Effect of the Novel Progesterone Receptor Modulator Vilaprisan on Ovarian Activity and Bleeding Pattern in Healthy Women

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Introduction
Vilaprisan is a highly potent and selective progesterone receptor modulator that markedly reduced growth of human leiomyoma tissue in a preclinical model of uterine fibroids. In Asteroid 1 (a phase 2, placebo-controlled dose finding study to assess safety and efficacy of vilaprisan in patients with uterine fibroids) vilaprisan stopped effectively heavy menstrual bleeding, led to shrinkage of the fibroids and improved quality of life in the dose range 1-4 mg. In a double-blind, multi-center phase 1 study we assessed the effect of vilaprisan on ovarian activity and bleeding pattern in healthy women.
Methods
After an ovulatory pre-treatment cycle healthy women (18–40 years) were treated with daily vilaprisan (0.5mg, 1mg, 2mg, or 4mg) for 84 days starting during the first week of menstrual cycle. Primary variables were ovarian activity categorized by Hoogland Score (combining follicle size, estradiol and progesterone serum concentrations) and bleeding pattern (induced amenorrhea defined as no bleeding/spotting).
Results
Seventy women received at least 1 dose of vilaprisan and were included in safety analyses; 66 women were analyzed for pharmacodynamics. Ovulation inhibition rates increased with dose: 0.5mg (29%), 1mg (82%), 2mg (81%), 4mg (94%). The dose-response relationship was estimated using a Bayesian model with maximum ovulation inhibiton rates above 80% (median point estimators) being reached at doses of 2mg and higher. Ovulation returned quickly after end of treatment. Follicular growth was not suppressed during treatment. Estradiol levels decreased during treatment but average values remained above 80pg/mL and returned to baseline after end of treatment (EOT). Bayesian analysis indicated a sigmoidal relationship between VPR doses and the estimated induced amenorrhea rate, with a value above 60% at 1mg vilaprisan and a point estimator (median) at 2mg vilaprisan of 78.3% (90% credible interval: [68.7%; 86.1%]). Menstrual bleeding reoccurred in all women with a mean value of approximately 3 weeks. No serious treatment-emergent adverse events were observed. All endometrium biopsies were diagnosed as benign. Histological features known as PAEC were frequently described at EOT in all dose groups and mostly disappeared after next menstrual bleeding.
Conclusions
Inhibition of ovulation and induced amenorrhea was observed during treatment in the majority of women at a dose of ≥ 1mg vilaprisan. These changes were quickly reversible after EOT.

Keywords : progesterone receptor modulator, vilaprisan, ovarian activity, bleeding pattern
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