

Population Pharmacokinetic Model of *Ixodes ricinus*-Contact Phase Inhibitor for patients with Spontaneous Intracerebral Haemorrhage

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Introduction

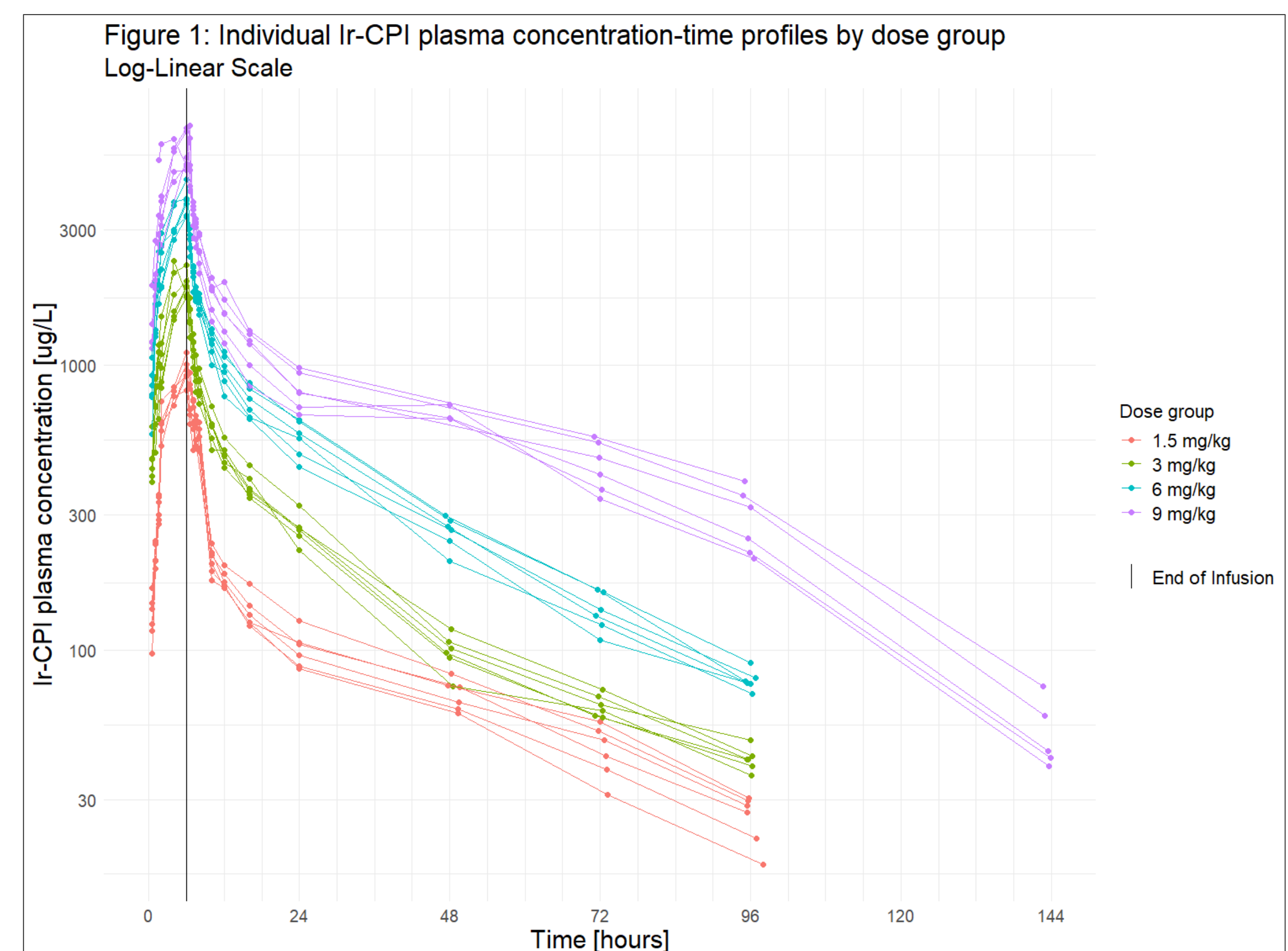
- Non-traumatic intracerebral haemorrhage (ICH) accounts for about 10-15% of all stroke cases and about 40% of all stroke deaths. [1]
- A major contributor to poor outcomes after ICH is the secondary brain injury (SBI).[1,2] No pharmacological treatments have demonstrated efficacy for SBIs caused by haemorrhage. Due to the risk of bleeding, classical anticoagulation is not indicated within the first hours (< 24-72h) of haemorrhage onset.
- Ixodes ricinus*-Contact Phase Inhibitor (Ir-CPI), also called BIOX-101, is a recombinant protein for the prevention of acute thromboinflammatory events, which does not increase the risk of bleeding. [3]

