Effect of the Novel Selective Progesterone Receptor Modulator Vilaprisan on Ovarian Activity in Healthy Women

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Abstract
This randomized, double-blind, parallel-group study in healthy young women investigated the effect of treatment with vilaprisan (0.5, 1, 2, or 4 mg/day for 12 weeks) on ovarian function by assessing the Hoogland score, which is based on the size of follicle-like structures as determined by transvaginal ultrasound and on estradiol and progesterone serum concentrations. Ovulation inhibition (ie, Hoogland score < 6 in treatment weeks 1-4 and 8-12) was observed in >80% of the subjects receiving vilaprisan ≥ 1 mg/day. The effect was dose dependent. With a Bayesian approach, the percentage of subjects with ovulation inhibition was estimated to increase from 37% in subjects receiving 0.5 mg/day vilaprisan to 76%, 86%, and 88% in subjects receiving 1, 2, and 4 mg/day, respectively. Follicle growth was not suppressed during treatment. The majority of subjects receiving ≥ 1 mg/day had a Hoogland score of 4 (active follicle-like structures, ie, follicle diameter > 13 mm, estradiol > 27.2 pg/mL, no progesterone increase) both at beginning and end of treatment. Mean average estradiol as well as mean maximum progesterone concentrations were noticeably decreased during treatment with vilaprisan ≥ 1 mg/day compared to pretreatment, but estradiol concentrations remained > 80 pg/mL. Both hormones returned to pretreatment levels after the end of treatment, indicating a rapid resumption of normal ovarian activity. Amenorrhea occurred in the majority of subjects during treatment at dosages ≥ 1 mg/day. The adverse events observed in this study confirm the known safety profile of vilaprisan. All in all, the results of this study support the development of vilaprisan for the long-term treatment of uterine fibroids.

Keywords
vilaprisan, clinical trial, phase I, selective progesterone receptor modulator, uterine fibroids, ovarian function

Vilaprisan (VPR) is a novel, promising selective progesterone receptor modulator (SPRM)¹⁻³ that is currently being developed for the long-term treatment of uterine fibroids.

Among the most prominent symptoms associated with uterine fibroids are heavy menstrual bleeding and pelvic pain. In a proof-of-concept (POC) study, Schütz et al showed that VPR effectively suppresses menstrual bleeding in healthy women when given at dosages of 1 to 5 mg/day over 12 weeks.² This finding was confirmed in a subsequent phase 2 study (ASTEROID1): in this study, VPR 0.5 to 4 mg/day over 12 weeks effectively induced amenorrhea and showed a beneficial effect on fibroid volumes and health-related quality of life in patients with heavy menstrual bleeding due to fibroids.³

Other known effects of SPRMs beside their effects on menstrual bleeding are changes in hormone concentrations and follicular development.⁴ The time courses of the concentrations of estradiol (E₂) and progesterone (P) in serum as well as the sizes of follicle-like structures (FLS) observed in the above POC study with VPR suggest that treatment with VPR leads to inhibition of ovulation.

The present study, which has a design similar to that of the POC study, was conducted to gain a thorough understanding of the impact of VPR on ovarian activity. The primary study objective was to investigate the impact of treatment with VPR on the Hoogland score, a score reflecting ovarian activity based on the size of FLS and the concentrations of E₂ and P in serum.⁵ Further study objectives were to assess the impact of treatment with VPR on follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels, that is, the effects of VPR on the pituitary-ovarian axis and on the subjects’ bleeding patterns (induction of amenorrhea).

Methods
The study protocol (ClinicalTrials.gov identifier: NCT 022 62 663) was reviewed and approved by the pertinent competent authority and the relevant

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Submitted for publication 26 June 2017; accepted 17 July 2017.

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independent ethics committee before the start of the study (Landesamt für Gesundheit und Soziales, Geschäftsstelle der Ethik-Kommission des Landes Berlin, Germany). All subjects gave their written informed consent before entry into the study.

Participants
Healthy women between 18 and 40 years of age (inclusive) with a body mass index between 18 and 32 kg/m² (inclusive) and an ovulatory pretreatment cycle were eligible for this study. In the time prior to the pretreatment cycle (baseline assessments), subjects had to discontinue any medications, including hormonal contraceptives, expected to interfere with the study objectives. Subjects at specific risks from administration of the study medication and subjects with conditions expected to have an impact on the aims of the study were not eligible. During the study, all women had to use 2 nonhormonal methods of contraception simultaneously when sexually active, unless safe contraception had been achieved by a permanent method. Prior to the pretreatment cycle, potentially eligible women underwent a physical and gynecological examination as well as blood and urine laboratory tests.

