



Background

- Moroctocog alfa is a B-domain deleted recombinant factor VIII (FVIII) indicated for the treatment and prophylaxis of bleeding in adults and children with haemophilia A (congenital FVIII deficiency).
- Information on the population pharmacokinetics (PK) of moroctocog alfa in a large group of patients is lacking.

Objective

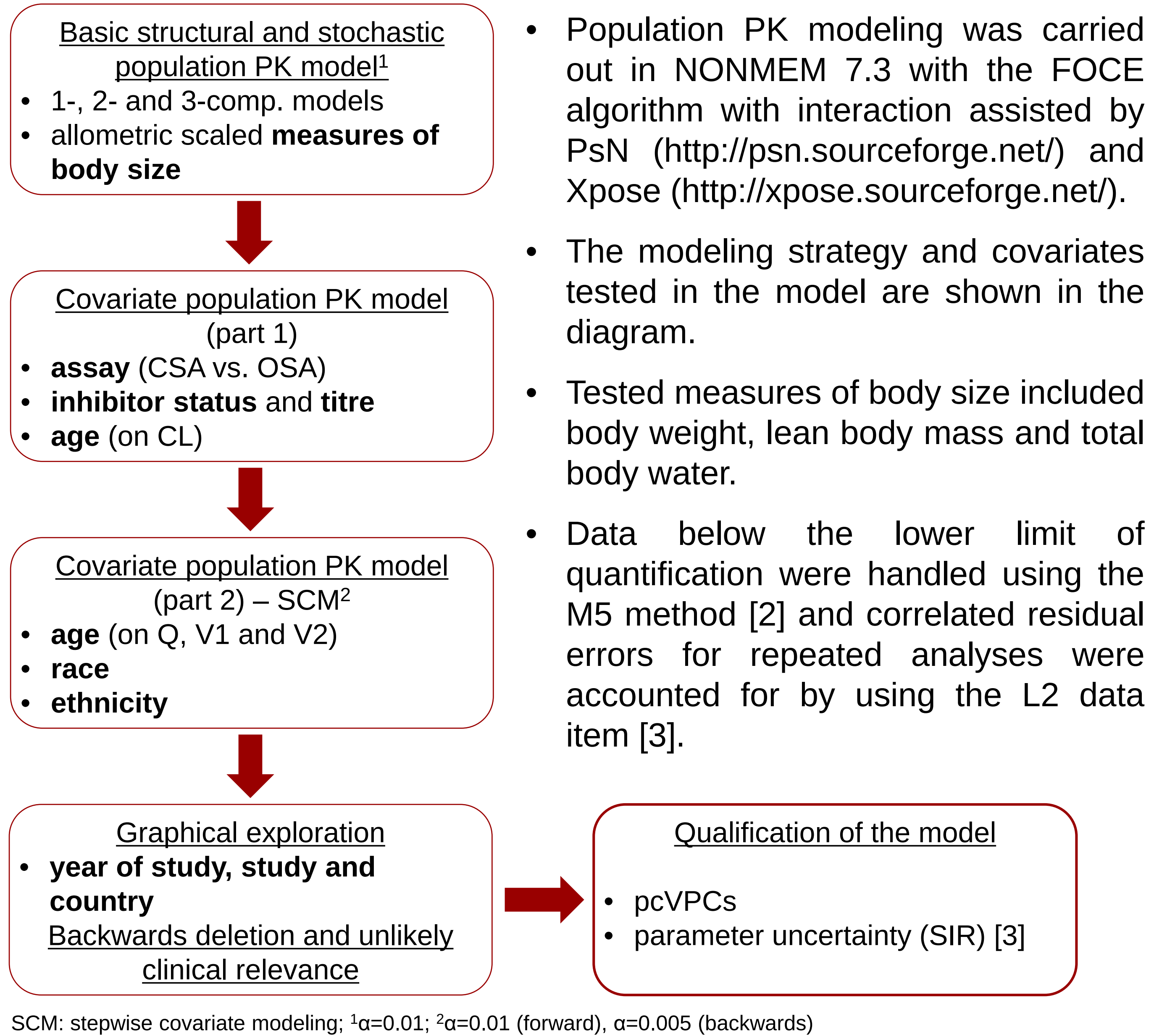
- To develop a population PK model of FVIII activity following moroctocog alfa treatment in haemophilia A patients based on all available clinical study data.

Methods

Data

- Combination of 13 trials with IV administration of second- and third-generation recombinant FVIII products containing moroctocog alfa (Refacto®, Refacto AF®, Xyntha® Wyeth Pharmaceuticals Inc. [Pfizer], Philadelphia, USA) to severe (FVIII <1 IU/dL) and moderate (1-5 IU/dL) haemophilia A patients:
 - Clinical trial phases II (n=2), III (n=8) and IV (n=3), from 1993 to 2013 in 25 countries;
 - Included rich sampling (≥10 samples post-dose, n=4), sparse sampling (2-3 samples per occasion, n=5) or both (n=4);
 - FVIII plasma activity was measured with the one-stage assay (OSA, n=4) or chromogenic substrate assay (CSA, n=9) in a central (n=12) or local (n=1) laboratory.

