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Pharmacodynamic Effects and Safety of the Novel Selective Progesterone Receptor Modulator Vilaprisan

A Double-blind, Randomized, Placebo-controlled Phase 1 Study in Healthy Women (#14723)

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Disclosures

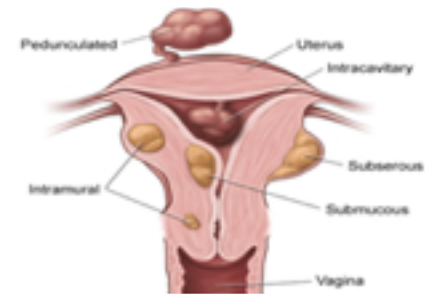
➤ The authors are employees of Bayer Pharma AG.

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Introduction and Objectives



- Vilaprisan (BAY 1002670) has been shown to be a very potent, highly selective progesterone receptor modulator (SPRM) in several *in vitro* and *in vivo* pharmacodynamic (PD) assays (1).
- Possible indications of SPRMs include treatment of uterine fibroids (2).
 - Main symptoms caused by uterine fibroids are menstrual bleeding abnormalities and/or bulk related symptoms.
 - The efficacy of SPRMs in reduction of menstrual bleeding in both, healthy women and patients with uterine fibroids, has been demonstrated with other SPRMs.



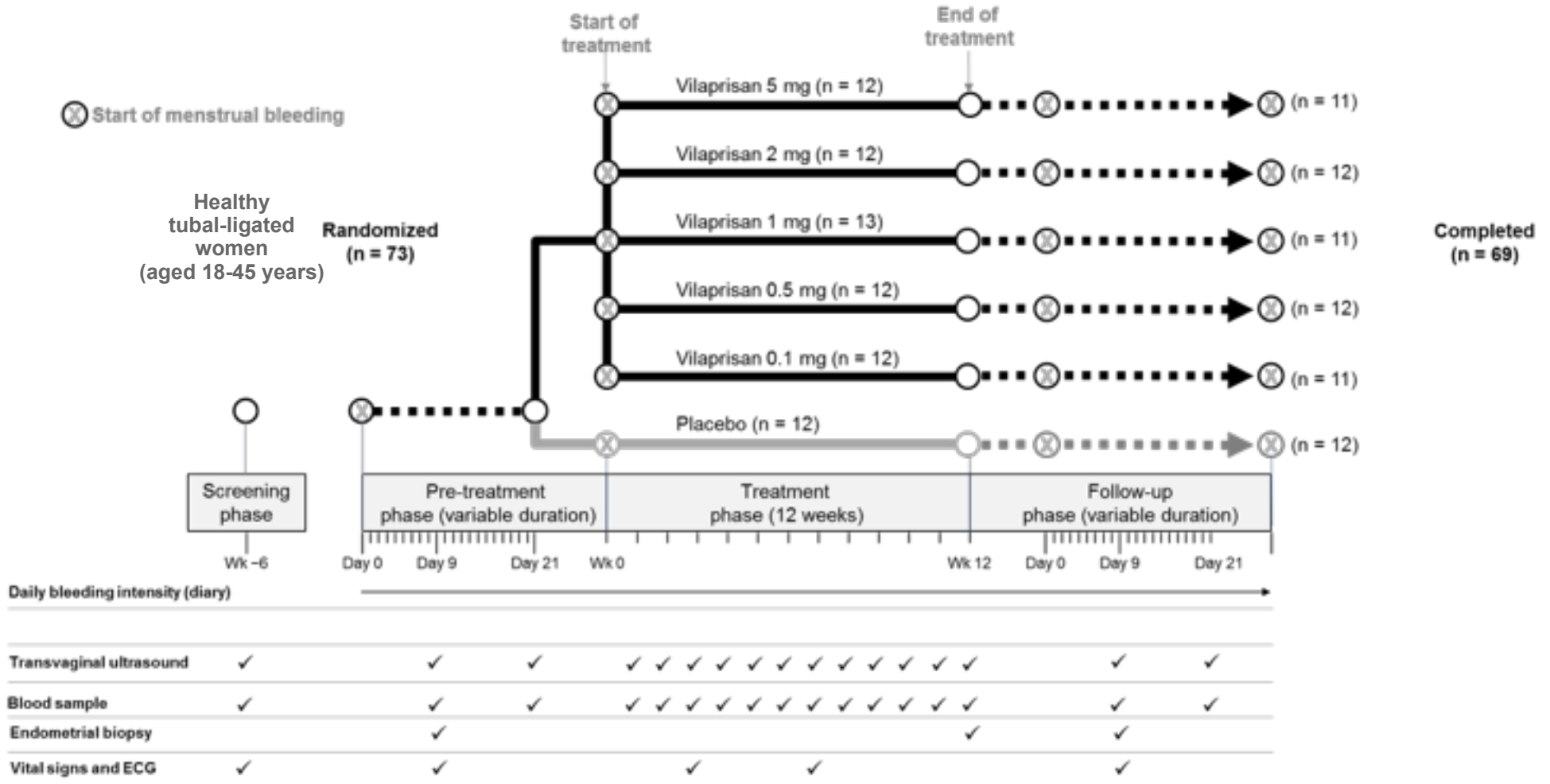
- **Aim of the presented study:**
Pharmacodynamic effects, with emphasis on menstrual bleeding, and safety in healthy tubal-ligated women aged 18 to 45 years over a three months treatment
- The results of the preceding early phase 1 studies in postmenopausal women following single and daily dosing over 4 weeks supported the conduct of the presented study.