Study Design and Conduct of the Study
This was a randomized, double-blind, parallel-group study without placebo control, conducted at 2 study centers in Germany between October 2014 and November 2015. Study subjects were randomly assigned to treatment with either 0.5, 1, 2, or 4 mg VPR per day for 12 weeks (84 days). The planned sample size was 17 subjects per dose group. The study comprised 5 periods: (1) screening, (2) pretreatment cycle, (3) 12-week treatment period (with frequent measurements during the first and the last 4 weeks of treatment), (4) follow-up cycle 1, and (5) follow-up cycle 2 (Figure 1). All study procedures were conducted on an outpatient basis.

Treatments
During the 12-week treatment period, subjects took 1 tablet containing 0.5, 1, 2, or 4 mg VPR per day. The tablets were taken independently of meals, preferably always at the same time of the day. Subjects started treatment during the first week of the menstrual cycle after the pretreatment cycle. To achieve blinding, all tablets were identical in appearance and smell.

The use of concomitant medication suspected to have an impact on the pharmacodynamics or pharmacokinetics of the study drug was prohibited. The use of analgesics for pain prophylaxis or relief before or after endometrial biopsies was permitted (except drugs influencing bleeding).

Measurements and Collection of Samples
At each visit (see Figure 1 for schedule of visits), the sizes of FLS were measured using transvaginal ultrasound (TVU), and blood samples were taken to determine the concentrations of E₂, P, FSH, and LH in serum. Maximum and average concentrations of these hormones were calculated for each subject and study period.

Ovarian activity was assessed using the Hoogland score, a combination score based on 3 variables: the diameter of the largest FLS in either ovary, the concentration of E₂ in serum, and the concentration of P in serum⁵ (see Supplemental Data S1 for scoring system). The diameter of the largest FLS was defined as the calculated mean of the longitudinal and transverse diameters (measured by TVU) of the largest FLS in each ovary. Based on these values, the maximum FLS diameter observed during each study period was described.

Ovulation inhibition was defined as a Hoogland score <6 (ovulation). One value each was obtained for the first and the last 4 weeks of treatment, when frequent measurements were done, as well as for each of the 2 follow-up cycles. Return to normal ovarian function was assumed when an ovulation was observed in the follow-up cycles.

Cervical function was assessed using the Insler score, an established semiquantitative method to monitor the menstrual cycle.⁶ The Insler score includes evaluation of the appearance of the external cervical os and the quantity, spinnbarkeit (spinnability), and ferning of the cervical mucus (see Supplemental Data S2 for scoring system).

The evaluation of the bleeding pattern (amenorrhea) was based on the subject’s daily self-assessment of the maximum bleeding intensity on a 5-point scale (1 = none, 2 = spotting, 3 = light, 4 = normal, and 5 = heavy). Amenorrhea was defined as “all treatment days with bleeding intensity 1 = none, excluding the initial bleeding at treatment start and the day of and 3 days after the endometrial biopsy.”

Blood samples for pharmacokinetic analysis were taken on any day between treatment day 28 and day 84, before study drug intake, and 1, 2, 3, 4, 8, and 12 hours after study drug intake. Quantitative analysis of the concentration of VPR in plasma was done by a validated liquid chromatography and tandem mass spectrometric method. The details of the assay and the results of the pharmacokinetic and exposure-response analyses will be published separately.

Sex-hormone-binding globulin concentrations were measured repeatedly during treatment and once in the pretreatment and the 2 follow-up cycles.

An endometrial biopsy was taken in the pretreatment cycle, at the end of the treatment phase, and in
Figure 1. Study periods and schedule of visits. Pretreatment cycle: visits (TVU, blood sampling hormones) every third day from day 9 to day 21 plus additional visits on days 24, 27, and 30 when ovulation was not observed until then (day 1 indicates first bleeding day). Treatment period: visits (TVU, blood sampling hormones) every third day from day 9 to day 28 and days 63 to 84. Day 1 indicates start of treatment; day 84, last day of treatment. *: weekly visits (days 35, 42, 49, and 56). Follow-up cycle 1: visits (TVU, blood sampling hormones) every third day from day 3 to day 27 plus additional, less-frequent visits until onset of first posttreatment bleeding (day 1 indicates day after last dose; the cycle ended with the first spontaneous bleeding postdose). Follow-up cycle 2: visits (TVU, blood sampling hormones) every third day from day 6 to day 24 plus additional, less-frequent visits until onset of next bleeding (day 1 indicates first bleeding day postdose; the cycle ended with the next spontaneous bleeding). Hoogland score assessment based on maximum size of follicle-like structure and estradiol and progesterone serum concentrations with frequent measurement (twice per week) at respective time intervals of study. Insler score evaluation included appearance of external cervical os and cervical mucus. VPR: Vilaprasin

the second follow-up cycle. The tissue was assessed in a blinded fashion by 3 expert pathologists for standard diagnosis (eg, benign [cycling, noncycling] endometrium, endometrial hyperplasia, malignant neoplasm) as well as for assessment of the occurrence of progesterone receptor modulator-associated endometrial changes (PAECs). Such histological features have been described after treatment with different SPRMs.7,8

Safety monitoring included the assessment of adverse events, measurements of standard clinical laboratory tests and vital signs (before, approximately every 4 weeks during and after treatment) and TVU findings (endometrial thickness). Urine pregnancy tests were carried out repeatedly before and during treatment with VPR.

