

Population Pharmacokinetic Modelling of Factor VIII Levels During Perioperative Dosing of Haemate® P (Humate P) in Patients Diagnosed with Von Willebrand Disease

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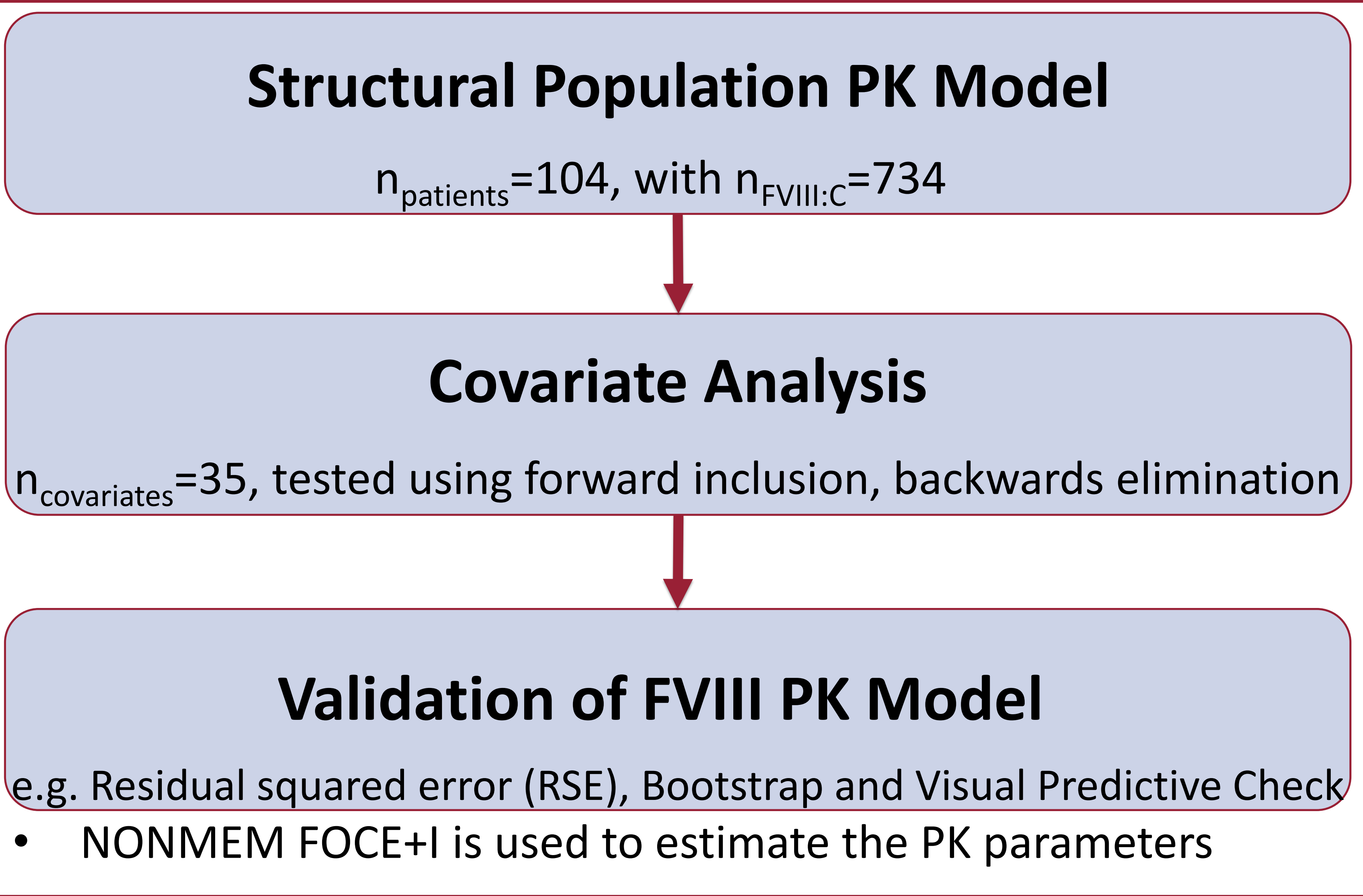
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Background

Von Willebrands Disease (VWD) is the most common inherited **bleeding disorder** and is characterised by a **qualitative or quantitative defect of Von Willebrand Factor (VWF)**. VWF is essential in primary- and secondary hemostasis as it mediates adhesion and aggregation of platelets at sites of vascular injury, and acts as a chaperone protein for **factor VIII (FVIII)** by protecting it from premature clearance. Evaluation of the current perioperative **Humate P** replacement therapy in VWD patients revealed **accumulation of FVIII concentrations (FVIII:C)** accompanied with potentially increased risk of **thrombosis development** and **high treatment costs**. The **complexity of treatment** in combination with the **variety of (un)known influencing factors regarding the pharmacokinetics (PK) of FVIII**, makes **PK modeling** an interesting tool to analyse and identify these matters. A PK model would allow accurate **individualized therapies** for all VWD patients.