(1) Wagenfeld et al., 2013, Human Reproduction, 28 (8): 2253–2264

(2) Bouchard et al., 2011, Fertility and Sterility, 96 (5): 1175–1189

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Study Design





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Study Parameters

Pharmacodynamics

- Impact on bleeding pattern:
 - **Primary variable:** Non-bleeding rate i.e. number of subjects showing either “no bleeding” or “spotting” during treatment days 10 - 84 (excluding day of biopsy + 2 days)
 - Return of bleeding after end of treatment
- Impact on ovarian function:
 - Follicle-Like Structures (FLS) by transvaginal ultrasound
 - Estradiol, progesterone, LH, FSH serum concentrations

Safety

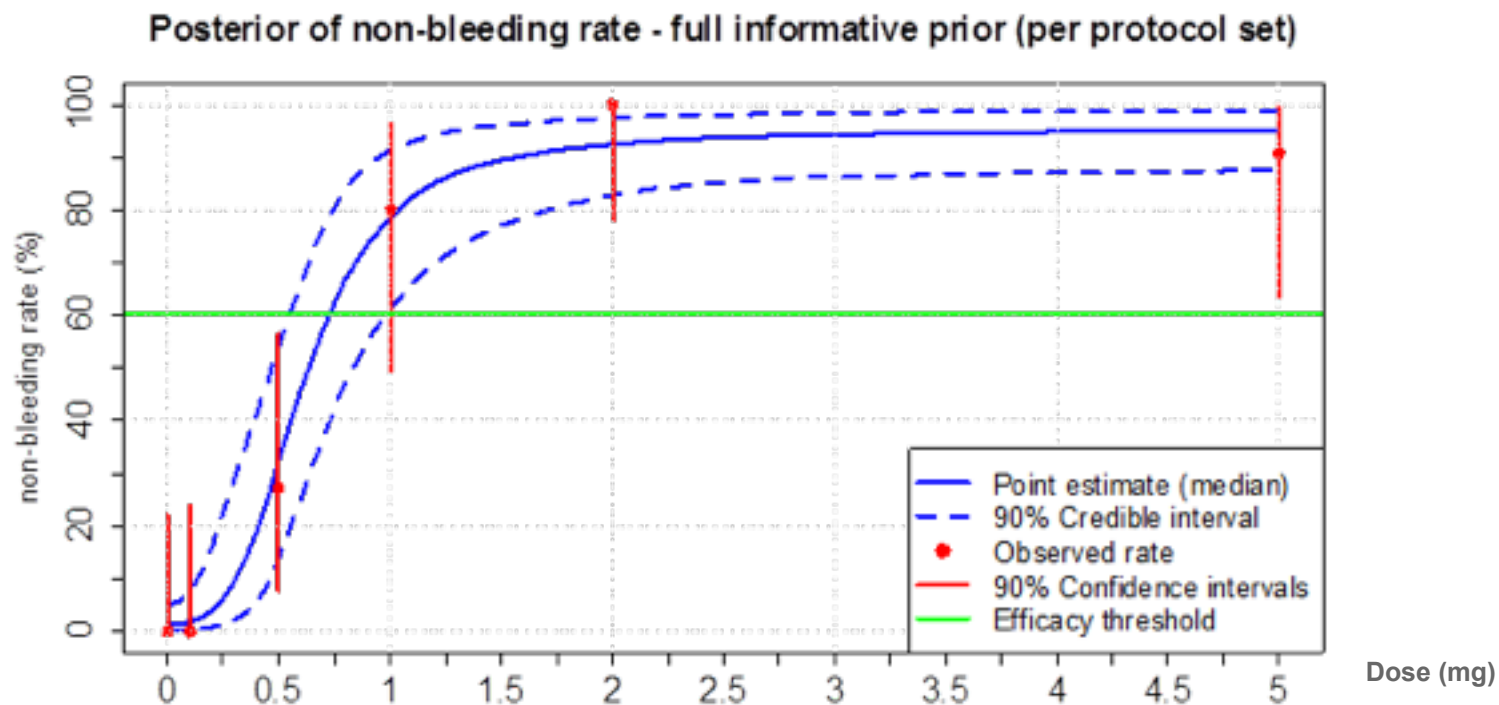
- Adverse Events
- Endometrial thickness and histology
- Vital signs, ECG, standard laboratory parameters