Statistical Analysis
All statistical analyses were explorative; a confirmatory statistical analysis was not intended. All data were summarized according to their type using descriptive statistics and frequency tables.

The primary variable was “ovulation inhibition,” defined as “both Hoogland scores during treatment < 6.” Dose-response functions for ovulation inhibition and amenorrhea were estimated using a Bayesian approach. The number of subjects with ovulation inhibition (or amenorrhea, respectively) at a certain dose was assumed to be binomially distributed. For the dose-response function, a 4-parameter sigmoidal maximum possible effect model (Emax model) was applied, and prior information from historical studies was incorporated (see Supplemental Data S3 for details).

Statistical analyses were done using the software SAS 9.2 (SAS Institute Inc, Cary, North Carolina). Estimation of the dose-response functions for ovulation inhibition and amenorrhea was done using WinBUGS 1.4.3 (University of Cambridge, Cambridge, UK) with cumulative patch no. 3 (06 Aug 2007) and software package R 3.0.3.

The sample size for this study was determined such that the dose-response function for ovulation inhibition could be estimated with sufficient precision. Here, a width of 90% credible interval of 20% on average or less at dose ≥2 mg was considered sufficient.

Results
Disposition of Subjects
In total, 137 healthy female volunteers were screened for this study. Of these, 70 eligible volunteers were randomized and received study medication. All 70 subjects
Figure 2. Disposition of subjects. aSubject withdrew consent during treatment (N = 1). bSubject withdrew consent during treatment (N = 1) or during follow-up (N = 1). cSubject withdrew during treatment because of protocol violation (N = 1). dSubject withdrawn due to adverse event during treatment (alopecia, N = 1); follow-up not completed due to pregnancy (N = 1). All 4 subjects who withdrew or were withdrawn during treatment were excluded from pharmacodynamic (PD) analysis. Withdrawal during follow-up did not lead to exclusion from pharmacodynamic analysis.

Table 1. Demographic Characteristics (Safety Analysis Set)

| Vilaprasin Dose Group | 0.5 mg | 1 mg | 2 mg | 4 mg | Total |
|-----------------------|--------|------|------|------|-------|
| N subjects            | 18     | 18   | 17   | 17   | 70    |
| Age [y]               | Mean ± SD (min-max) | 31.7 ± 4.1 (21-38) | 31.0 ± 4.2 (25-39) | 32.2 ± 4.8 (25-40) | 31.5 ± 4.6 (24-40) | 31.6 ± 4.3 (21-40) |
| BMI [kg/m²]           | Mean ± SD | 22.4 ± 3.6 | 22.0 ± 3.3 | 22.4 ± 2.9 | 22.8 ± 3.3 | 22.4 ± 3.2 |
| Race                  | White 18 (100%) | 17 (94.4%) | 17 (100%) | 17 (100%) | 69 (98.6%) |
|                       | Mixed   | 0    | 1 (5.6%) | 0    | 1 (1.4%) |

BMI indicates body mass index; max, maximum; min, minimum.

were valid for safety analysis, and 66 subjects were valid for pharmacodynamics analysis. The data of 4 subjects (1 subject per dose group) were excluded from pharmacodynamics analysis because of premature discontinuation of treatment. An overview of the subject disposition is given in Figure 2. The demographic characteristics of the subjects are summarized in Table 1. The 4 treatment groups were similar in size and demographic characteristics.

Ovarian Activity During Treatment With VPR

Treatment with VPR had a pronounced effect on ovarian activity.

Both at the beginning (first 4 weeks) and at the end (last 4 weeks) of treatment with VPR, more than 80% of the subjects receiving VPR at dosages ≥1 mg/day had Hoogland scores <6 (Figure 3), which are indicative of ovulation inhibition. As shown in Figure 3 and Table 2, the number of subjects without ovulation during treatment increased with increasing dose and duration of treatment. In the 0.5-mg group, ovulation was still relatively common (11/17 subjects [65%] at the beginning of treatment and 7/17 subjects [41%] at the end). In the 4-mg group, in contrast, an ovulation was observed in only 1 subject at the beginning of treatment and in none of the subjects at the end of treatment.

The estimated dose-response function for ovulation inhibition (ie, both Hoogland scores during treatment <6) based on Bayesian data analysis using informative
prior is shown in Figure 4. The increase in response rate starts to saturate around 1.5 mg/day. At 2 mg VPR, the ovulation inhibition rate is estimated to be 86.1% (point estimator) with a 90% credible interval of 76.2% to 92.9%. The maximum rate in the investigated dose range was reached at the dose of 4 mg (point estimator 87.9%; 90% credible interval 78.8% to 94.5%).

