Effect of Food Intake on the Pharmacokinetics of the Selective Progesterone Receptor Modulator Vilaprisan: A Randomized Clinical Study in Healthy Postmenopausal Women

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Abstract

This exploratory, open-label, randomized, 3-period crossover study in 12 healthy postmenopausal women investigated the effects of food intake on the pharmacokinetics of vilaprisan. Single doses of vilaprisan (2 mg) were administered under fasting conditions, after intake of a high-fat, high-calorie meal, and after intake of a moderate-fat, moderate-calorie meal. The intake of food had only a marginal impact on the oral bioavailability of vilaprisan. The mean exposure of vilaprisan (area under the plasma concentration-time curve [AUC]) was increased by approximately 20% when the drug was taken after a meal and not on an empty stomach (point estimate for AUC ratios [%] and 90% confidence interval: high-fat and -calorie meal/fasting 121 [114–128]; moderate-fat and -calorie meal/fasting 118 [111–125]). The rate of absorption was slightly decreased when the drug was taken after a meal as indicated by approximately 10% lower mean maximum concentrations (C_{max}) of vilaprisan in plasma (C_{max} ratios: high-fat and -calorie meal/fasting 87.9 [75.6–102]; moderate-fat and -calorie meal/fasting 89.4 [76.9–104]) and a prolonged time to C_{max} (fasting: 1.5 hours; fed conditions; ∼4 hours). Overall, the results of this study indicate that vilaprisan can be administered equally well with or without food.

Vilaprisan is a highly potent selective progesterone receptor modulator currently under investigation as a drug for the treatment of symptomatic uterine fibroids. It is a well-characterized, low-solubility, high-permeability drug (class 2 drug according to the Biopharmaceutics Classification System), which is predominantly cleared from plasma by hepatic cytochrome P450 3A metabolism.[1–7] It has an oral bioavailability of about 60%[1] and shows dose-proportional pharmacokinetics in the dose range between 1 and 30 mg/d.[2] As vilaprisan is practically insoluble in water (∼0.0005 mg/mL without pH dependency), its absorption from the gastrointestinal tract might be affected by food intake. Therefore, the present food-effect study was conducted early during the clinical development of the drug as recommended in the relevant guidelines issued by the US Food and Drug Administration (FDA) and the European Medicines Agency. The primary objective of this study was to investigate whether the rate and the extent of absorption of orally administered vilaprisan are affected by the concomitant intake of a high-fat, high-calorie meal or a moderate-fat, moderate-calorie meal.

Methods

The study was conducted at the sponsor's Clinical Research Unit in Berlin between September 2011 and