Methods



Results

Population PK modelling

- A **one-compartment model** resulted in the best fit of the concentration over time profiles of FVIII.
- As a wide variety of weights and ages were present in the data, **a priori allometric scaling using weight** was applied on the volume of distribution- and clearance parameters.
- A **virtual dose with corresponding bioavailability (F)** parameter was introduced, when a pre-dose FVIII:C was measured. **PK parameter estimates remained unaffected**.

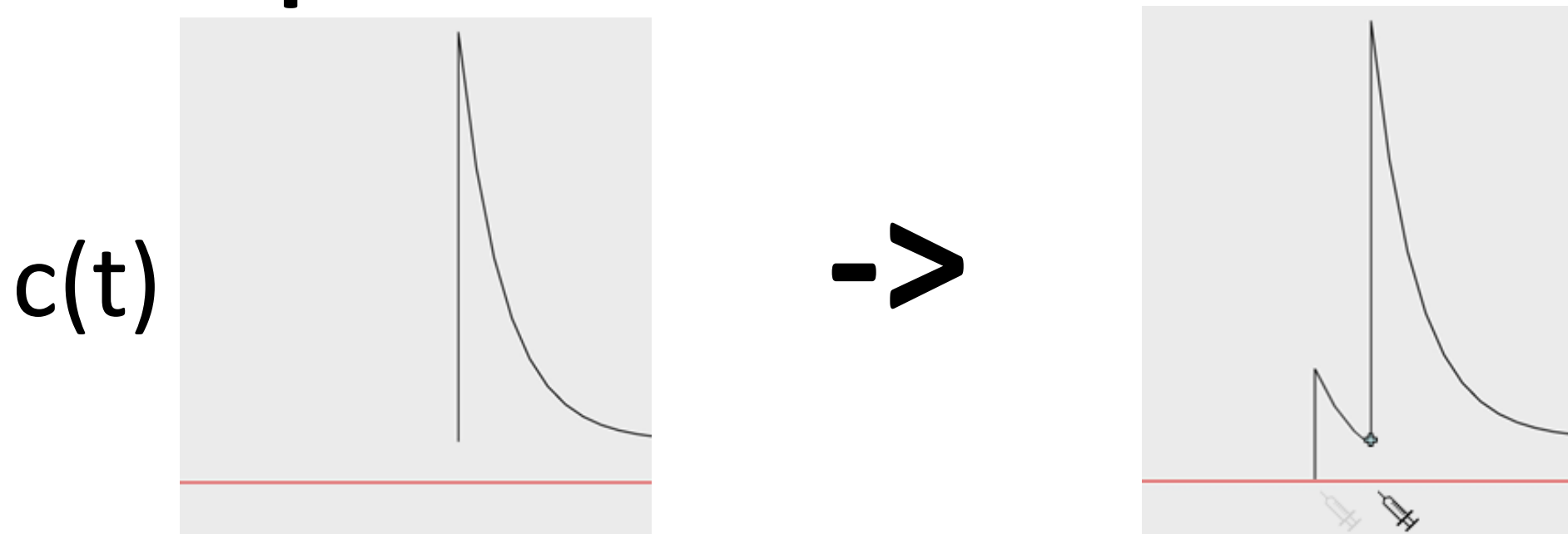


Table 1: FVIII PK parameter estimates of the structural and final model

Parameter	Structural PK model	Final PK model
	Estimate (RSE)	Estimate (RSE)
Proportional error	0.235 (7%)	0.227 (7%)
Volume of distribution (L/70 kg)	3.27 (4%)	3.2 (4%)
Clearance (Lh ⁻¹ /70 kg)	0.0417 (10%)	0.0453 (9%)
Bioavailability	0.197 (21%)	0.195 (20%)
Inter-individual variability		
Volume of distribution (%)	33.3 (13%)	34.1 (12%)
Clearance (%)	85.2 (11%)	68.2 (13%)
Inter-occasion variability		
Bioavailability (%)	165.6 (22%)	167.9 (22%)
Covariates		
Duration of intervention	-	-0.422 (22%)
ASA* classificatie 3/4	-	0.594 (11%)

*ASA = The American Society of Anesthesiologists (ASA) physical status classification system

Covariate Analysis

- Patients classified as ASA 3 or 4 have a 0.6-fold decreased clearance; with increasing duration of the intervention, clearance decreases.

$$CL = 0.0417 * \left(\frac{weight}{70}\right)^{0.75} * \frac{duration\ of\ intervention^{-0.422}}{81} * (ASA_{3,4} * 0.594)$$

Validation of FVIII PK Model

- Bootstrap indicated **strong robustness** of the FVIII PK Model.