Despite the evidence for ovulation inhibition, follicle growth was not suppressed during treatment. The majority of subjects from the 1-, 2-, and 4-mg groups had a Hoogland score of 4 (active FLS, i.e., follicle > 13 mm, \(E_2 > 27.2\) pg/mL, no progesterone increase), both at the beginning and at the end of treatment. Even in the 4-mg group, most of the subjects developed a FLS with a diameter > 13 mm at least once during treatment. An overview of the distribution of maximum FLS diameters by dose group and study period is given in Table 2. The mean maximum FLS diameters were larger on treatment with VPR than prior to treatment (pretreatment cycle). The categorized analysis of maximum FLS diameters showed that 13 out of 66 subjects (20%) developed a FLS with a diameter ≥30 mm at least once during treatment, whereas none was observed during pretreatment. Generally, these large FLS disappeared during ongoing treatment (representative examples of individual time courses of hormone levels and FLS during pretreatment, treatment, and follow-up phase are provided in Figure 5). Concomitant symptoms, such as mild pelvic or lower abdominal pain, were reported by 3 of the 13 subjects affected (1 subject each in the 0.5-, 1-, and 2-mg groups). The increased follicle sizes were additionally documented as adverse events, but none of these findings required premature discontinuation of treatment. No persistent follicles or ovarian cysts of critical size were detected.

The mean average \(E_2\) concentrations were noticeably decreased during treatment with VPR at dosages ≥1 mg/day compared to the values of the pretreatment cycle (Table 2). However, they remained above 80 pg/mL in all dose groups. The lowest individual average \(E_2\) value observed during treatment was 37 pg/mL in a subject from the 0.5-mg group. The mean maximum \(E_2\) concentrations were decreased vs pretreatment values only in the 2 highest dose groups. In the 2 lowest dose groups, in contrast, the mean maximum \(E_2\) values were increased during treatment compared to the pretreatment values. Occasionally, rather low \(E_2\) concentrations were measured: during treatment, \(E_2\) concentrations <27 pg/mL were measured at least once in 3 subjects from the 0.5-mg group and in 1 subject each from the other groups. These episodes of low \(E_2\) concentrations were generally short-lived (single visit). \(E_2\) values <27 pg/mL at consecutive measurements were observed in only 1 subject during treatment (2 visits). Of the 6 subjects with \(E_2\) concentrations <27 pg/mL, only 1 subject from the 2-mg group reported hot flushes—a symptom indicative of estrogen deficiency.

The mean maximum progesterone concentrations were also noticeably decreased during treatment with VPR compared to the pretreatment cycle (Table 2). Progesterone concentrations >1.57 μg/L, which are indicative of luteinization of the follicle or ovulation, were rare during treatment with VPR at dosages ≥1 mg/day.

Ovarian Activity After Discontinuation of Treatment

Ovulatory cycles returned quickly after the end of treatment. During the first follow-up cycle, 50/66 subjects (76%) had an ovulation, as indicated by a Hoogland score of 6 (10/17 [59%], 13/17 [76%], 12/16 [75%], and 15/16 [94%] in the 0.5-, 1-, 2-, and 4-mg groups, respectively).
respectively). Thirteen of 66 subjects (20%) were not assessable, mostly because the time period between the end of treatment and the next menstrual bleeding was too short. During the second follow-up cycle, an ovulation was observed in 65/66 subjects (98%), and a luteinized unruptured follicle was observed in the remaining subject.

Both progesterone and E2 concentrations returned to pretreatment levels in the second follow-up cycle, indicating a rapid resumption of normal ovarian activity (Table 2).

### Menstrual Bleeding

Amenorrhea—defined as neither bleeding nor spotting from end of initial bleeding episode until end of treatment, excluding the day of and 3 days after the endometrial biopsy—occurred in the majority of subjects during treatment with VPR at dosages ≥1 mg/day (37 of 49 subjects receiving VPR 1, 2, or 4 mg/day [75%]). The estimated dose-response function for amenorrhea based on Bayesian data analysis using an informative prior is shown in Figure 6. At 2 mg, the amenorrhea rate reached saturation (point estimator 78.3%; 90% credible interval 68.7% to 86.1%). The maximum rate in the investigated dose range was reached at the 4-mg dose. Thus, maximum effect is achieved at 2 mg, and no additional effect is expected at higher doses.

After the end of treatment, menstrual bleedings recurred in all subjects within 1 to 51 days. The mean time to first menstrual bleeding after treatment was between 19 and 25 days over all dose groups with a rate between those doses. Thus, maximum effect is achieved at 2 mg, and no additional effect is expected at higher doses.