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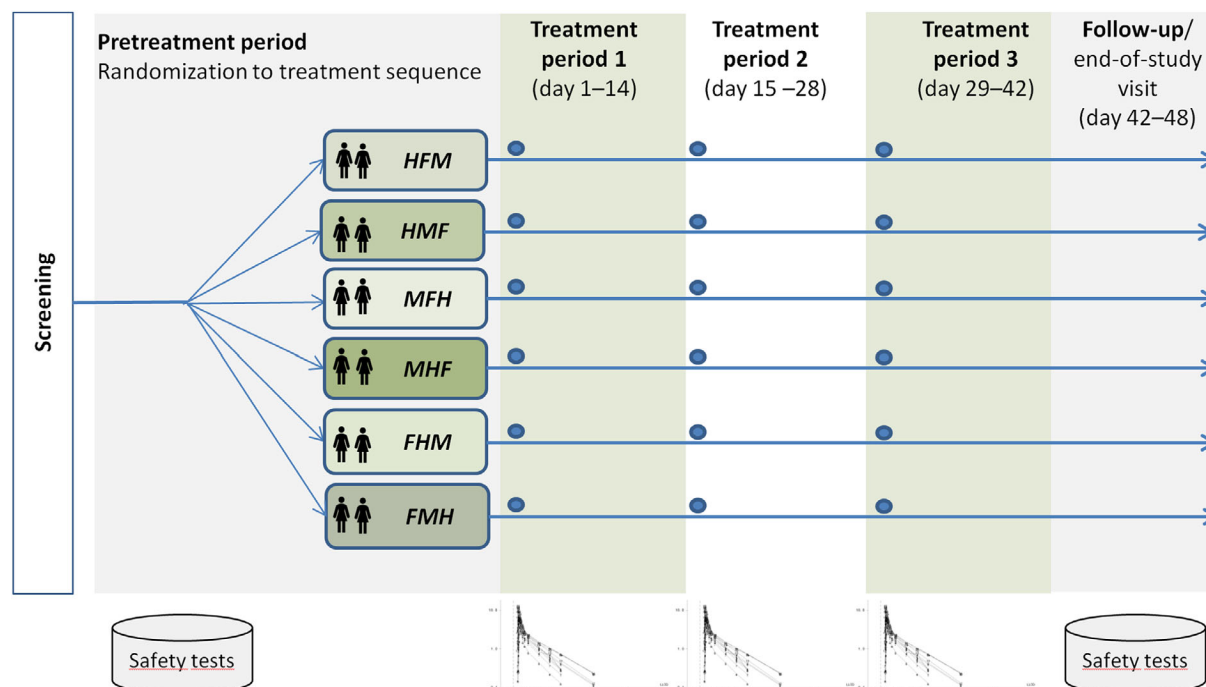(e-mail: marcus.schultze-mosgau@bayer.com)

Figure 1. Study design. Blue dots indicate the treatments (that is, intake of vilaprisan 2 mg on the first day of each period, either on an empty stomach or 30 minutes after the start of the assigned meal). Concentration-time curves indicate blood sampling for pharmacokinetic analyses (30 minutes before dosing and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 16.0, and 24 hours and 2, 3, 4, 6, 8, 11, and 14 days after dosing). Safety tests included clinical laboratory tests, electrocardiograms, and measurement of vital signs. The occurrence of AEs was monitored throughout the study. H, drug intake after a high-fat, high-calorie breakfast; M, drug intake after a moderate-fat, moderate-calorie breakfast; F, drug intake on an empty stomach (fasting condition). HFM, HMF, etc. indicate the sequence of treatment conditions to which the subject was assigned (2 subjects per sequence).

January 2012. The study protocol was reviewed and approved by the Ethics Committee of the Landesamt für Gesundheit und Soziales, Berlin, Germany. All participants gave their written informed consent before entry into the study. The study was completed as planned.

This was an exploratory, randomized, balanced, single-dose, 3-treatment (fasting condition and 2 fed conditions), 3-period, 6-sequence crossover study in 12 healthy subjects (2 subjects per treatment sequence). Eligible for participation were healthy, postmenopausal women between 45 and 70 years of age and a body mass index between 20 and 30 kg/m^2. Noneligible were individuals with conditions expected to interfere with the aims of the study.

In total, 33 women were screened, and 12 of these were assigned to a treatment sequence, received their treatments as planned, and completed the study. The other 21 prospective subjects did not meet the admission criteria or withdrew their consent before randomization. The 12 participants were White, with a mean age of 64.3 years (range, 52–70 years) and a mean body mass index of 24.7 kg/m^2 (range, 21.1–29.6 kg/m^2). These 12 subjects were included in all pharmacokinetic and safety analyses.

