12° CONGRESS of the EUROPEAN SOCIETY of Gynecology
BARCELONA 18/21 OCTOBER 2017

EXPOSURE-RESPONSE ANALYSIS TO ASSESS THE SAFE AND EFFICACIOUS DOSE OF THE SELECTIVE PROGESTERONE RECEPTOR MODULATOR VILAPRISAN (VPR) FOR THE TREATMENT OF PATIENTS WITH UTERINE FIBROIDS

Ploeger B (DE) [1], Frei M (DE) [2], Solms A (DE) [3], Schultze-Mosgau M (DE) [4], Petersdorf K (DE) [5], Seitz C (DE) [6], Sutter G (DE) [7]

OBJECTIVE: The objective of the analysis was to evaluate the relationship between VPR plasma exposure and induced-amenorrhea (IA) or serum estradiol concentrations (E2) as efficacy or safety parameters, respectively, to assess the efficacious and safe dose for the treatment of patients with uterine fibroids.
METHODS: We conducted exposure-response analyses for IA and E2 using data from 2 randomized, parallel-group, double-blind, placebo-controlled phase-2 studies: ASTEROID 1, a safety and efficacy study with different VPR dosages (0.5, 1, 2 or 4 mg/day for 12 weeks), and ASTEROID-2, a safety and efficacy study with 2 mg/day VPR for 12 and 24 weeks. VPR exposure [area under the concentration versus time curve over 24 hours at steady state (AUC(0-24)ss)] was estimated based on sparsely sampled plasma concentration data using population PK modeling. The relationship between exposure and IA (no bleeding/spotting after end of the initial bleeding episode until end of treatment) was analyzed using logistic regression. Model qualification was performed by comparing the predicted and observed fraction of patients with IA in both ASTEROID 1 and 2. Also, the model was used to simulate the percentage of patients reaching 90% of the estimated maximum effect (Emax), which was defined as the desired effect level for clinical efficacy. The exposure-E2 relationship was analyzed visually.
RESULTS: The exposure-response relationship for IA in 267 patients in ASTEROID 1 was steep with a maximum of 59% (49 - 68) (mean and 95% confidence interval) probability of achieving IA with an AUC(0-24)ss of 36.9 Î¼g*h/L (27.7 – 48.7) for 50% of Emax. This model adequately describes the exposure-IA relationship in ASTEROID 2 also. Simulations show that 36% of the patients taking the 1 mg/day dose will be below 90% of Emax, whereas after 2 mg/day 90% of Emax will be reached in 98% of the patients. While a trend of lower E2 at higher VPR exposure was observed after a dose of 4 mg/day, this reduction was moderate after 2 mg/day (i.e. a change from of 97 pg/mL at baseline to 50 pg/mL at end of treatment) with a rapid return to baseline after treatment cessation.
CONCLUSIONS: A 2 mg/day VPR dose results in a close to maximum probability for IA and this dose is well tolerated with a moderate and transient decrease in E2 levels. These data support selection of the 2 mg/day dose to be evaluated in the VPR phase-3 program.

[1] Bayer AG, [2] Bayer AG, [3] Bayer AG, [4] Bayer AG, [5] Bayer AG, [6] Bayer AG, [7] Bayer AG