Table 2. Ovulation Inhibition, Size of Maximum FLS, and Hormone Concentrations During Treatment With VPR (Pharmacodynamic Analysis Set)

| Time                        | Vilaprisin Dose group | N  | C<sub>max</sub> FSH [U/L] | C<sub>av</sub> FSH [U/L] | C<sub>max</sub> LH [U/L] | C<sub>av</sub> LH [U/L] |
|-----------------------------|-----------------------|----|---------------------------|--------------------------|--------------------------|--------------------------|
| Pretreatment cycle 0.5 mg   | 17                    | 17 | 13.7 ± 11.0 (6-54)        | 7.7 ± 6.3 (4-32)         | 35.0 ± 31.2 (5-116)      | 12.9 ± 8.1 (4-36)        |
| 1 mg                        | 17                    | 17 | 11.0 ± 4.5 (6-20)         | 6.6 ± 1.6 (4-49)         | 28.7 ± 16.8 (8-58)       | 12.8 ± 6.3 (5-26)        |
| 2 mg                        | 16                    | 16 | 10.6 ± 3.0 (4-17)         | 6.3 ± 1.8 (3-10)         | 33.1 ± 18.6 (8-68)       | 13.8 ± 5.7 (6-25)        |
| 4 mg                        | 16                    | 16 | 10.3 ± 3.1 (5-17)         | 6.2 ± 1.9 (3-10)         | 22.4 ± 14.4 (7-49)       | 10.4 ± 4.5 (5-20)        |
| Treatment phase 0.5 mg       | 17                    | 17 | 9.5 ± 3.3 (6-17)          | 4.6 ± 1.3 (3-7)          | 30.1 ± 18.1 (9-58)       | 7.8 ± 2.4 (5-14)         |
| 1 mg                        | 17                    | 17 | 8.1 ± 0.9 (7-10)          | 4.0 ± 0.8 (3-5)          | 14.5 ± 8.6 (5-44)        | 7.0 ± 2.2 (3-11)         |
| 2 mg                        | 16                    | 16 | 8.0 ± 2.0 (6-13)          | 4.2 ± 1.0 (3-6)          | 18.8 ± 19.4 (7-86)       | 7.8 ± 4.2 (4-19)         |
| 4 mg                        | 16                    | 16 | 7.9 ± 1.7 (6-11)          | 4.6 ± 1.3 (3-8)          | 13.4 ± 6.5 (7-33)        | 6.6 ± 2.6 (4-14)         |
| Follow-up cycle 0.5 mg       | 17                    | 17 | 11.8 ± 6.2 (5-28)         | 6.0 ± 1.9 (4-10)         | 30.5 ± 16.9 (9-68)       | 9.8 ± 3.5 (5-18)         |
| 1 mg                        | 17                    | 17 | 9.8 ± 3.5 (6-17)          | 5.6 ± 1.2 (4-8)          | 23.4 ± 20.2 (8-86)       | 9.5 ± 5.0 (4-23)         |
| 2 mg                        | 16                    | 16 | 9.9 ± 3.7 (5-19)          | 5.5 ± 1.5 (3-9)          | 21.6 ± 14.7 (6-52)       | 8.2 ± 3.3 (3-13)         |
| 4 mg                        | 16                    | 16 | 10.0 ± 3.9 (5-17)         | 5.7 ± 1.5 (4-8)          | 27.6 ± 19.4 (6-74)       | 8.8 ± 2.7 (4-13)         |

C<sub>av</sub> indicates average concentration of the analyte during the respective period of time; C<sub>max</sub>, maximum concentration of the analyte during the respective period of time; E<sub>2</sub>, estradiol; FLS, follicle-like structure; FSH, follicle-stimulating hormone; LH, luteinizing hormone; P, progesterone; VPR, vilaprisan.

*Hoogland scores < 6 at both assessments during treatment (first and last 4 weeks).
Other Variables

In all dose groups, the mean, maximum, and average serum FSH levels were decreased during treatment compared to pretreatment values (Table 2). The mean maximum and average serum LH levels were decreased at dosages ≥1 mg/day compared to pretreatment. Both hormones returned to pretreatment levels after the end of treatment. The interindividual variability in maximum and average LH levels was generally moderate. Visual inspection of individual LH concentration-time curves revealed that the frequency of LH surges was decreased during treatment with VPR at dosages ≥1 mg/day. It has to be noted, however, that single increases might have been missed because hormones were measured only every third day (or once per week in the period of less-frequent measurements).

Relevant changes in the Insler scores were observed in none of the 4 treatment groups during treatment compared to the pretreatment cycle, indicating that administration of VPR had no impact on cervical function. The majority of subjects had a full score (10 to 12), which is indicative of good mucus quality and sperm penetrability, during both the pretreatment cycle and the treatment period.

No relevant changes in sex-hormone-binding globulin levels were observed during the course of the study.

After multiple dosing with VPR 0.5, 1, 2, or 4 mg/day, plasma concentrations of VPR increased dose-dependently, with mean peak plasma concentrations reached between 2 and 3 hours after administration. Maximum plasma concentrations and systemic exposure to VPR increased dose proportionally in the dose range of 0.5 to 4 mg. The pharmacokinetic data obtained in this study were in the range of values observed in prior studies with VPR and confirmed that treatment compliance was good.