Each study subject received 3 single doses of vilaprisan (2 mg given in the form of four 0.5-mg immediate-release tablets) with a washout period of at least 14 days between doses. (The 2-mg dose of vilaprisan has been identified in phase 2 studies as the optimum dose for treating uterine fibroids[8,9] and is used in phase 3 studies.) The study drug was given in randomized sequence according to a Williams design[10]: (1) on an empty stomach (10-hour fasting); (2) after the intake of a moderate-fat, moderate-calorie breakfast; and (3) after the intake of a high-fat, high-calorie breakfast (Figure 1). The composition of the high-fat, high-calorie meal followed the recommendations of the 2002 FDA food-effect guideline. It had 970 kcal in total, that is, 140, 280, and 550 kcal from protein, carbohydrates, and fat, respectively. The moderate-fat, moderate-calorie breakfast had 800 kcal in total, that is, 100, 410, and 290 kcal from protein, carbohydrates, and fat, respectively. The relative fat content of the 2 meals was 57% and 36%, respectively. The subjects were instructed to eat their breakfast within 30 minutes. The study drug was administered with a glass of milk 30 minutes after the start of breakfast. Under fasting conditions, the study drug was administered with noncarbonated water

Table 1. Pharmacokinetic Parameters of Vilaprisan in Plasma and Analysis of Food Effects on the Pharmacokinetics of Vilaprisan (Pharmacokinetic Analysis Set, N = 12)

Parameter	Treatment Condition	Arithmetic Mean (SD)	Geometric Mean (CV%)	Range	Ratio	Point Estimate (LS Means), %	90%CI	CV%
AUC	High-fat and -calorie (H)	169 (50.8)	161 (33.2)	79.5-248	H/F	121	114-128	8.19
$\mu g \cdot h/L$	Moderate-fat and -calorie (M)	163 (47.0)	157 (29.7)	91.2-249	M/F	118	111-125	8.19
	Fasting (F)	139 (39.2)	134 (30.0)	80.9-205	H/M	103	96.8-109	8.19
C_{max}	High-fat and -calorie (H)	7.74 (2.86)	7.33 (34.4)	4.79-13.8	H/F	87.9	75.6-102	21.6
$\mu g/L$	Moderate-fat and -calorie (M)	7.55 (1.27)	7.46 (15.9)	5.87-10.4	M/F	89.4	76.9-104	21.6
	Fasting (F)	8.52 (1.83)	8.34 (22.0)	5.67-12.0	H/M	98.3	84.6-114	21.6
t_{max}	High-fat and -calorie (H)	4.01[a]		1.50-7.92	…	…	…	…
Hours	Moderate-fat and -calorie (M)	4.00[a]		1.50-6.12	…	…	…	…
	Fasting (F)	1.52[a]		0.983-2.98	…	…	…	…
$t_{1/2}$	High-fat and -calorie (H)	33.8 (8.22)	32.9 (24.5)	24.7-47.4	…	…	…	…
Hours	Moderate-fat and -calorie (M)	34.4 (8.91)	33.4 (26.8)	23.7-47.1	…	…	…	…
	Fasting (F)	34.7 (8.45)	33.8 (24.1)	23.7-48.0	…	…	…	…

AUC, area under the plasma concentration–time curve from time 0 to infinity; C_{max}, maximum observed plasma concentration; CI, confidence interval; CV%, coefficient of variation (%); F, drug intake under fasting conditions; H, drug intake 30 minutes after start of a high-fat, high-calorie breakfast; LS, least squares; M, drug intake 30 minutes after start of a moderate-fat, moderate-calorie breakfast; SD, standard deviation; t_{max}, time to C_{max}; $t_{1/2}$, half-life associated with the terminal slope.

Treatment conditions: Vilaprisan (2 mg) was taken either on an empty stomach after a 10-hour *fasting* period, or 30 minutes after the start of a *high-fat, high-calorie* breakfast, or 30 minutes after the start of a *moderate-fat, moderate-calorie* breakfast.

[a] Median.

after a fasting period of at least 10 hours. Thereafter, standardized meals were served at 4, 7, and 11 hours after dosing. For details, see Supplement 1.

