

Allometric and Population Pharmacokinetic Modeling for Human Dose Prediction in a First-in-Human Trial: A Case Study with Retrospective Evaluation



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Background

First-in-human (FIH) clinical trials are designed to assess the pharmacokinetics (PK), tolerability, and safety of an investigational medicinal product in humans [1]. These trials typically follow a stepwise exposure escalation approach, employing single ascending dose (SAD) and multiple ascending dose (MAD) designs. Given the paramount importance of participant safety, dose selection is usually guided by quantitative modeling techniques to predict human exposure based on preclinical data, supplemented by real-time assessments of emerging clinical data to refine subsequent dose levels, if needed.

Quantitative modeling approaches including population pharmacokinetic (popPK) modeling with allometric scaling, play a crucial role in predicting human PK while informing and optimizing key design elements of the FIH trial. These include determining an appropriate starting dose, defining a dose range to be explored that is expected to be safe and efficacious, optimizing the PK sampling schedule, and selecting tablet strengths for manufacturing. Accurate human exposure and dose predictions streamline decision-making and reduce operational burden. Retrospective evaluation of human PK prediction is essential for improving prediction methods and strategies for future candidate drugs [2].

Objectives

This analysis aimed to predict human PK and dose for the FIH trial of GRT6018, a potent and selective agonist of the nociceptin/orphanin FQ peptide (NOP) receptor, supporting the determination of the starting dose and the anticipated therapeutic dose (ATD) range. Additionally, we present a retrospective evaluation of the “pre-trial” exposure predictions.

Methods

Human PK was predicted using an integrated analysis of *in vivo* concentration-time data from multiple animal species, applying a nonlinear mixed-effects modeling approach combined with allometric scaling. PK data were collected from four different animal species (mouse, rat, monkey, and dog) across 11 preclinical studies following intravenous or oral administration of single or multiple doses, up to 35 mg/kg (Table 1). Data analysis was conducted using NONMEM software (version 7.4; ICON Development Solutions), supplemented with the PsN toolkit (version 3.6.2) [3].

Table 1. General outline of the animal data included in the analysis

Species	Route	Dose range (mg/kg)	Nr. of animals
Mouse	IV / PO	1 – 10 mg/kg	18
Rat	IV / PO	1 – 30 mg/kg	49
Monkey	IV / PO	0.2 – 2 mg/kg	6
Dog	IV / PO	0.2 – 35 mg/kg	18
			Total = 91

Following the preclinical popPK model development, clinical trial simulations (CTS) were performed to predict human drug exposure, using the estimated model parameters and assuming a reference body weight of 60 kg and a human oral bioavailability (F) of 35%. Additional data, including plasma protein binding, nonclinical drug biodistribution, and results from native NOP binding assays, were integrated to estimate systemic and tissue target engagement (TE), supporting the determination of the starting dose and the ATD range.

Results

GRT6018 PK was best described by a two-compartment model with linear absorption and elimination (Figures 1 and 2, Table 2). Bodyweight-based allometric scaling was applied to all disposition parameters. The allometric exponents for clearance (CL) and intercompartmental clearance (Q) were fixed at 0.75, while volume parameters (V_c and V_p) were fixed at 1, with no significant difference in results if these exponents were estimated. Extrapolating to human, the predicted human systemic CL and steady-state volume of distribution (V_{ss}) in a 60-kg subject were 28.2 L/h (0.47 L/h/kg) and 184.2 L (3.07 L/kg), respectively, with a predicted terminal half-life of 4.5 h.