Safety and Tolerability

TVU examinations showed that the maximum endometrial thickness during treatment was similar in the 4 dose groups. In all groups maximum endometrial thickness increased slightly during treatment, was highest in follow-up cycle 1 (mean maximum values 12.7 to 13.9 mm), and decreased again after the onset of bleeding at the end of follow-up cycle 1. The number of subjects with at least 1 value >18 mm did not increase with increasing dose (Table 4).

Findings on the uterus observed during the ultrasound examinations were documented in predefined categories (eg, cystic appearance of endometrium, inhomogeneous endometrium, enlarged cervical mucosa, vacuoles within endometrium) and free text. The number of specific features, mainly cystic appearance and
Figure 5. Examples of individual time courses of FLS diameters and serum E2, P, FSH, and LH concentrations during 12-week treatment with VPR 0.5 or 4 mg/day. E2 indicates estradiol; P, progesterone; LH, luteinizing hormone; FSH, follicle-stimulating hormone. Dotted lines indicate follicle-like structures (FLS, left and right); vertical dotted lines indicate the start and the end of the treatment period. The rightmost vertical dotted line indicated the first bleeding episode after the end of treatment. Of note, single hormone peaks (increases) might have been missed because hormones were measured only approximately once per week between treatment days 28 and 56 and every third day during the other time periods.
Amenorrhea during treatment with VPR – dose-response relationship, observed data and Bayesian estimates (Pharmacodynamic analysis set). Amenorrhea was defined as neither bleeding nor spotting during the treatment period, except for the initial bleeding episode when treatment started and bleeding on the day of the biopsy + 3 days.

Table 3. Recurrence of Bleeding After the End of Treatment (Pharmacodynamic Analysis Set)

| Dose Group | N_{subj} | Time to First Bleeding Episode After Treatment |
|------------|----------|-----------------------------------------------|
|            |          | Mean ± SD Median (Min-Max)                     |
| 0.5 mg     | 17       | 18.6 ± 15.1 18.0 (1-51)                       |
| 1 mg       | 17       | 21.5 ± 6.2  21.0 (10-32)                      |
| 2 mg       | 16       | 22.4 ± 11.7 20.5 (3-45)                       |
| 4 mg       | 16       | 24.5 ± 9.2  28.5 (1-32)                       |

Bleeding episode was defined as day(s) with bleeding/spotting of which at least 1 day was of intensity “light” or higher, preceded and followed by at least 2 days with diary entry “none.”

inhomogeneous endometrium, was clearly increased during treatment, but without dose dependency, and decreased again after the first posttreatment menstrual bleeding. The findings observed during ultrasonography were additionally documented as adverse events.

All biopsies taken during the study were diagnosed as benign endometrium. Biopsy tissue taken at the end of treatment was diagnosed most commonly as secretory endometrium in all treatment groups. Assessments for PAEC showed that none of subjects had PAEC in the pretreatment cycle. The number of subjects with PAEC at the end of treatment was dose-dependently increased, reaching values between 70% and 95% after doses ≥1 mg VPR. Most of the changes disappeared after the first posttreatment bleeding. In a total of 8 subjects PAEC were still present at the follow-up biopsy (0.5 mg 2/16 samples [13%], 1 mg 1/17 [6%], 2 mg 2/16 [13%], 4 mg 3/16 [19%]). Four out of the 8 subjects with PAEC in follow-up cycle 2 agreed to an additional follow-up biopsy 4 to 6 months after the end of treatment. All these biopsies showed benign endometrium with no PAEC.

All 70 subjects who received VPR in this study had at least 1 treatment-emergent adverse event (TEAE), and 68 subjects (97.1%) had at least 1 TEAE the investigator assessed as related to treatment with VPR. The majority of TEAEs were of mild intensity. The most frequently (>10%) reported drug-related TEAEs (MedDRA preferred terms sorted by descending frequency) were headache, endometrial disorder (inhomogeneous/cystic endometrium, detected at TVU), ovarian cyst (defined as FLS ≥30 mm, detected at TVU), pelvic pain, acne, hemorrhagic ovarian cyst (corpus luteum cyst, detected at TVU), nausea, proteinuria present, hot flush, and dizziness (Supplemental Data S4). Frequency and intensity of TEAEs did not increase with increasing dose. No serious TEAEs or deaths after randomization were reported. One subject discontinued her study participation prematurely due to the drug-related TEAE “alopecia.”