The study comprised 6 periods: screening, a pretreatment period, treatment period 1, treatment period 2, treatment period 3, and follow-up. The use of drugs expected to interfere with the pharmacokinetics of vilaprisan such as preparations containing sex hormones or cytochrome P450 3A inducers or inhibitors was not allowed during the study. Blood samples to determine vilaprisan in plasma were taken at predefined intervals up to 14 days after dosing (Figure 1). To determine the concentration of vilaprisan in plasma samples, the same liquid chromatography–tandem mass spectrometry method was used as in previously published studies with vilaprisan. This method was described by Liu et al,[11] for example. An overview of the performance of the method in the present study is given in Supplement 2.

Based on the actual concentration-time data, pharmacokinetic parameters of vilaprisan were calculated by a standard noncompartmental approach using Win-Nonlin, version 4.1 (Pharsight Corporation, Mountain View, California). The primary variables were the area under the plasma concentration–time curve from time 0 to infinity (AUC) and the observed maximum drug concentration (C_{max}). Further pharmacokinetic parameters were the time to reach C_{max} and the terminal half-life. Safety assessments included recording of adverse events (AEs), vital signs, electrocardiograms, and clinical laboratory tests (blood and urine, hematology and biochemistry).

Comparisons of the pharmacokinetic parameters AUC and C_{max} between treatment conditions were done by analysis of variance on log-transformed data. Sequence, subject (sequence), period, and treatment effects were included as fixed effects in the model. Point estimates and 90% confidence intervals (CIs) of AUC and C_{max} ratios were derived by retransformation of the calculated least squares means differences and CIs of the analysis of variance to the original scale. All analyses were exploratory and descriptive.

A sample size of N = 9 subjects was estimated to be necessary to meet the objectives of the study, assuming a geometric coefficient of variation of 30% for C_{max} and AUC based on previous clinical data. Taking dropouts into account, 12 subjects were planned to be randomized.

Results

An overview of the pharmacokinetic parameters determined is given in Table 1; the distribution of C_{max} and AUC values is shown in Figure 2; the mean vilaprisan plasma concentration–time curves are shown in Figure 3.

Following single oral administration of 2 mg of vilaprisan, maximum concentrations of vilaprisan in plasma were observed after approximately 1.5 hours, on average, when the drug was taken under fasting conditions. Under both fed conditions, this time was markedly longer, that is, approximately 4 hours on average. The mean C_{max}, in contrast, was slightly decreased under both fed conditions compared to fasting
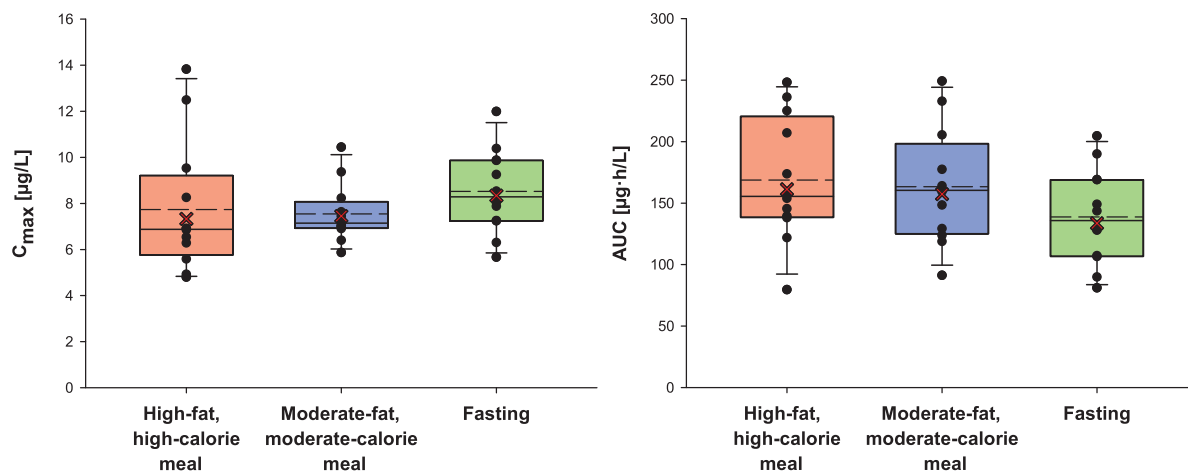
Figure 2. Maximum plasma concentrations and exposure of vilaprisan under fed and fasting conditions. Boxes depict the 25th to 75th percentiles, solid horizontal lines within the boxes depict the medians, and dashed horizontal lines the arithmetic means. Geometric means are indicated by crosses, individual values by dots. Vertical lines (whiskers) extend to the 10th and 90th percentiles. AUC, area under the plasma concentration–time curve from time 0 to infinity; C_{max}, maximum observed plasma concentration.

