Exposure-response analysis of vilaprisan describing uterine fibroid size by population PK/PD modelling

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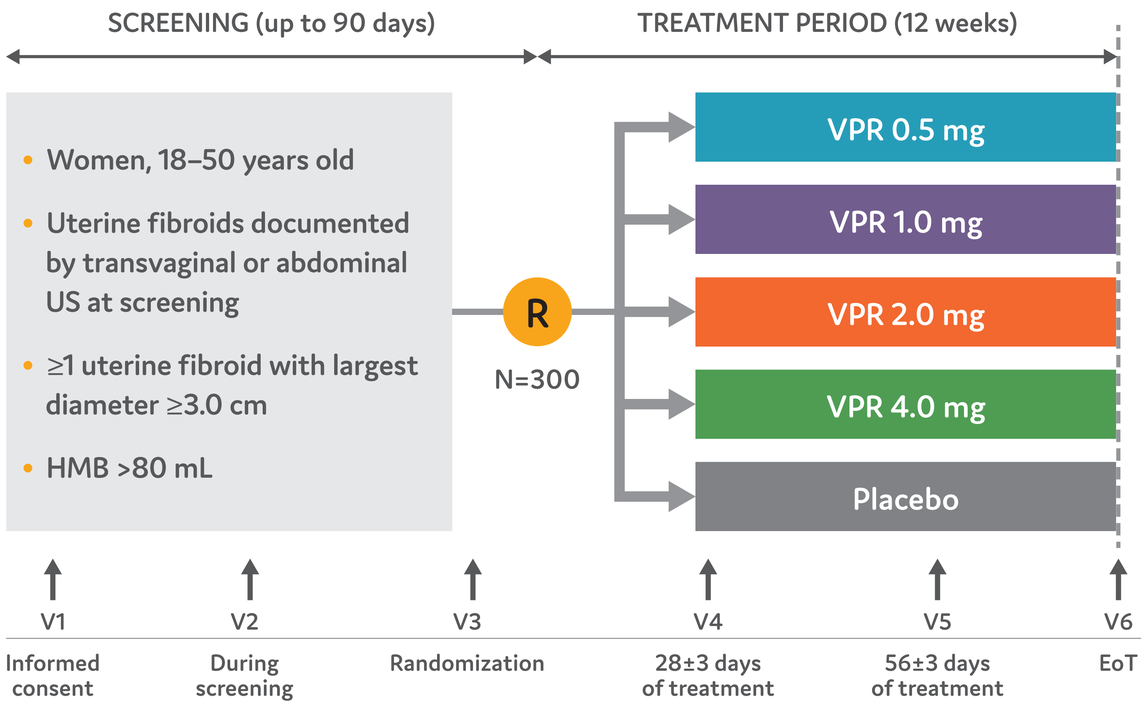
INTRODUCTION AND OBJECTIVES

- Vilaprisan (VPR) is a highly potent and selective progesterone receptor modulator (SPRM) which is currently being developed for the long-term treatment of uterine fibroids. Evidence for efficacy in reducing heavy menstrual bleeding associated with uterine fibroids is based on the clinical experience with other SPRMs.
- **Assess the exposure–response relationship of vilaprisan on uterine fibroids in a Phase 2b dose finding study**
- **Characterize the variability and uncertainty of the estimated parameters**

METHODS

- Data from a Phase 2b study [1], investigating efficacy and safety of different daily oral VPR doses over a treatment period of 3 months in women with symptomatic uterine fibroids, was analyzed by nonlinear mixed-effects modelling using NONMEM 7.3 [2].

Figure 1: Study design of ASTEROID 1



US: ultra sound; HMB: heavy menstrual bleeding; EoT: end of treatment

- A population PK model based on healthy subject data from two Phase 1 studies was applied to the data of the Phase 2b study in order to estimate the Empirical Bayes PK estimates and derive individual steady-state exposure ($AUC(0\text{-}24)_{SS}$).
- The change in fibroid volume over time of the largest fibroid at baseline (shrinkage) was analyzed.