No clinically relevant changes in vital signs or standard laboratory parameters (hematology, clinical
Table 4. Maximum Endometrial Thickness Measured by TVU (Safety Analysis Set)

| Time                  | Dose Group | N  | Endometrial Thickness [mm] | Endometrial Thickness >18 mm |
|-----------------------|------------|----|----------------------------|------------------------------|
|                       |            |    | Mean ± SD                  | (Min-Max)                    |
|                       |            |    |                            | N   | (%)                      |
| Pretreatment cycle    | 0.5 mg     | 18 | 11.0 ± 2.1                 | (7-15)                       | 0  | (0)                      |
|                       | 1 mg       | 18 | 10.0 ± 3.6                 | (6-17)                       | 0  | (0)                      |
|                       | 2 mg       | 17 | 10.0 ± 2.2                 | (6-15)                       | 0  | (0)                      |
|                       | 4 mg       | 17 | 9.3 ± 2.1                  | (6-13)                       | 0  | (0)                      |
| Treatment phase       | 0.5 mg     | 18 | 12.2 ± 4.0                 | (7-24)                       | 1  | (6)                      |
|                       | 1 mg       | 18 | 10.8 ± 2.9                 | (6-15)                       | 0  | (0)                      |
|                       | 2 mg       | 17 | 11.3 ± 2.5                 | (7-16)                       | 0  | (0)                      |
|                       | 4 mg       | 17 | 11.0 ± 3.4                 | (7-18)                       | 0  | (0)                      |
| Follow-up cycle 1     | 0.5 mg     | 13 | 13.0 ± 5.6                 | (7-24)                       | 2  | (15)                     |
|                       | 1 mg       | 17 | 12.7 ± 4.8                 | (5-23)                       | 1  | (6)                      |
|                       | 2 mg       | 16 | 12.9 ± 3.8                 | (5-18)                       | 0  | (0)                      |
|                       | 4 mg       | 16 | 13.9 ± 4.0                 | (7-23)                       | 3  | (19)                     |
| Follow-up cycle 2     | 0.5 mg     | 18 | 12.5 ± 3.3                 | (4-18)                       | 0  | (0)                      |
|                       | 1 mg       | 18 | 10.4 ± 2.3                 | (8-15)                       | 0  | (0)                      |
|                       | 2 mg       | 17 | 12.0 ± 4.7                 | (5-26)                       | 1  | (6)                      |
|                       | 4 mg       | 17 | 12.2 ± 4.5                 | (7-26)                       | 1  | (6)                      |

chemistry, hemostasis, and urinalysis) were observed. Specifically, the evaluation did not indicate any effect of the study medication on coagulation parameters (prothrombin time, international normalized ratio, activated partial thromboplastin time, and fibrinogen). A transient increase in liver enzymes >1.5 × upper limit of normal was observed at least once in a total of 5 subjects (1 subject each from the 0.5, 1, and 4 mg group; 2 subjects from the 2 mg group). An increase >3 × upper limit of normal was observed in 1 subject receiving 2 mg VPR (AST 3.1 × upper limit of normal) who simultaneously had an extensive increase in creatine kinase. The parallel increase of liver parameters and creatine kinase provides a strong hint that the increase is of muscular origin. Values returned to normal during ongoing treatment. When TEAEs of elevated liver enzymes were compared, the frequency of TEAEs was not found to increase with dose. None of the mild increases in liver enzymes pointed to drug-induced liver injury.10

**Discussion and Conclusions**

The data obtained in this phase 1 study in healthy young women showed that VPR effectively inhibits ovulation. Ovulation inhibition, defined as both Hoogland scores during treatment being below 6, was observed in more than 80% of the women receiving VPR at dosages ≥1 mg/day. The effect was dose dependent. By use of a Bayesian approach, the percentage of subjects with ovulation inhibition was estimated to increase from 37% in subjects receiving VPR 0.5 mg/day to 76%, 86%, and 88% in subjects receiving 1, 2, and 4 mg/day, respectively.

The inhibitory effect on ovulation observed with VPR is consistent with results of similar investigations with other SPRMs such as mifepristone11 or ulipristal acetate,4 indicating that this is a pharmacodynamic effect typical of SPRMs. However, a quantitative comparison of results across different clinical studies is difficult because different definitions of “ovulation inhibition” were used: Chabbert-Buffet et al, for example, defined ovulation inhibition as absence of progesterone values above 3 μg/L at any time during the third treatment month.4 In the present study, in contrast, P levels, E2 levels, and follicle sizes—the 3 variables making up the Hoogland score—were used to decide about the subject’s ovulatory status. The criteria for ovulation used in the present study were more complex and more strict: P levels and E2 levels plus follicle sizes—the 3 variables making up the Hoogland score—were used to decide about the subject’s ovulatory status. The criteria for ovulation used in the present study were more complex and more strict: P levels and E2 levels plus follicle sizes in the first and third treatment months were to be considered and not only P levels in the third month; they were less strict with a threshold of 1.57 μg/L for P instead of 3 μg/L. Thus, if at all, only the Hoogland scores observed for the third month in the present study may be compared with the anovulation rates reported by Chabbert-Buffet. When VPR and ulipristal acetate are compared at doses effective for treatment of fibroids—2 mg and 5 mg, respectively—VPR seems to be slightly more effective in inhibiting ovulation than ulipristal acetate (94% vs 82%).