conditions. The AUC was slightly increased. The variability of C_{max} and AUC values was similar under all 3 food conditions.

The analysis of the C_{max} and AUC ratios (high-fat and -calorie meal/fasting; moderate-fat and -calorie meal/fasting; high-fat and -calorie meal/moderate-fat and -calorie meal) did not reveal any major differences between the 2 fed conditions (Table 1). Point estimates for C_{max} ratios (fed/fasting) indicated a decrease in C_{max} by approximately 10% when the drug was given in the fed state. Both corresponding 90%CIs included 100%. Point estimates for AUC ratios (fed/fasting) indicated an increase in AUC by approximately 20% when the drug was given in the fed state. The corresponding 90%CIs did not include 100%, but were still completely (moderate-fat and -calorie meal/fasting) or almost completely (high-fat and -calorie meal/fasting) within the standard bioequivalence range of 80% to 125%.

The mean elimination half-life of vilaprisan ranged between 33 and 34 hours under all 3 treatment conditions, confirming that the washout period of 14 days was adequate.

Safety

The most common treatment-emergent AEs (*Medical Dictionary for Regulatory Activities,* version 14.1, preferred terms) were *headache* (5 subjects) and *vessel puncture site hematoma* (2 subjects). All AEs were resolved at the end of the study. There were no serious AEs or study discontinuations due to AEs. Safety data did not suggest an influence of food intake on the occurrence of treatment-emergent AEs.

Discussion and Conclusions

This study showed that the intake of food shortly before the administration of vilaprisan immediate-release tablets had only a marginal impact on the oral bioavailability of the drug. This was true for both a high-fat, high-calorie meal and a moderate-fat, moderate-calorie meal. The rate of absorption was slightly decreased when the drug was taken at the end of a meal and not on an empty stomach, as reflected in approximately 10% lower C_{max} values and a shift in time to reach C_{max} from about 1.5 hours under fasting conditions to about 4 hours under fed conditions. The extent of absorption, in contrast, was increased by approximately 20% when the drug was taken under fed conditions. However, a food effect of this small magnitude can be considered clinically irrelevant in view of the wide safety margin of the drug.[2] Furthermore, the distributions of individual AUC values were largely overlapping among all 3 treatment conditions (Figure 2) and the 90%CIs for the AUC ratios (fed/fasting) were completely (moderate-fat and -calorie meal/fasting) or almost completely (high-fat and -calorie meal/fasting) within the traditional 80% to 125% bioequivalence limits, that is, the limits set to ensure similarity in terms of safety and efficacy.