Method

- A First-in-Human (FIH) Phase I study, double-blind, placebo-controlled, single dose escalation of Ir-CPI provided an initial assessment of the safety, tolerability, PK, and pharmacodynamics (PD) of Ir-CPI after 6 hour-IV infusion to 32 healthy adult male participants.
- The study included four groups of eight participants randomized to Ir-CPI doses of 1.5, 3, 6 and 9 mg/kg versus placebo (6-active: 2-placebo).
- A Population PK analysis was conducted via nonlinear mixed effects modeling using NONMEM, V7.5. The First-Order Conditional Estimation with Interaction (FOCEI) method was used during the estimation process. Assessment of model adequacy and decisions about increasing model complexity were driven by the data and guided by goodness-of-fit criteria (visual inspection of diagnostic plots, plausibility and precision of parameter estimates, objective function value, visual predictive checks). After graphical exploration and preliminary analyses (see Figure 1), a two-compartment population PK (popPK) model with a first-order elimination from the central compartment was assumed for the initial structural model.

Objective

The objective is to characterize the pharmacokinetics (PK) of plasma Ir-CPI concentrations in healthy volunteers as basis to support the further clinical development in patients with spontaneous ICH.



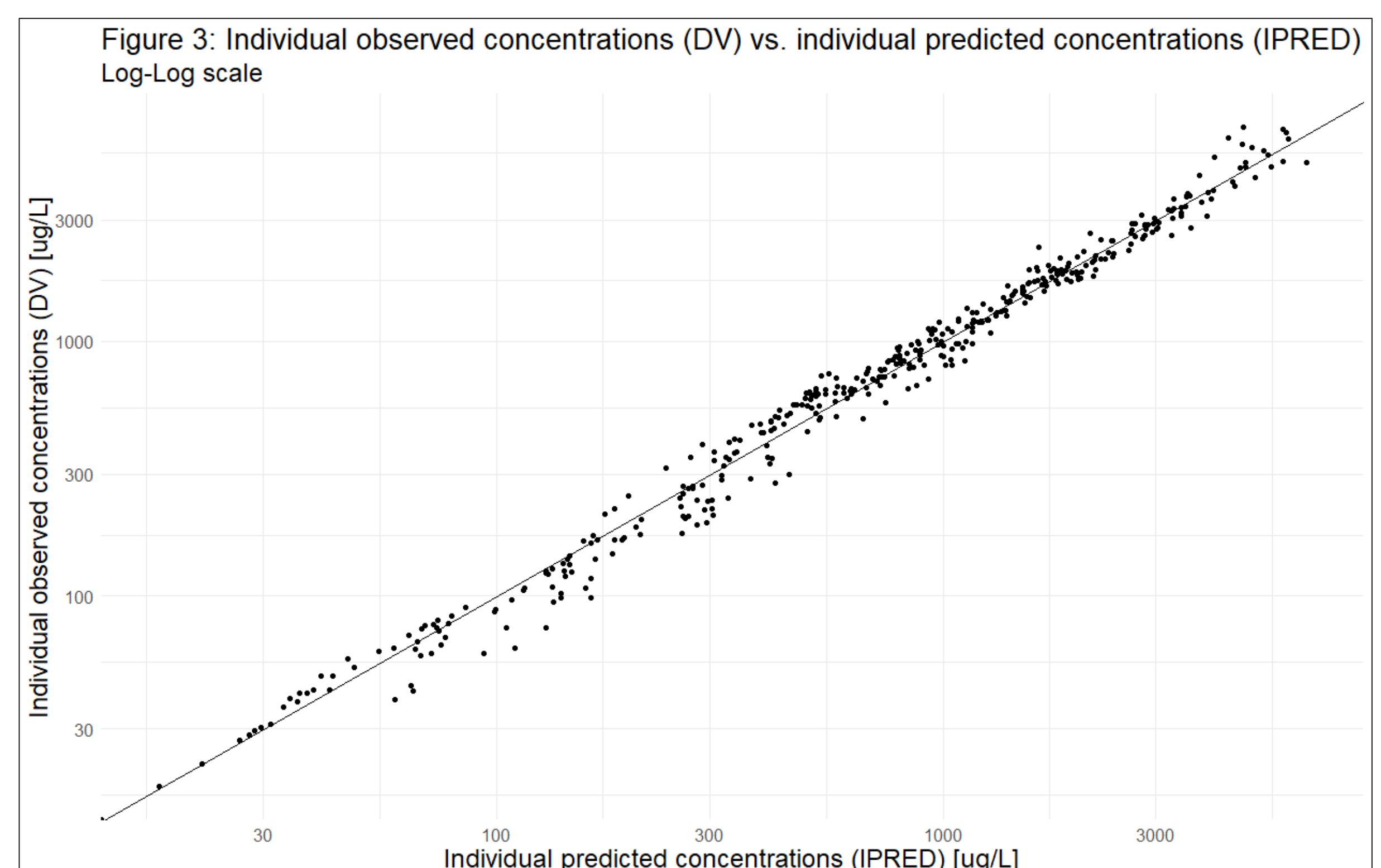
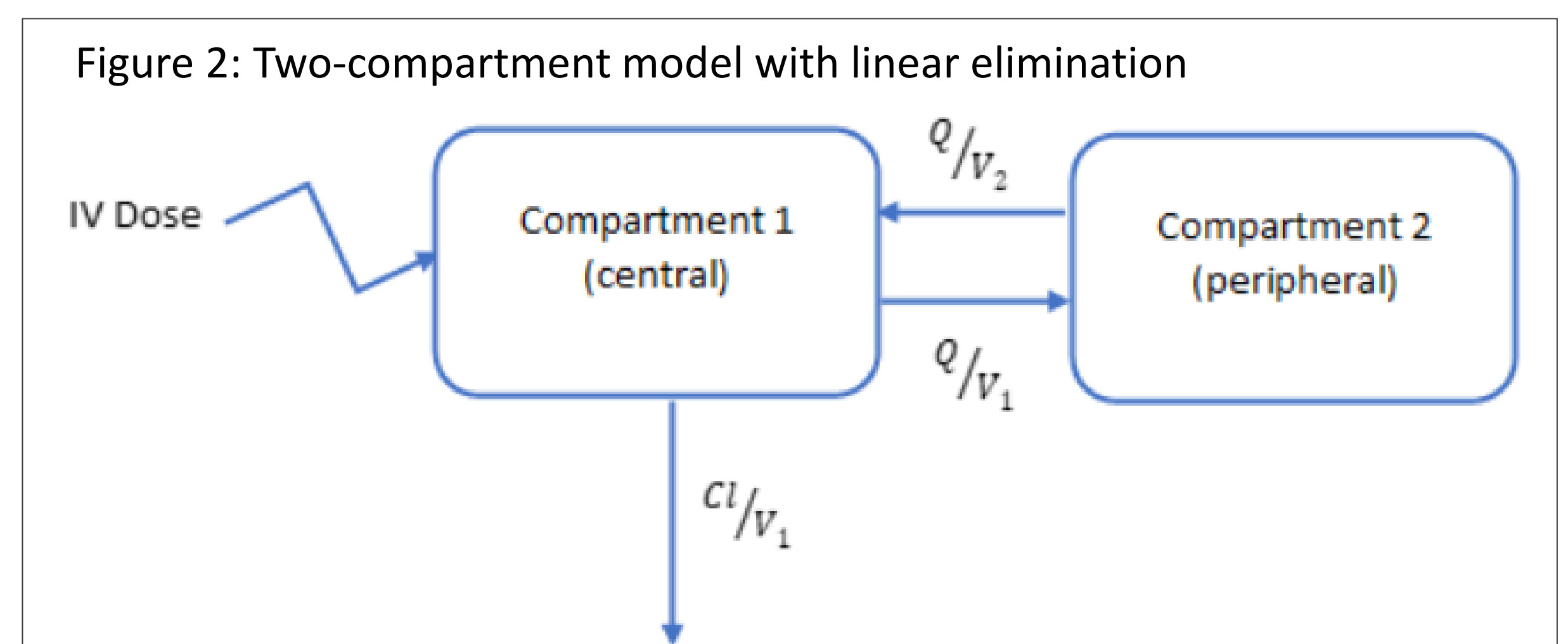
Results