RESULTS AND CONCLUSIONS

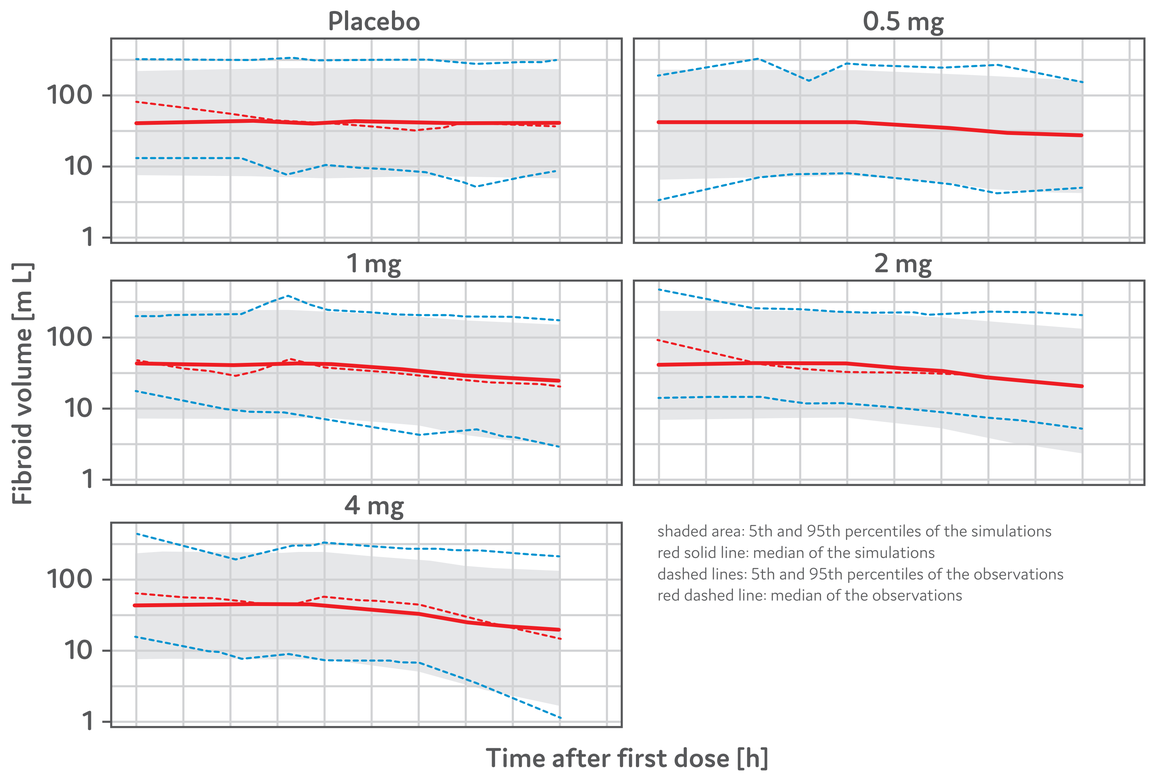
- The untreated fibroid volume was described as a constant volume, where the drug effect was implemented by an E_{max} model on a first order decrease in fibroid volume.

Table 1: Mean serum hormone concentrations during treatment

Parameter	Estimate (RSE%)	Variability (CV%)	Description
BSL [mL]	44.5 (6.22)	132	Untreated fibroid volume
E_{max} [1/year]	3.55 (16.3)	95.8	Max. shrinkage of the fibroids under treatment
$EAUC_{50}$ [µg*h/L]	59.0 (42.9)	–	$AUC(0\text{-}24)_{SS}$ level of VPR at which half of E_{max} was reached