The minor changes in the pharmacokinetics of vilaprisan observed with food intake are consistent with the expectations for a compound with a low solubility. However, the likelihood of seeing more substantial effects tends to be low for drugs that have, like vilaprisan, a high oral absolute bioavailability (under fasting conditions) and show also dose-proportional pharmacokinetics in a wide dose range that exceeds the administered dose many times.
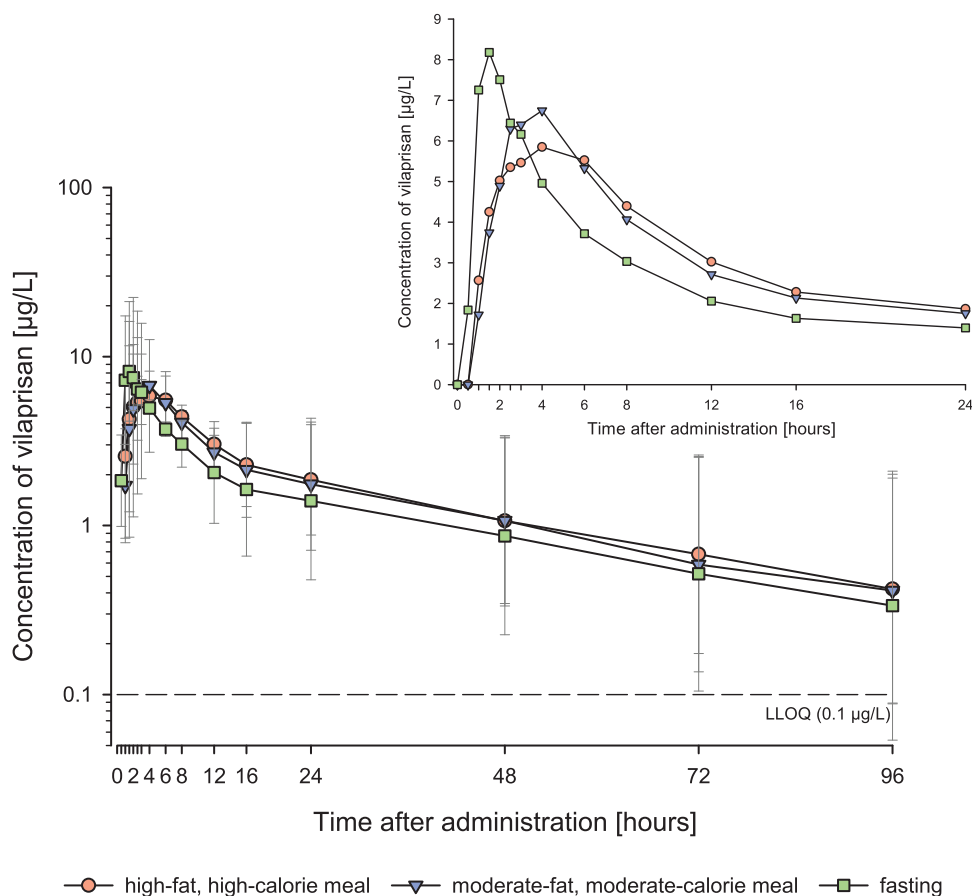
Figure 3. Vilaprisan plasma concentration–time curves (arithmetic means ± SD) after administration of a single oral 2 mg dose of vilaprisan under fed and fasting conditions. Planned sampling times were used; the predose sample was set to 0 hour. Means were not calculated if fewer than 2 of 3 individual values were above the LLOQ. This was the case for all measurements >96 hours after dosing and the 0.5-hour measurements under fed conditions. Values below the LLOQ were included as $\frac{1}{2}$LLOQ in the calculation of means and SDs. This was the case for a few subjects 1 to 1.5 hour postdose under fed conditions. LLOQ, lower limit of quantitation (0.1 μg/L).

In accordance with the 2002 FDA guidance on food-effect studies, a high-fat, high-calorie breakfast was chosen for this study, as such a meal can be expected to provide the greatest impact on the physiology of the gastrointestinal tract and the absorption of the test drug. However, a high-fat breakfast is not regarded as the standard breakfast worldwide. Therefore, the effects of a lighter meal were investigated as well. The total caloric content of this "moderate meal" (800 kcal) is approximately 18% lower than that of the high-fat, high-calorie meal and exceeds the recommendations for a moderate or low-fat meal given in the 2012 European Medicines Agency guidance on drug interactions and the 2019 FDA draft guidance on food-effect studies, respectively, by approximately 60%. Its fat content (36%), however, roughly meets the recommendations in these guidelines (30%-38% and 25%, respectively) and is clearly different from that of the high-fat meal (57%).