After the end of treatment, ovulatory cycles returned quickly as evidenced by growing follicles and increased estradiol values followed by follicle rupture and rise of progesterone values. Nearly all subjects (>95%) had an ovulation in the cycle following the first posttreatment bleeding, indicating a rapid resumption
of normal ovarian activity. There are no indications that treatment with VPR might prevent or delay pregnancies after discontinuation of the treatment. It has to be emphasized that because VPR interacts with the same target receptor as the progestin component present in combined oral contraceptives, comedication of VPR with combined oral contraceptives may lead to unpredictable effects. Therefore, adequate nonhormonal contraceptive measures have to be used during treatment with VPR as well as during treatment breaks.

Although VPR effectively inhibited ovulation, the development of active follicle-like structures was maintained under treatment (Table 2). Most of the subjects had FLS >13 mm during the treatment period. Because no rupture occurred, maximum FLS size was slightly increased during treatment in all dose groups compared to pretreatment. This also resulted in an increased number of subjects showing a FLS ≥30 mm, an observation that was also documented as an adverse event (“ovarian cyst”). However, most of these large follicles disappeared during ongoing treatment. In fewer than 25% of the subjects affected, abdominal or pelvic pain (without further specification) was reported during the time period of occurrence of the ovarian cyst. None of the ovarian cysts required premature discontinuation of treatment with VPR. No persistent follicles or ovarian cysts of critical size were observed.

In line with the development of follicles, average E2 values remained above 80 pg/mL. Critically low values as typically seen under treatment with GnRH analogues or in postmenopausal women were not observed. The decrease in E2 levels was fully reversible after the end of treatment. During the first follow-up cycle, average E2 values were similar to those measured in the pretreatment cycle. However, long-term studies in a large number of patients with uterine fibroids are necessary to finally assess the clinical relevance of the E2 decrease during the treatment period.

Changes in FSH and LH values suggest that the impact on the hypothalamic-pituitary-ovarian axis contributes to the inhibition of ovulation. During the treatment period, the mean maximum FSH and LH values were lower than pretreatment values in all dose groups without dose dependency. In the follow-up cycles the mean maximum FSH and LH values were increased again. Because blood samples for hormone measurements were taken only every third or fourth or even seventh day, individual peak FSH values and especially the LH surge might have been missed. Nevertheless, visual inspection of individual LH concentration-time curves revealed that the number of LH peaks was clearly decreased in subjects receiving doses ≥1 mg VPR (see sample curves in Figure 5).

The incidence of amenorrhea observed in this study (>70% at dosages ≥1 mg/day) was similar to that observed in the above-described POC study and in the ASTEROID1 study in patients with uterine fibroids.

As previously seen with ulipristal, VPR did not cause relevant effects on the cervix as deduced from lack of difference in Insler score between pretreatment and the first treatment cycle.

No new safety signals were detected. The adverse events observed in this study confirmed the known safety profile of VPR as determined in previous clinical studies. No treatment-emergent serious adverse events occurred in this study. There were no indications of potential liver toxicity. All endometrial biopsies were assessed as benign histology. Histologic features known as PAEC increased after dosages ≥1 mg/day; however, after the next menstrual bleeding most PAEC had disappeared, as confirmed by the follow-up biopsy. Similar observations were made in studies with already marketed SPRMs, which have been in use for some time.

All in all, the results of this study support further development of VPR for the long-term treatment of uterine fibroids. The induction of amenorrhea after treatment with VPR was confirmed. In addition, it could be shown that, despite ovulation inhibition, the development of active follicles and sufficiently high E2 levels were maintained. Normal ovarian activity returned quickly after the end of treatment. A phase 3 program has been initiated that should demonstrate the efficacy of VPR in the treatment of symptoms associated with uterine fibroids, targeting, among other symptoms, bleeding reduction and fibroid size.

**Acknowledgments**

This study was funded by Bayer AG. All authors are employees of or work(ed) for Bayer AG.

The clinical part of the study was conducted at CRS Clinical Research Services Berlin GmbH and at dinox GmbH Female Health Research, both located in Berlin, Germany. Clinical lab analyses including hormone measurements were carried out at the Laboratorium für Klinische Forschung GmbH, Schwentimental, Germany. VPR concentrations were analyzed at Bayer AG. Endometrial biopsies were assessed by 3 expert pathologists, George L. Mutter from the Department of Pathology, Brigham and Women’s Hospital, Boston, MA, USA; Christine Bergeron from the Department of Pathology, Laboratoire Pasteur-Cerba, Cergy Pontoise, France; and Alistair R.W. Williams from the Department of Pathology, University of Edinburgh, Edinburgh, UK. Medical writing assistance for this manuscript was provided by C. Hilka Wauschkuhn, Bonn, Germany, on behalf of Bayer AG, Berlin, Germany.
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