Results

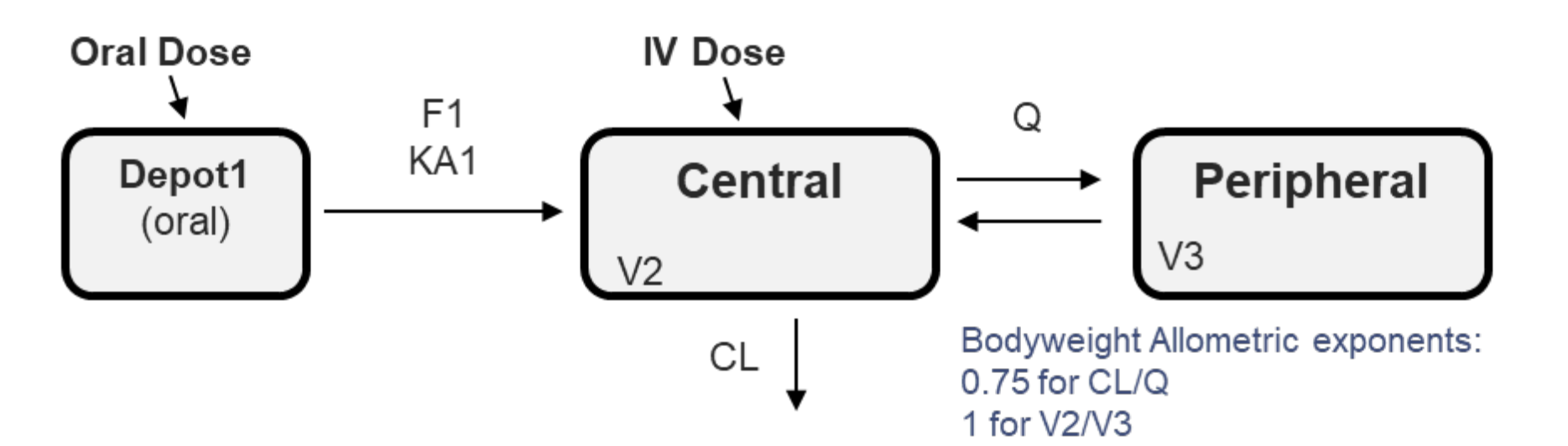
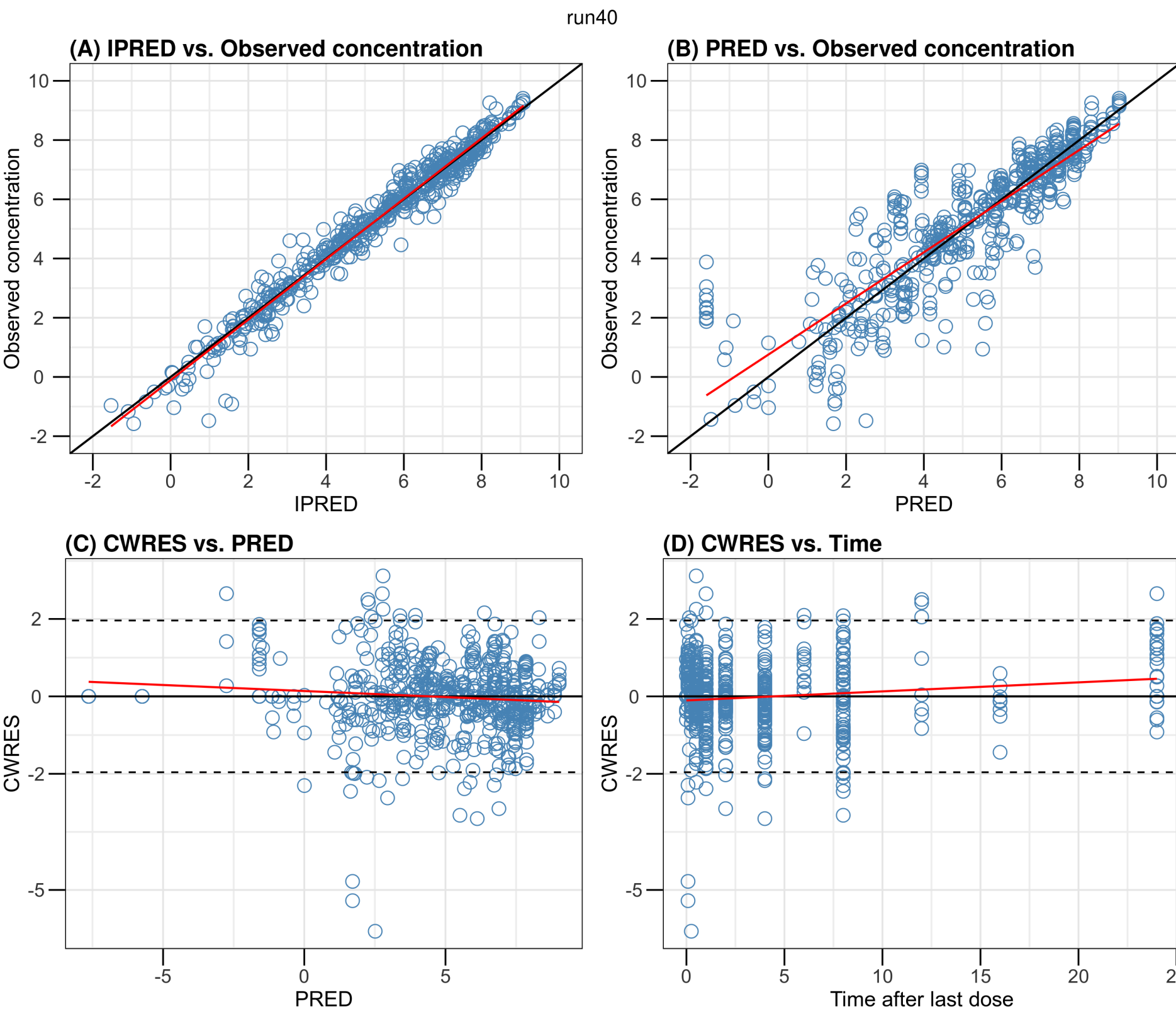