Model development and qualification



- Population PK modeling was carried out in NONMEM 7.3 with the FOCE algorithm with interaction assisted by PsN (<http://psn.sourceforge.net/>) and Xpose (<http://xpose.sourceforge.net/>).
- The modeling strategy and covariates tested in the model are shown in the diagram.
- Tested measures of body size included body weight, lean body mass and total body water.
- Data below the lower limit of quantification were handled using the M5 method [2] and correlated residual errors for repeated analyses were accounted for by using the L2 data item [3].

Results (cont.)

Population PK results

- A 2-compartment model with first-order elimination and allometrically scaled body weight on disposition was found to adequately describe the combined data.
- The following parameter-covariate relationships were found to be statistically significant and potentially clinically relevant: analytical assay on bioavailability, inhibitor status on clearance, age on clearance and black race on peripheral volume of distribution (table 2).

Table 2 – Population PK parameter estimates for Refacto/Refacto AF in 20-year-old 70-kg patients with severe or moderate haemophilia A.

Parameter	Population estimate	SIR 95%CI lower	upper
Structural model			
Clearance (CL), dL/h	2.76	2.65	2.88
Central volume of distribution (V1), dL	24.5	23.5	25.7
Intercompartmental clearance (Q), dL/h	25.1	19.7	31.8
Peripheral volume of distribution (V2), dL	9.23	8.33	10.4
Allometric exponent for V1 and V2	0.812	0.792	0.835
Endogenous FVIII activity severe haemophilia ¹ , IU/dL	0.474	0.468	0.479
Endogenous FVIII activity moderate haemophilia ¹ , IU/dL	1.59	1.53	1.65
Covariate model			
Assay on bioavailability (F) ² , % difference if OSA	-39.0	-41.6	-36.3
Inhibitor status on CL ² , % difference if positive	166	125	188
Age on CL up to 1 year old ³	0.149	0.0116	0.352
Age on CL above 1 year old ³	-0.00678	-0.0054	-0.00526
Race on V2 ² , % difference if black	88.4	36.7	151
Assay on residual error, % difference if OSA	41.0	32.7	47.9
Inter-subject variability parameters			
F, %CV	13.0	11.7	14.4
CL, %CV	30.5	26.3	35.6
Endogenous FVIII activity, %CV	7.19	4.95	9.34
Inter-occasion variability parameters			
CL, %CV	34.7	31.8	38.6
V2, %CV	41.0	33.1	49.1
Residual variability parameters			
Proportional residual error, %CV	19.2	18.5	19.9
Proportional replicate error, %CV	10.4	9.63	11.3

¹fraction of patients belonging to subpopulations *severe* or *moderate* haemophilia was estimated using the \$MIXTURE functionality. The probability to belong to subgroup *severe* hemophilia was 80.3% or 11.0%, depending on the study.

²covariate effect (Θ) parameterized as *PK parameter* = *typical estimate* × (1 + Θ × *binomial covariate value*)

³age effect (Θ) parameterized as a piece-wise linear function: if *age* ≤ 1 year: *PK parameter* = *typical estimate* × (1 + Θ₁ × (*age*-1)-19 × Θ₂); if *age* > 1 year: *PK parameter* = *typical estimate* × (1 + Θ₂ × (*age*-20))

Parameters fixed: bioavailability for Xyntha relative to Refacto/Refacto AF (1.38); allometric exponent for CL and Q (0.75).

- Estimation of endogenous FVIII activity was refined with the estimation of an additive component (extra) accounting for residual activity from previous unknown doses (2.84 IU/dL) with inter-individual variability (119%CV for the 1st observation and 152%CV for other observations before the first dose) and declining over time in line with the estimated FVIII disposition.
- The predictive ability of the model, the influence of inhibitors on the FVIII activity profile and age/weight on the clearance of FVIII are shown in figures 1 and 2.