Population Pharmacokinetics/ Pharmacodynamics (Dose-Exposure-Response analysis)
– not presented

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Non-bleeding rate during the treatment phase

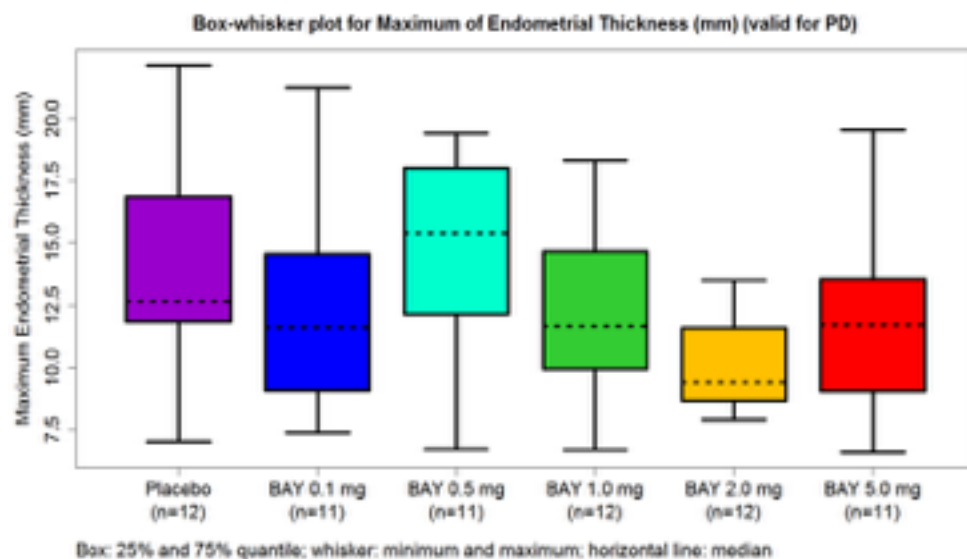
Observed and Bayesian estimates



- Marked and dose-dependent increase in non-bleeding rate. Maximum rate was achieved after ≥ 2 mg vilaprisan with point estimates $> 90\%$
- Upon discontinuation of treatment, return of menstrual bleeding was observed in all women.

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Endometrial thickness and histology



Maximum endometrial thickness:

- No dose-dependent increase and no relevant difference between vilaprisan groups and placebo group
- Number of subjects with maximum thickness >16 mm did not differ between placebo (4 out of 12 subjects) and vilaprisan groups (0-4 out of 11-12 subjects)

Endometrial histology:

- Observed changes in endometrial histology following treatment with vilaprisan imposed similar to those known from other SPRMs, compatible to PAECs (1) (Progesterone Receptor Modulator Associated Endometrial Changes), and were reversible after end of treatment
- No treatment-emergent critical endometrial findings occurred.