Figure 1. Schematic representation of the allometric popPK model

Table 2. Final Parameter estimates of the preclinical allometric popPK model

	Parameter	Estimate	RSE (%)	95%CI (Shrinkage%)
Fixed Effects	CL (L/h)	1.4	9.9	[1.13-1.67]
	V_c (L)	2.3	8.4	[1.92-2.68]
	KA (1/h)	4.33	30.7	[1.72-6.94]
	Q (L/h)	0.175	16.4	[0.12-0.23]
	V_p (L)	0.765	11.3	[0.6-0.94]
	expKA	-0.183	53.3	[-0.37-0.008]
	F Dog	0.104	16.3	[0.07-0.14]
	F NHP	0.0267	30.3	[0.01-0.04]
	F Mouse	0.766	FIXED	-
	F Rat	0.301	15.2	[0.21-0.39]
Random effects (IIV)	ω^2_{CL}	0.359	21.9	(4.2)
	ω^2_{V2}	0.0837	63.6	(41.3)
	ω^2_{KA}	0.663	65.5	(43.9)
	ω^2_{F1}	0.147	56.2	(57)
Residual Error	σ_{prop}	0.239	7.7	(13)

CL= systemic clearance; V_c = volume of distribution of central compartment; V_p = volume of distribution of peripheral compartment Q= inter-compartmental clearance, KA= absorption rate constant, F= oral bioavailability, NHP=non-human primate IIV= inter-individual variability; Cov= covariance; σ = standard deviation; ω^2 = variance; RSE= relative standard error; CI= confidence interval. Allometric scaling was implemented as TVPAR*WT**exponent. Exponent for CL/Q is 0.75; exponents for $V2/V3$ is 1.



IPRED = individual predicted, PRED = population predicted, CWRES, conditional weighted residuals. Observed concentration versus population predicted (A) and versus population predicted (B), conditional weighted residuals versus population predicted (C) and versus time (D). The black line represents the identity line (in A, B) or the zero line (in C, D), the red line represents a linear regression line.

Figure 2. Basic Goodness of Fit plots for the preclinical popPK model

CTS of the FIH trial supported the selection of a starting dose (1 mg) based on minimal anticipated biological effect level (MABEL) and a TE-guided anticipated therapeutic dose range (20–150 mg).



The observed half-life of GRT6018 across all SAD and MAD cohorts ranged from a mean of 3.6 to 6.5 hours, showing very good agreement with the predicted typical value of 4.5 hours.

Furthermore, predicted concentration-time profiles, and key exposure metrics (maximum concentration [C_{max}], area under the concentration-time curve within the dosing interval [AUC_{tau}] or extrapolated to infinity [AUC_{inf}]) aligned well with observed values (Figures 3, 4 and 5).

