

Does the drug dose affect the volume of distribution?

A revised population pharmacokinetic model for recombinant fusion protein linking recombinant coagulation factor IX with recombinant albumin

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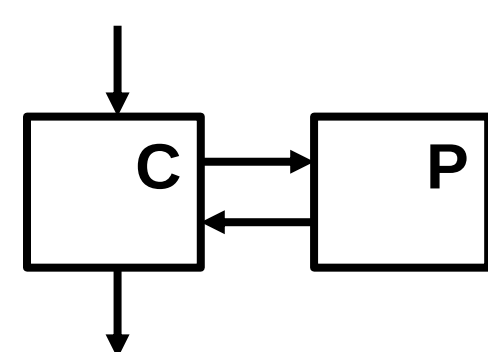
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Background

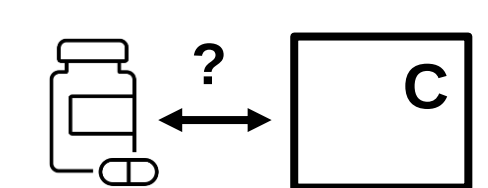


Currently, one population pharmacokinetic model has been published for describing the rIX-FP pharmacokinetics (PK) based on the PROLONG-9FP clinical trials¹

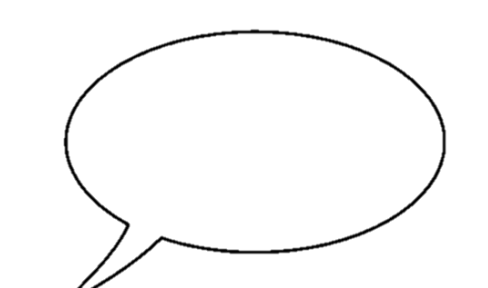


In the published model, the volume of the central compartment (V_c) augments with increasing administered doses:

$$V_c = \theta_{V_c} * \left(\frac{WT}{70}\right)^{0.79} * \left(\frac{Dose}{50}\right)^{0.38}$$



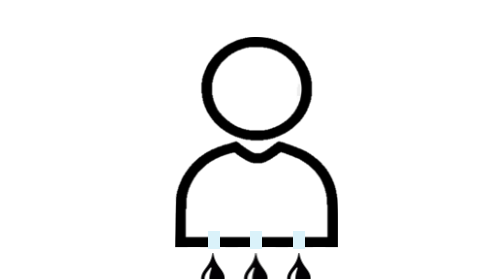
No good pharmacological/physiological explanation for this phenomenon (dose is not a body-related parameter)



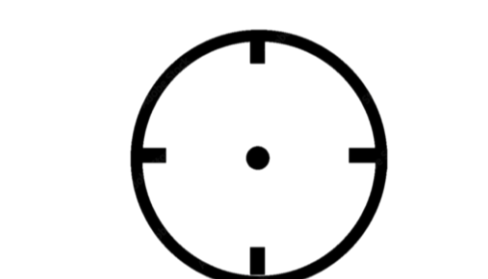
We hypothesize that inclusion of a dose-dependent parameter entails a form of selection bias in treatment allocation



In the trial design, the treating physician was able to select a pre-specified rIX-FP starting dose². Lack of randomization herein causes:

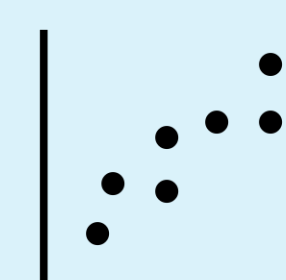


Patients with a higher bleeding risk due to an increased volume of distribution may have received a higher pre-specified rIX-FP dose



Aim: Create a revised population PK model based on PROLONG-9FP data, with *a priori* exclusion of a dose-dependent parameter

Conclusions



Due to the hydrophilic drug properties of rIX-FP, FFM may explain more variability in PK parameters than body weight



We pose an alternative and pharmacologically-sound model to the published model to perform PK-guided dosing with

Discussion (with you)



- Could it be that selection bias in treatment allocation is the underlying reason why V_c augments with increasing doses?
- We would like to hear your opinion! Are we missing something? Please find the QR-code to get in touch

Methods



PROLONG-9FP clinical trial (table 1):

- Severe haemophilia B patients (FIX activity level ≤2 IU/dL)
- Children included
- Treated with rIX-FP
- FFM is calculated³



Model evaluation and comparison:

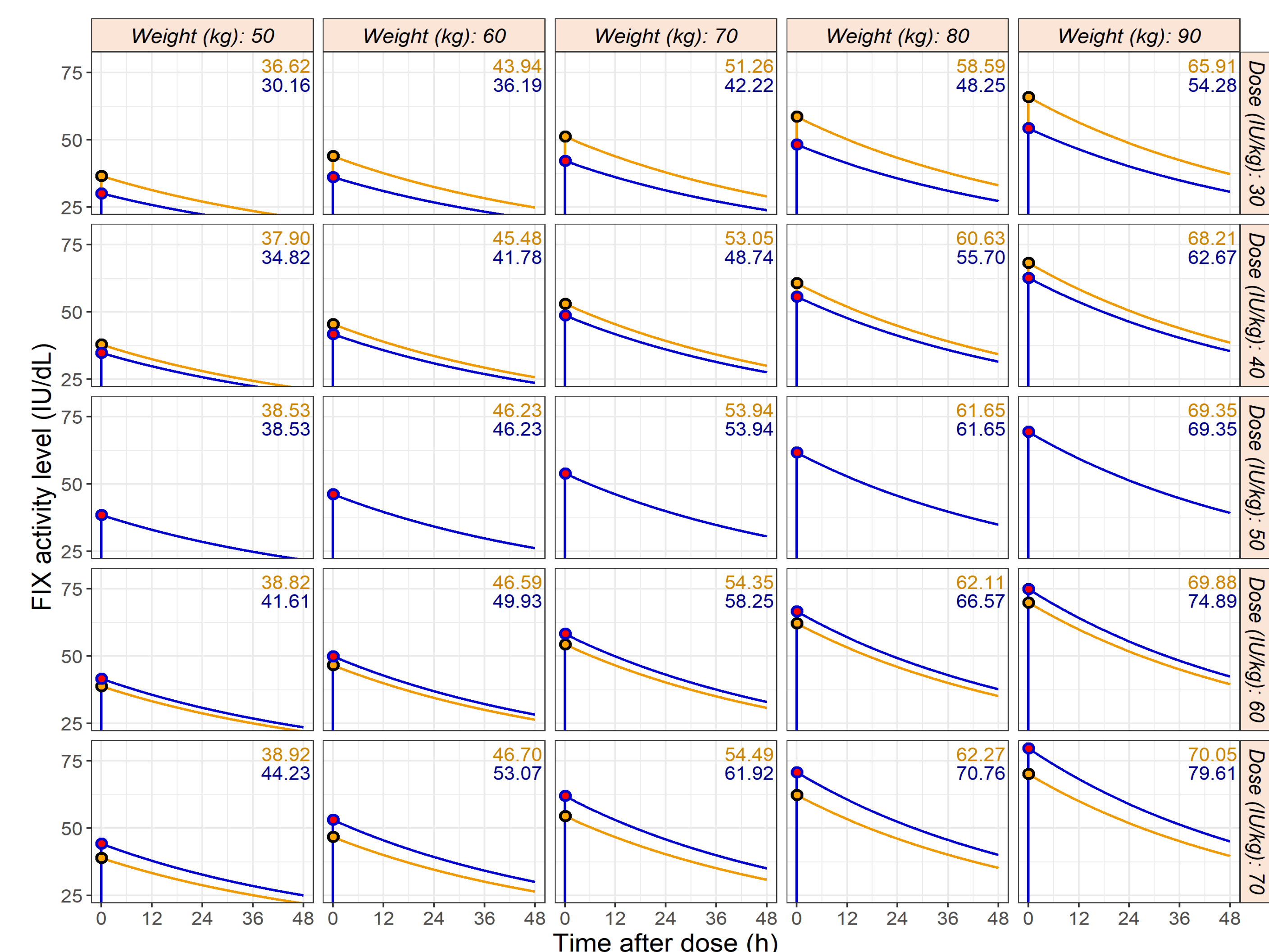
- Mean prediction error (MPE)
- Required dose to yield FIX activity level >3 IU/dL (Dose_{3%}) one week post administration for a typical patient

Results



Published model simulations (figure 1):

- Simulations made with mrgsolve⁴
- V_c increases with dose (unexpected)



• **Figure 1: Effect of dose-dependent parameter.** Simulated peak FIX activity level (IU/dL) in the central compartment for a range of weight (kg; columns) and dose (IU/kg; rows) combinations using the published model¹. Exclusion of the dose-dependent parameter is denoted in blue (red dots), its inclusion is denoted in orange (orange dots).



Model comparison (table 2) and characteristics (table 3):

- Revised model shows similar performance to published model with *a priori* exclusion of a dose-dependent parameter

• **Table 1: Patient characteristics**

Characteristic	Median	Range
Participants (n)	113	
Follow-up time (days)	484	(7-2492)
Age (years)	25	(1-61)
Weight (kg)	63.1	(11-130)
Height (cm)	172	(78-190)
BMI (kg/m ²)	21.5	(13-62)
Fat-free mass (kg)	51.2	(9-72)

• **Table 2: Published and revised model performance comparison**

Measure	Published	Revised
MPE (%)	17.6	15.7
Dose _{3%} (IU/kg)	30	30

• **Table 3: rIX-FP population PK parameters from the published and revised model**

Parameters	Published ^a		Revised ^b	
	Estimate	(RSE %)	Estimate	(RSE %)
CL (dL/h)	0.57	(3)	0.51	(2)
WT ^b /FFM ^b on CL	0.53	(9)	0.63	(5)
V _c (dL)	64.8	(2)	55.5	(2)
WT ^b /FFM ^b on V _c	0.79	(7)	0.87	(5)
Dose (weight-adjusted) on V _c	0.38	(17)	-	
Q (dL/h)	0.29	(36)	0.30	(12)
V _p (dL)	21.6	(8)	21.6	(8)
WT ^b /FFM ^b on V _p	0.79	(7)	0.87	(5)
IIV on CL (%)	22.6	(21)	15.6	(8)
IIV on V _c (%)	26.9	(26)	17.2	(9)
Correlation IIV CL and V _c (%)	-		74	(22)
IOV on CL (%)	-		13.1	(12)
Proportional error (%)	18.0/35.0	(11)/(7)	13.2	(9)
Published model: Phase 2 error / Phase 3 error				
Additive error (IU/dL)	0.66/1.24	(28)/(17)	1.25	(10)
Published model: Phase 2 error / Phase 3 error				

References

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Contact



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