(1) GL Mutter et al, 2008, Modern Pathology 21: 591-598

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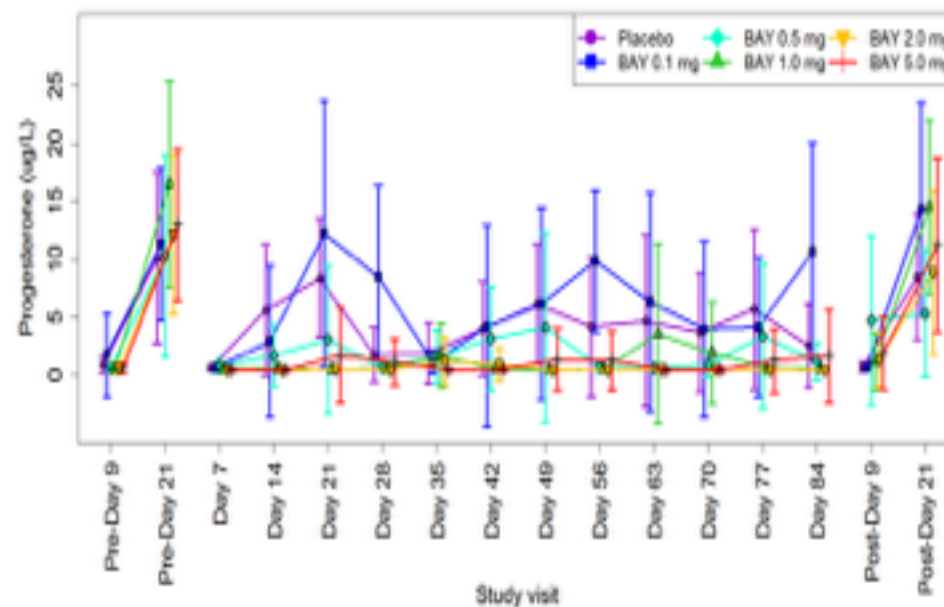
Impact on ovarian activity



Maximum size of Follicle Like Structures (FLS) during treatment (no. of subjects per group)

	≤ 13 mm	> 13 ≤ 30 mm	> 30 mm
Plac. (n = 12)	2	9	1
0.1 mg (n = 11)	1	9	1
0.5 mg (n = 11)	0	8	3
1 mg (n = 12)	1	5	6
2 mg (n = 12)	0	9	3
5 mg (n = 11)	1	9	1

