Development and application of an integrated population pharmacokinetic model for rivaroxaban across multiple patient populations

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Objectives: To develop an integrated population pharmacokinetic (PopPK) model for rivaroxaban across all approved indications using pooled PK data obtained from global phase 2 and 3 clinical trials and to perform exposure simulations in relevant patient subgroups (area under the concentration-time curve, maximum and trough concentration at steady state).

Methods: Available rivaroxaban concentration-time data from 4,918 patients from seven global clinical trials of rivaroxaban in four different indications were used. A one-compartment model was used to describe rivaroxaban PK, as consistently suggested by previous separate PopPK modelling studies for phase 2 and 3 patient populations. The influence of various covariates such as age, body size, and renal function on rivaroxaban PK was tested. Virtual sub-populations for exposure simulations were defined by age, renal function and body size.

Results: Rivaroxaban PK was adequately described by a one-compartment disposition model with first- order absorption and elimination across all indications. Creatinine clearance, use of comedication and study population were identified as covariates on the apparent clearance (CL/F); age, weight, and sex were identified as covariates on the apparent volume parameter (V/F); and dose was identified as covariate on the relative oral bioavailability (F). Model diagnostics indicated a robust and precise determination of all parameters as well as an adequate description of the observed data. Simulations for virtual sub-populations showed that renal function had a modest influence on exposure, the influence of age and body weight on rivaroxaban PK was minor (Figure 1).

Conclusions: The developed Pop PK model that integrates data from four different indications describes the observed PK of rivaroxaban very well. Pooling data from different indications and various dose groups substantially supported the identification of covariate-effects. This model will serve as the basis for individual exposure estimates to be used in exposure-response studies across all rivaroxaban indications.

Figure 1: Simulation results (AUC at steady state following rivaroxaban 20 mg once daily) for the subgroups according to renal function (top), age (middle; adults: 18–<65 yrs., elderly: 65–<75yrs., very elderly: >75yrs.), and weight (bottom) in the indication VTE-T (treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults). [AUC: area under the curve for 0–24 hours; RI: renal impairment; IQR: interquartile range]