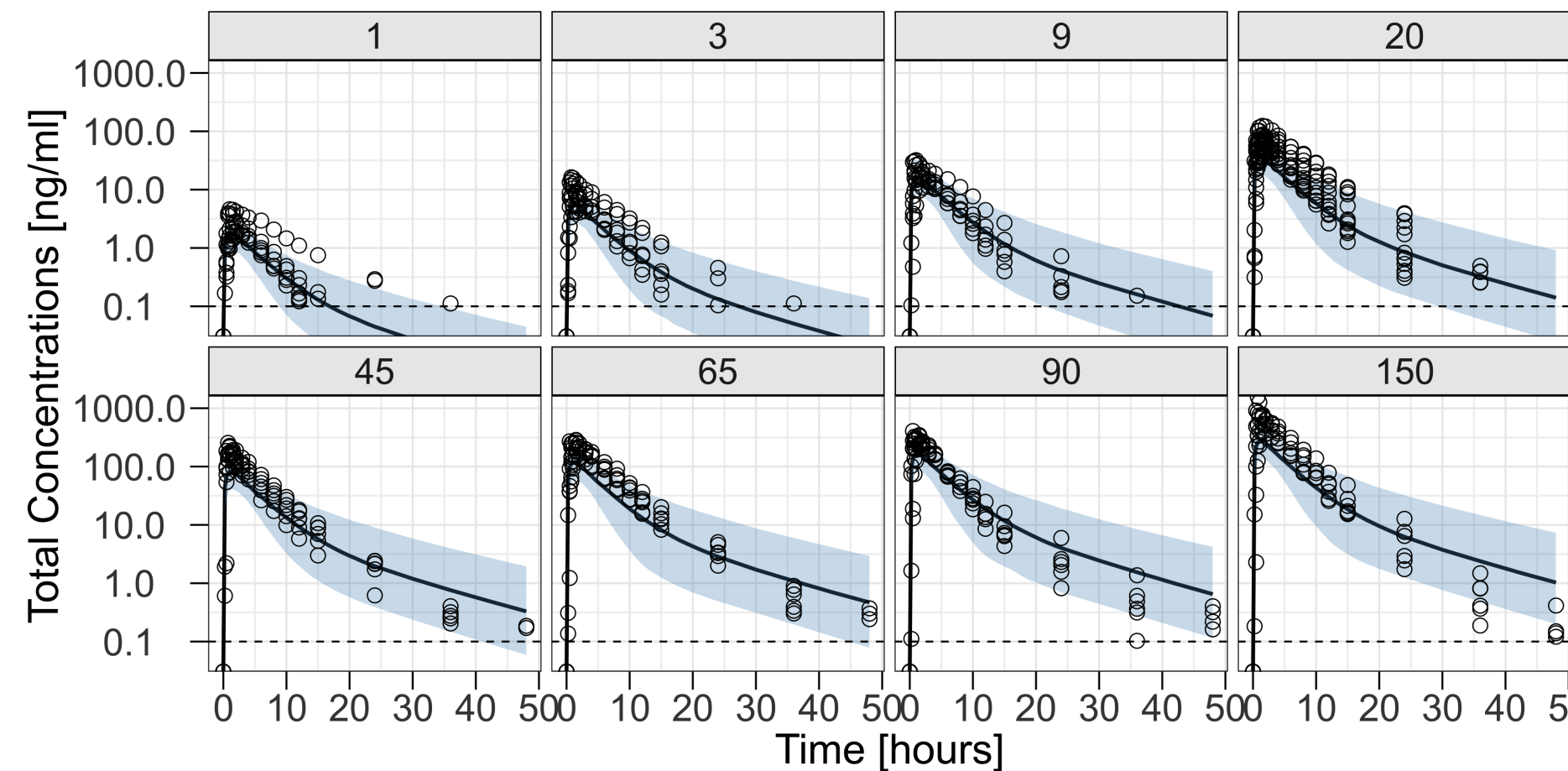


Figure 3. Comparison of “pre-trial predicted” and observed PK profiles of GRT6018 for all SAD cohorts – assumed human oral F =35%