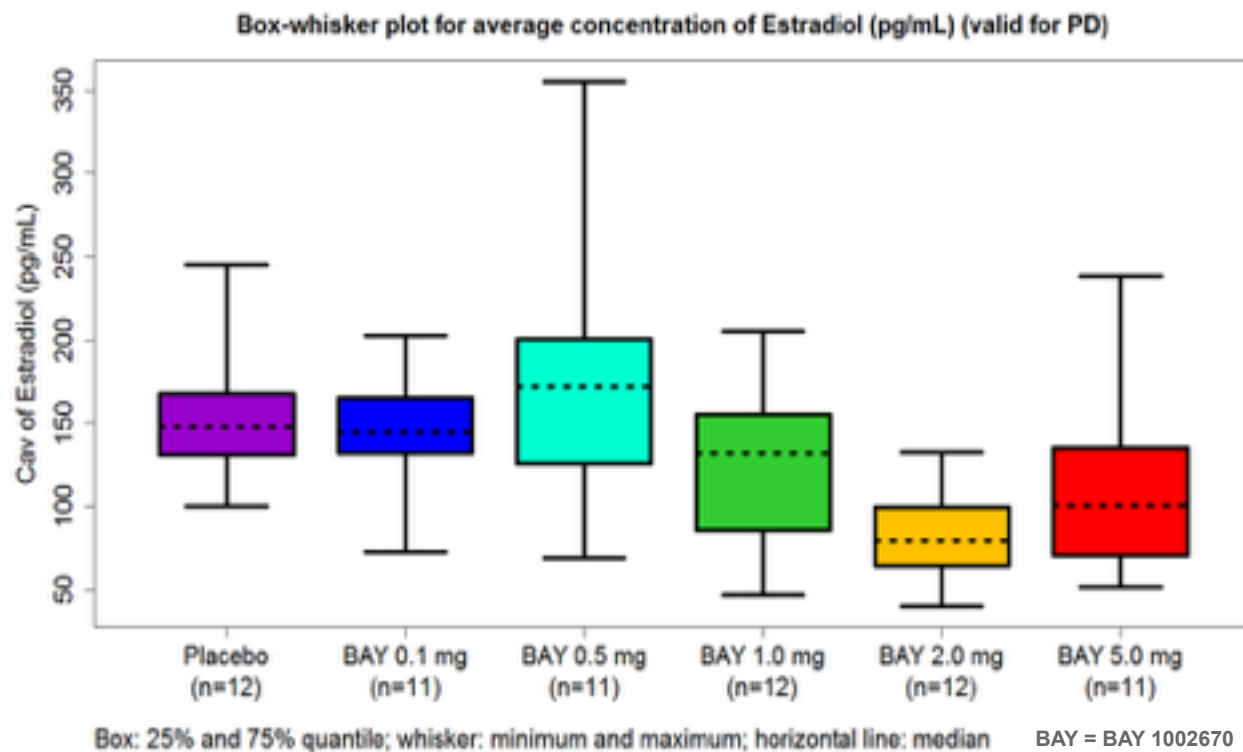
Mean progesterone serum concentrations (µg/L)
Mean +/- SD



- Follicular growth was not suppressed during treatment
- No persistent follicles / ovarian cysts > 28 days observed .
- Low progesterone levels (< 1.57 µg/L) indicating for ovulation inhibition/ lack of luteinization were observed in 29 out of 35 women during treatment with ≥ 1mg /d

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Average estradiol concentrations in serum



- None of the subject treated with vilaprisan showed an average E2 level < 40 pg/mL over the 3 months treatment period.



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Results on safety and tolerability

- No serious adverse events (SAEs) or AEs that led to premature discontinuation of treatment
- Most common drug related AEs (> 5% of subjects) were
 - Headache (19,7% vs 25%; Vilaprisan vs Placebo)
 - Fatigue (11,5% vs 8,3%; Vilaprisan vs Placebo)
 - Ovarian cysts (9,6% vs 0%; Vilaprisan vs Placebo)
 - Abdominal pain (6,8% vs 0%; Vilaprisan vs Placebo)
- No clinically relevant changes in vital signs, ECG or standard safety laboratory parameters (incl. e.g. hematology, hemostasis, kidney and liver function)
 - Specifically no increase in aminotransferases (ALT/AST) > 3 x ULN, no hints for drug induced liver injury (1)

(1) FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, Jul 2009

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Conclusion



- Vilaprisan showed dose-dependent pharmacodynamic effects.
- The observed reduction of menstrual bleeding in healthy subjects in dosage ≥ 1 mg/ d suggests that vilaprisan is a promising treatment option for uterine fibroids
- Oral administration of vilaprisan for 12 weeks up to 5 mg/d in healthy women aged 18-45 years is considered well tolerated.
- The results supported initiation of the currently ongoing Phase 2 study ASTEROID in patients with uterine fibroids.

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Principal investigators

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Bayer Study Team

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Andrea Hoehmann (Data Manager)

Kathrin Machens (Biomarker)

Esther Groettrup-Wolfers (Pharmacovigilance)

And many more



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Thank you for your attention

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Statistics



- **Primary variable:** Non-bleeding rate
- Dose-response relationship was estimated using a Bayesian approach
- As dose-response function a 4-parametric sigmoidal E_{\max} model was applied (see figure)
- Prior information was incorporated
 - placebo rate from historical studies and literature
 - maximal non-bleeding rate in previous clinical studies with predecessor compound lonaprisan (data on file)
 - ED_{50} as observed in preclinical studies in rabbits with lonaprisan and the marketed SPRM ulipristal (data on file)