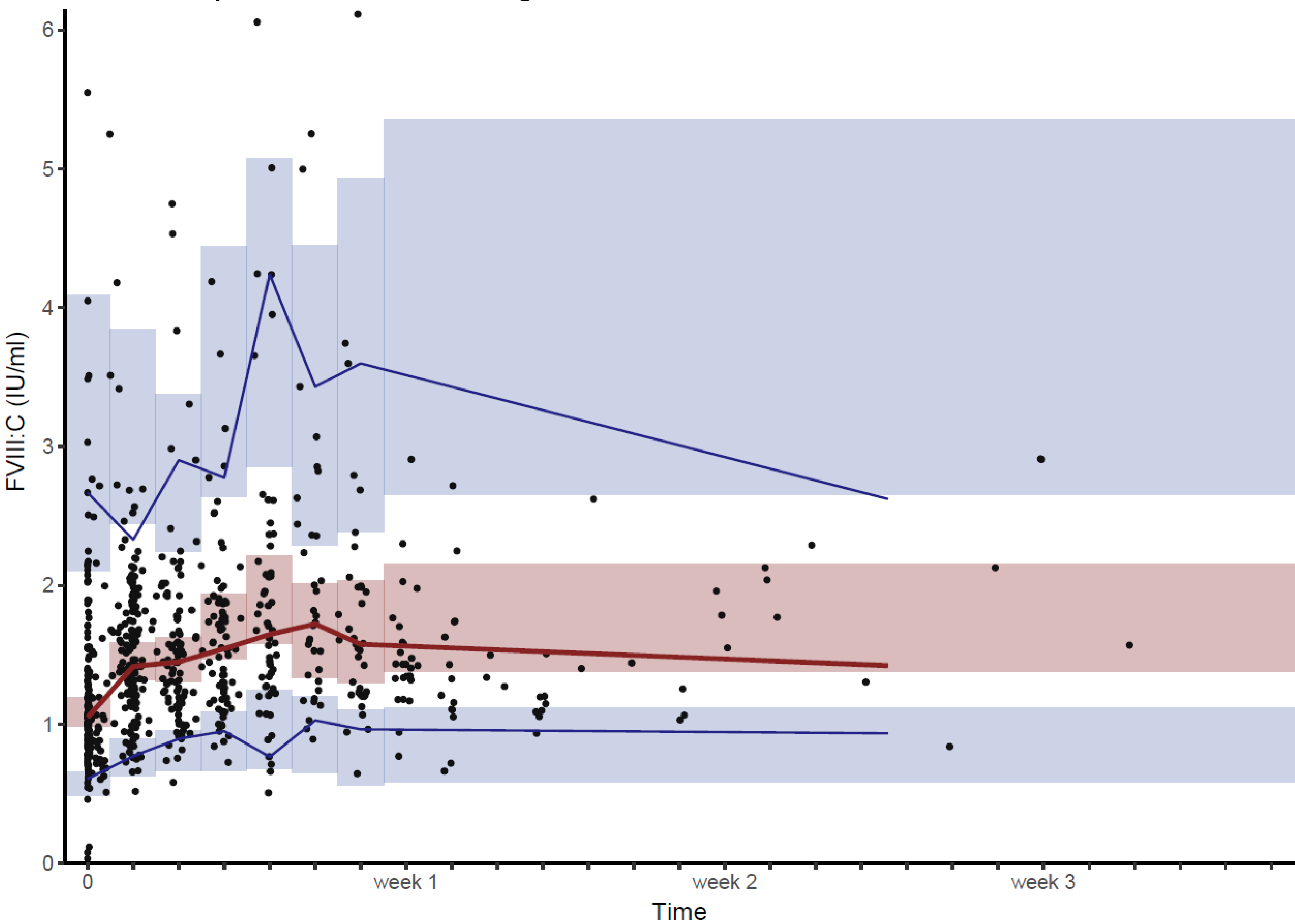


Figure 1: Prediction-corrected visual predictive checks of the FVIII PK model. The solid black line represents the median of the FVIII:C and the dashed lines indicate the corresponding 2.5th and 97.5th quantiles. The highlighted areas visualise the simulated 95% prediction intervals for the median (red) and quantiles (blue).

Conclusions

Time-courses of obtained perioperative FVIII:C after administration of Humate® P can be adequately described by the developed FVIII PK model. Covariate relations have been identified between the covariates ‘duration of surgery’ and ‘ASA classification’ and PK parameter clearance. This model facilitates PK-guided dosing of Humate® P in VWD patients, which might result in improvement of quality and cost-effectiveness of care.

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