treatment	Geom. Mean/geom. CV% (range)	N	Estimated ratio [a] [%]	90% confidence interval	95% prediction interval	Geom. CV%
EO	AUC(0–24)$_{md}$	ng·h/L	COC+VPR	969/31.7 (379–1,560)	31	101	[88.3; 115]	[40.8; 250]	32.3
			COC+placebo	960/32.9 (530–1710)	31				
	C$_{max,md}$	ng/L	COC+VPR	89.8/31.2 (42.7–171)	31	90.2	[78.5; 104]	[35.2; 231]	33.6
			COC+placebo	99.6/35.9 (49.7–176)	31				
LNG$_{total}$	AUC(0–24)$_{md}$	µg·h/L	COC+VPR	79.7/52.1 (21.2–174)	31	95.2	[80.5; 113]	[30.4; 298]	41.4
			COC+placebo	83.7/28.0 (50.5–129)	31				
	C$_{max,md}$	µg/L	COC+VPR	7.06/32.3 (2.62–11.3)	31	97.3	[86.4; 110]	[43.4; 218]	28.6
			COC+placebo	7.26/24.5 (4.12–9.99)	31				
LNG$_{unbound}$	AUC(0–24)$_{md,u}$	µg·h/L	COC+VPR	0.885/36.6 (0.242–1.56)	31	NC	-	-	-
			COC+placebo	0.967/24.1 (0.609–1.68)	31				
	C$_{max,md,u}$	µg/L	COC+VPR	0.0812/19.2 (0.0505–0.107)	31	NC	-	-	-
			COC+placebo	0.0870/19.8 (0.0468–0.119)	31				
VPR	AUC(0–24)$_{md}$	µg·h/L	VPR+COC	167/42.5 (39.5–280)	31 [b]	112	[102; 122]	[60.5; 206]	21.1
			VPR alone	149/40.1 (35.7–318)	32				
	C$_{max,md}$	µg/L	VPR+COC	13.3/27.1(5.82–19.0)	31 [b]	108	[101; 116]	[66.6; 176]	16.7
			VPR alone	12.3/25.7(5.25–20.7)	32				

[a]ratio COC+VPR/COC+placebo for EO, LNG $_{total}$ and LNG $_{unbound}$ and ratio VPR+COC/VPR+placebo for VPR (intraindividual comparison).

[b]One subject was excluded from analysis due to intake of concomitant medication shortly before PK profile 1. AUC(0–24)$_{md}$, area under the plasma concentration-time curve in the dosing interval after multiple dosing; C$_{max,md}$ observed maximum concentration in plasma after multiple dosing; COC, combined oral contraceptive; CV, coefficient of variation (%); EO, ethinyloestradiol; LNG, levonorgestrel; NC, not calculated; u, unbound drug; VPR, vilaprisan.

Unbound concentrations of LNG were calculated based on the total concentration of LNG and the respective concentrations of sex hormone-binding globulin and albumin.

previous studies with VPR[5] (e.g. *cystic appearance, inhomogeneous endometrium, enlarged cervical mucosa* or *vacuoles within endometrium*). These findings were documented as TEAEs and coded as *endometrial and/or cervix disorder* using the Medical Dictionary for Regulatory Activities version 21.1. Such disorders were documented more frequently after start of treatment for subjects in the COC+VPR group than for subjects in the COC+placebo group (about 75% *vs* about 30%), but all of them were recovered at the end of the study.

No clinically relevant changes were observed in mean values for the clinical laboratory tests or vital signs during the study. A liver enzyme elevation (alanine aminotransferase) of 3.8 × the upper limit of normal was observed in 1 subject from the COC+placebo group at the end of TC1. There were no indications of a drug-induced liver injury[23] (i.e. no increased bilirubin values or other suspicious adverse findings). After premature discontinuation of study drug intake, values returned to normal within 4 weeks.

4 | DISCUSSION

The analyses of the Hoogland scores did not show any statistically relevant differences between the 2 treatment groups. However, there was a consistent pattern toward less suppression of ovarian activity in majority of related PD parameters (higher Hoogland scores and lower FSH and LH concentrations in the COC+VPR group than in the COC+placebo group). Furthermore, in 2 of 32 subjects (6%) from the COC+VPR group an ovulation was detected while none of the subjects from the COC+placebo group showed an ovulation or luteinized unruptured follicles. These findings suggest that ovarian activity can be reduced when the COC is taken in combination with VPR.

It was somewhat surprising that the extent of PD interaction between the COC and VPR was quite different for ovarian activity, cervical function, bleeding pattern and appearance of the endometrium. More pronounced than the effect on ovarian activity were the effects of VPR coadministration on cervical function. As expected, the Insler scores were low in the COC+placebo group, i.e. the cervical mucus appeared more viscous, which is known to inhibit sperm penetration and motility. When VPR was coadministered with the COC, higher Insler scores were found, indicating that the cervical mucus might be more permeable for sperm. Both, suppression of ovulation and thickening of the cervical mucus are relevant for the COC's contraceptive effect. Thus, it is not possible to assume full contraceptive effectiveness for the COC when coadministered with VPR.