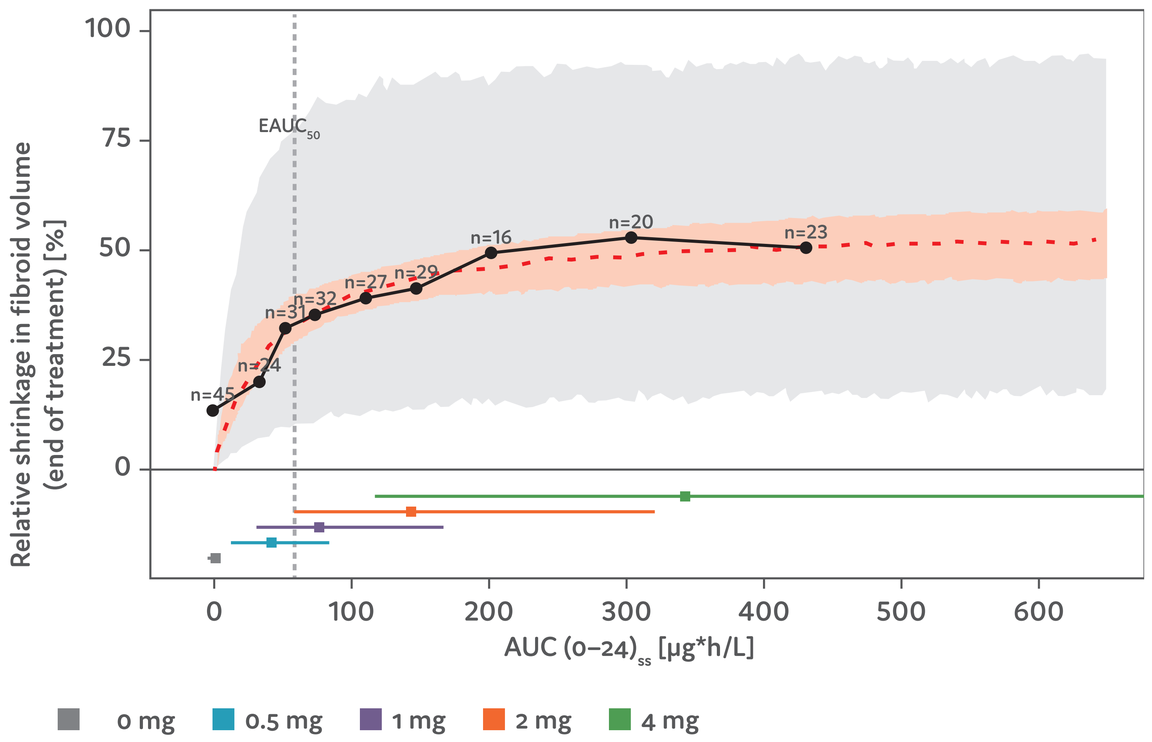
- The predictive performance of the model was evaluated by performing visual predictive checks (VPC) of fibroid volume vs. time and shrinkage vs. exposure.

Figure 2. VPC of the fibroid volume vs. time after dose by treatment arm



shaded area: 5th and 95th percentiles of the simulations
red solid line: median of the simulations
dashed lines: 5th and 95th percentiles of the observations
red dashed line: median of the observations

Figure 3. Shrinkage of the fibroid volume vs. AUC



shaded area: 5th and 95th percentiles of the simulations with inter-individual variability
red area: 5th and 95th percentiles of the simulations with parameter uncertainty
red dashed line: median of the simulations
black circles with solid line: median of the binned observations
colored symbols with lines: median and minimum and maximum of AUC of the respective dose

- **An exposure-response relationship for vilaprisan could be established by population PK/PD modelling, showing a high exposure driven effect of vilaprisan on uterine fibroid size.**
- **The predictive performance of the developed model could be demonstrated by VPCs.**
- **At the highest dose a shrinkage in fibroid volume relative to baseline of 53.0% was determined after 3 months of treatment.**

REFERENCES

1. Bradley L, Results of the ASTEROID (AssessSafety and Efficacy of Vilaprisan in Patients with Uterine Fibroids) 1 study: A Phase 2, Placebo-controlled dose finding study. 2016.
2. Beal SL, Sheiner LB, Boeckmann AJ & Bauer RJ (Eds.) NONMEM Users Guides. 1989-2011. Icon Development Solutions, Ellicott City, Maryland, USA.

ACKNOWLEDGEMENTS

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Asteroid