Title: Meta Analyses of Drug X using a Population Pharmacokinetic Approach

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Objectives: To develop a population pharmacokinetic (PK) model that describes the data from three clinical trials to identify the covariates that affect the PK of the drug.

Methods: Population PK analysis was conducted by pooling data from one clinical trial in which drug X was administered alone as a multiple dose regimen in healthy subjects as well as in patients, and two other trials which used a different formulation of Drug X in patients in combination with another drug. Drug X concentration-time data were analyzed using nonlinear mixed effects modeling approach (NONMEM®) with FOCE. Interoccasion variability was evaluated before covariate selection. Formulation and treatment were assessed as the categorical covariates. Covariates were tested using GAM in Xpose®[1], and further by forward inclusion and backward elimination.

Results: A one-compartmental population PK model was developed with a linear elimination process. The absorption of Drug X was best described as a Weibull function for the first dose [2], and first order absorption for the subsequent doses. The bioavailability of Drug X was expressed as a function of dose. Inclusion of interoccasion variability for clearance significantly improved individual predictions. Formulation was a significant covariate on the first-order absorption rate constant, Gama coefficient in Weibull Function, and bioavailability. The final model was validated with 500 simulations via a posterior predictive check (PPC) approach [3]. Covariates such as age, gender, and body weight did not have any significant effect on the objective function and were not included in the final model.

Conclusions: The population PK model for Drug X adequately described the concentration–time profiles obtained in clinical trials. This PK model may be used in future simulations studies.

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