Even more impressive than the impact on the COC's effect on ovarian activity and cervical function was the strong influence of VPR on the bleeding pattern. The expected scheduled withdrawal bleedings, as observed in the COC+placebo group, were completely suppressed by VPR, resulting in a high percentage of subjects with induced amenorrhoea. The thickness of the endometrium, in contrast, was similar in both treatment groups and lower during treatment than in the pretreatment cycle. Thus, over the 3-month treatment period, the combined use of a COC plus VPR obviously restricted endometrial growth even in the absence of monthly bleedings. Of special note is that the influence on the bleeding pattern was similar to that observed in a dose-finding study with VPR, where an amenorrhoea rate of around 80% was reached with the 2-mg dose.[5] However, the endometrium did grow with 2-mg VPR monotherapy in that study (maximum endometrial thickness: 11.3 ± 2.5 mm), which is in contrast to the results of the current study, which showed lower maximum values in both groups. Even though the thickness of the endometrium was similar in both groups, its histology clearly differed. The combined use of COC+VPR led to a high percentage of subjects with an atrophic or inactive endometrium. In subjects from the COC+placebo group, in contrast, the endometrium was mostly assessed as secretory. It also needs to be kept in mind that the standard histopathology criteria[16] were developed to assess the normally cycling endometrium and not to describe endometria during pharmacological interventions such as the administration of an SPRM. Using specific criteria for the description of the endometrium under treatment with SPRMs[17] revealed that the percentage of subjects with PAECs at the end of treatment was markedly higher in the COC+VPR group than in the COC+placebo group (36% [8/22 samples] *vs* 4% [1/28 samples]). But the PAEC frequency was lower than the PAEC frequency observed with ≥1 mg/d VPR alone (70–95%) in a prior study[5] and similar to the frequency observed in a study with 0.5 mg/d VPR alone (35%, 6/17 samples; data on file at Bayer AG, Berlin, Germany). It remains speculative if the relatively low PAEC frequency in the COC+VPR group is related to a specific interference of the COC's progestin component or if it simply reflects the challenges of evaluating fragmented tissue, which was frequently seen in subjects on COC+VPR. Endometrial changes were completely reversible. With the simultaneous administration of an agonist and an antagonist on the progesterone receptor, a predominance of the estrogen component of the COC might have been expected. However, no indications of such effects, e.g. no endometrial hyperplasia, were observed. All endometrial biopsies obtained during the study had a majority consensus as benign histology. There were also no indications of an impact of VPR on the known effects of EO and LNG on hepatic proteins as demonstrated by the lacking difference in SHBG concentrations between the 2 groups.

The exposure to LNG and EO itself was not affected by the coadministration of VPR, indicating that the above described changes were *not* mediated by a PK interaction. As expected, the COC and VPR did not interfere via PK but via PD mechanisms.

Overall, the combined administration of VPR with an LNG/EO-containing COC over 3 months did not raise any safety concerns. Specifically, the current study did not reveal any hints for concerns with regard to hepatic safety parameters. However, the study included only a small number of healthy women and the treatment duration was limited. Therefore, no conclusions on the long-term safety of combined use can be drawn.

To our knowledge, this is the first study investigating the complex PD interactions between an SPRM and a COC when both are taken *simultaneously*. The results of the studies conducted by Cameron

et al.[24] and Edelman *et al.*[25] with the marketed SPRM ulipristal acetate cannot be compared with the results of our study, because the intake of the COC was started only *after* administration of the SPRM, which was given as a single dose in these studies.

5 | CONCLUSIONS

In summary, the study showed the anticipated PD interaction between the SPRM VPR and an LNG/EO-containing COC. Surprisingly, the strongest impact of VPR was on the uterus with complete blocking of the typical COC-induced menstrual withdrawal bleeding. The typical COC-effects on the cervical function (more viscous cervical mucus) were moderately affected whereas the known COC-driven suppression of the ovarian activity was only slightly affected by VPR. Overall, based on the results of this study, full contraceptive effectiveness cannot be assumed for the concomitant intake of the COC with VPR, but for a final judgement on the contraceptive effectiveness of such a combination, a Pearl index study would be necessary. Therefore, women under treatment with SPRMs should continue to follow the current recommendation to use nonhormonal contraception methods and to not combine an SPRM with a COC.

COMPETING INTERESTS

All authors are current or former employees of Bayer AG or work for Bayer AG.

DATA AVAILABILITY STATEMENT

The study protocol and the datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.