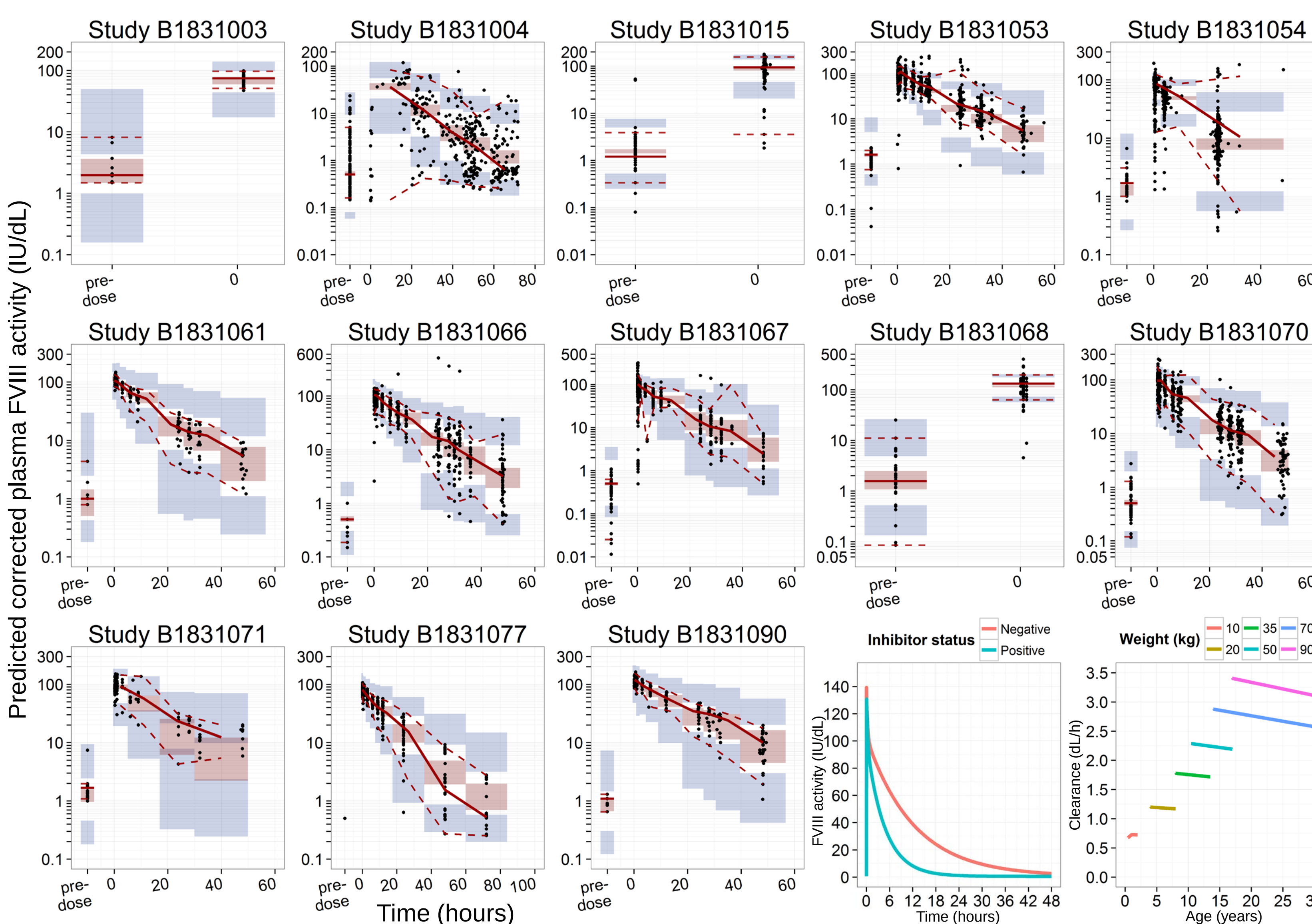


Figure 1 – Population prediction-corrected visual predictive checks, stratified by study, showing the 2.5th, 50th and 97.5th percentiles of the observed data (lines) and respective simulation-based 95% confidence intervals (shaded areas).

Figure 2 – Effect of inhibitor status (left panel) on plasma FVIII activity (50 IU/kg) and age and weight (right panel) on the predicted values of clearance.

Results

Patients and FVIII activity data

- In total, 756 patients with moderate to severe haemophilia A (FVIII ≤5 IU/dL) and 7363 samples were included in the analysis.

Table 1 – Summary of patient characteristics and number of observations.

Group	N	Female/ Male (N)	Age (years)	Body weight (kg)	Race Black (N)	No. observations (%BLQ)
Age<18	259	1/259	9.17±6.51 (1 day - 17)	40.2±27.2 (3 - 114)	3	2385 (12.6)
Age≥18	497	0/497	33.1±11.6 (18 - 73)	76.0±14.3 (41 - 134)	7	4978 (12.2)
Total	756	1/756	24.9±15.2 (1 day - 73)	63.8±26.0 (3 - 134)	10	7363 (12.4)

N, number of patients; BLQ, value below the lower limit of quantification. Statistics for continuous variables expressed as mean±standard deviation (range)

References

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Conclusion

- The model is capable of describing and predicting reasonably well the plasma disposition of factor VIII activity following treatment with moroctocog alfa.
- When used with patient observations in a therapeutic drug monitoring context, the model may be an aid in dose individualization with the ultimate goal of a safer and more effective treatment with moroctocog alfa.



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