The study was conducted in healthy postmenopausal women and not in the envisaged target population for vilaprisan. However, no different food effects related to disease (symptomatic uterine fibroids) or age (women of reproductive age) are expected in the envisaged target population as compared to healthy postmenopausal women. This assumption is supported by a population pharmacokinetic-pharmacodynamic exposure-response analysis of data from phase 1 and phase 2 studies (Bayer, data on file).

In conclusion, this study showed that the intake of food had only a marginal impact on the oral bioavailability of vilaprisan from immediate-release tablets, irrespective of the composition of the meal consumed. Considering the large overlap of exposure values among the 3 treatment conditions, the observed intersubject variability within each treatment condition, and the wide safety margin, the results of this study

indicate that vilaprisan can be administered equally well with or without food.

Acknowledgments

Conflicts of Interest

Funding

Data Availability Statement

The study protocol and the data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Schultze-Mosgau M-H, Höchel J, Prien O, et al. Characterization of the pharmacokinetics of vilaprisan: bioavailability, excretion, biotransformation, and drug-drug interaction potential. *Clin Pharmacokinet*. 2018;57(8):1001-1015.
2. Schultze-Mosgau M-H, Schütt B, Hafner F-T, et al. Pharmacokinetics and safety of the selective progesterone receptor modulator vilaprisan in healthy postmenopausal women. *Int J Clin Pharmacol Ther*. 2017;55(1):16-24.
3. Chattopadhyay N, Kanacher T, Casjens M, et al. CYP3A4-mediated effects of rifampicin on the pharmacokinetics of vilaprisan and its UGT1A1-mediated effects on bilirubin glucuronidation in humans. *Br J Clin Pharmacol*. 2018;84(12):2857-2866.
4. Chattopadhyay N, Riecke K, Ligges S, Zimmermann T, Halabi A, Schultze-Mosgau M-H. Effect of hepatic impairment on the pharmacokinetics of vilaprisan: an open-label, single-dose, parallel-group study. *Br J Clin Pharmacol*. 2019;85(9):2011-2021.
5. Schultze-Mosgau M-H, Lasseter KC, Marbury T, Loewen S, Riecke K. Pharmacokinetics and safety of the novel selective progesterone receptor modulator vilaprisan in participants with renal impairment. *J Clin Pharmacol*. 2020;60(8):1030-1038.
6. Schütt B, Kaiser A, Schultze-Mosgau M-H, et al. Pharmacodynamics and safety of the novel selective progesterone receptor modulator vilaprisan: a double-blind, randomized, placebo-controlled phase 1 trial in healthy women. *Hum Reprod*. 2016;31(8):1703-1712.
7. Schütt B, Schultze-Mosgau M-H, Draeger C, et al. Effect of the novel selective progesterone receptor modulator vilaprisan on ovarian activity in healthy women. *J Clin Pharmacol*. 2018;58(2):228-239.
8. Seitz C, Bumbuliene Z, Costa AR, et al. Rationale and design of ASTEROID 2, a randomized, placebo- and active comparator-controlled study to assess the efficacy and safety of vilaprisan in patients with uterine fibroids. *Contemp Clin Trials*. 2017;55:56-62.
9. Bradley LD, Singh SS, Simon J, et al. Vilaprisan in women with uterine fibroids: the randomized phase 2b ASTEROID 1 study. *Fertil Steril*. 2019;111(2):240-248.
10. Jensen JT. Vaginal ring delivery of selective progesterone receptor modulators for contraception. *Contraception*. 2013;87(3):314-318.
11. Liu H, Jiang J, Chen Z, et al. Pharmacokinetics and safety of the selective progesterone receptor modulator vilaprisan in Chinese healthy postmenopausal women [published online ahead of print July 27, 2020]. *Clin Pharmacol Drug Dev*. https://doi.org/10.1002/cpdd.851.

Supplemental Information

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