- 407 quantifiable Ir-CPI concentrations from a total of 24 healthy male volunteers.
- Ir-CPI PK was characterized using a 2-compartment model with linear elimination (Figure 2).
- Inter-individual variability was estimated on all parameters. Body weight (WT) was included as a covariate on all clearances and volumes parameters using allometric scaling with fixed exponents.
- Residual variability was modeled using a proportional residual error and exponential model was used for the Inter-Individual Variability (IIV)

Table 1: Population PK parameters estimates

Parameter	Estimate	RSE (%)	IIV - CV (%)
Cl (L/h)	7.65	6.44	15.1
V ₁ (L)	39.3	13.2	21.4
Q (L/h)	12.8	5.95	15.9
V ₂ (L)	178.0	7.19	14.5
σ ² prop - CV(%)	16.2	4.93	-
WT ~ CL	0.75	-	-
WT ~ V ₁	1	-	-
WT ~ Q	0.75	-	-
WT ~ V ₂	1	-	-

Cl = Clearance from central compartment, V₁ = Volume of distribution of central compartment, Q = inter-compartmental clearance, V₂ = Volume of distribution of peripheral compartment, WT = Body Weight, RSE = Relative Standard Error, CV = Coefficient of variation, IIV = Inter-Individual Variability



Conclusions

- The popPK model built on Phase I data provided good results in terms of goodness-of-fit plots (Figure 3) and PK parameters with accurate estimates (Table 1).
- Although fitting reasonably well the observed PK data, the selected popPK model could not perfectly characterize the elimination process at higher exposure. [4,5] Model development will be further investigated at higher exposures with a larger sample size when Phase II data will be available.

References

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