Results

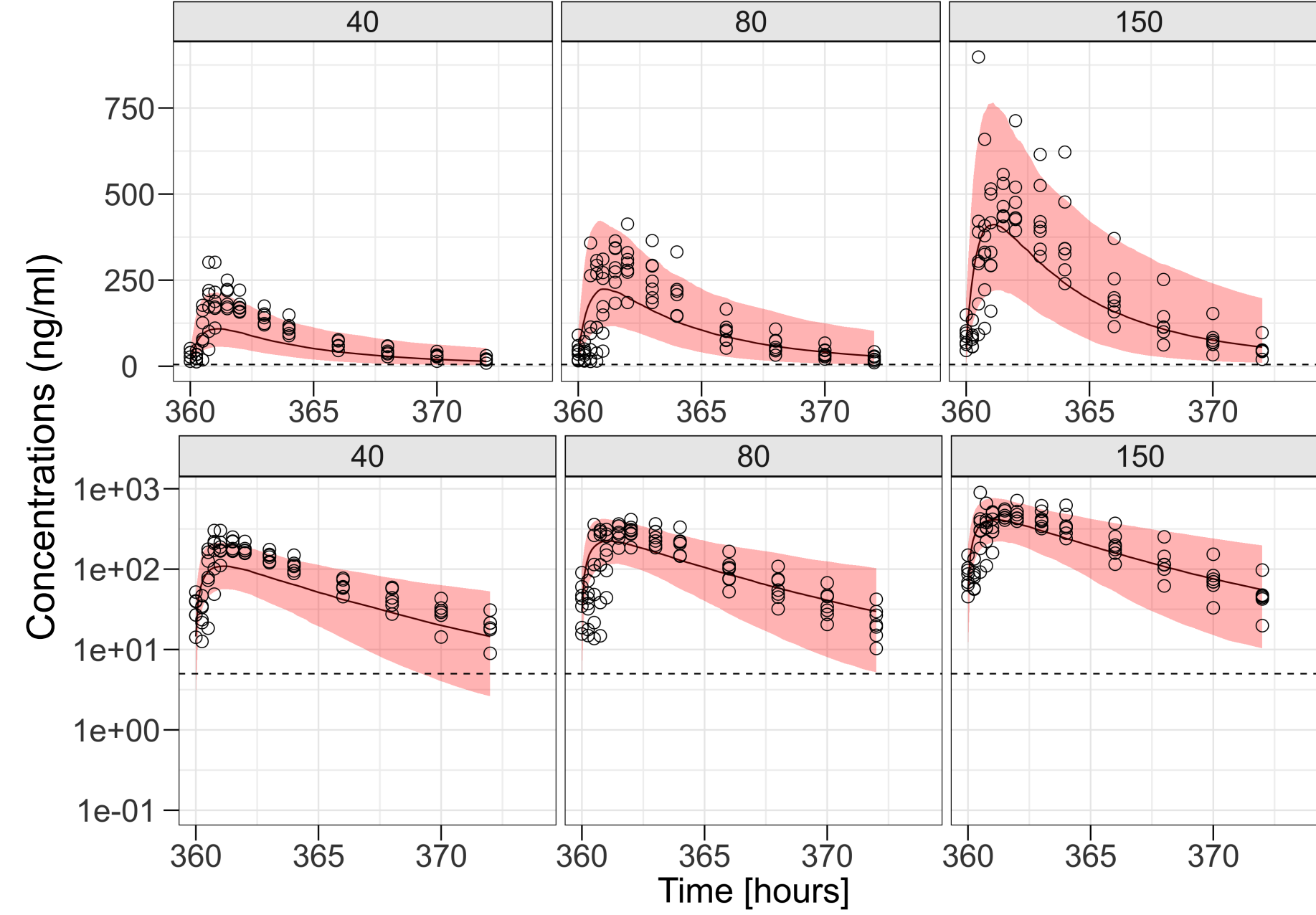


Figure 4. Comparison of “pre-trial predicted” and observed PK profiles of GRT6018 for all MAD cohorts – assumed human oral F =35%

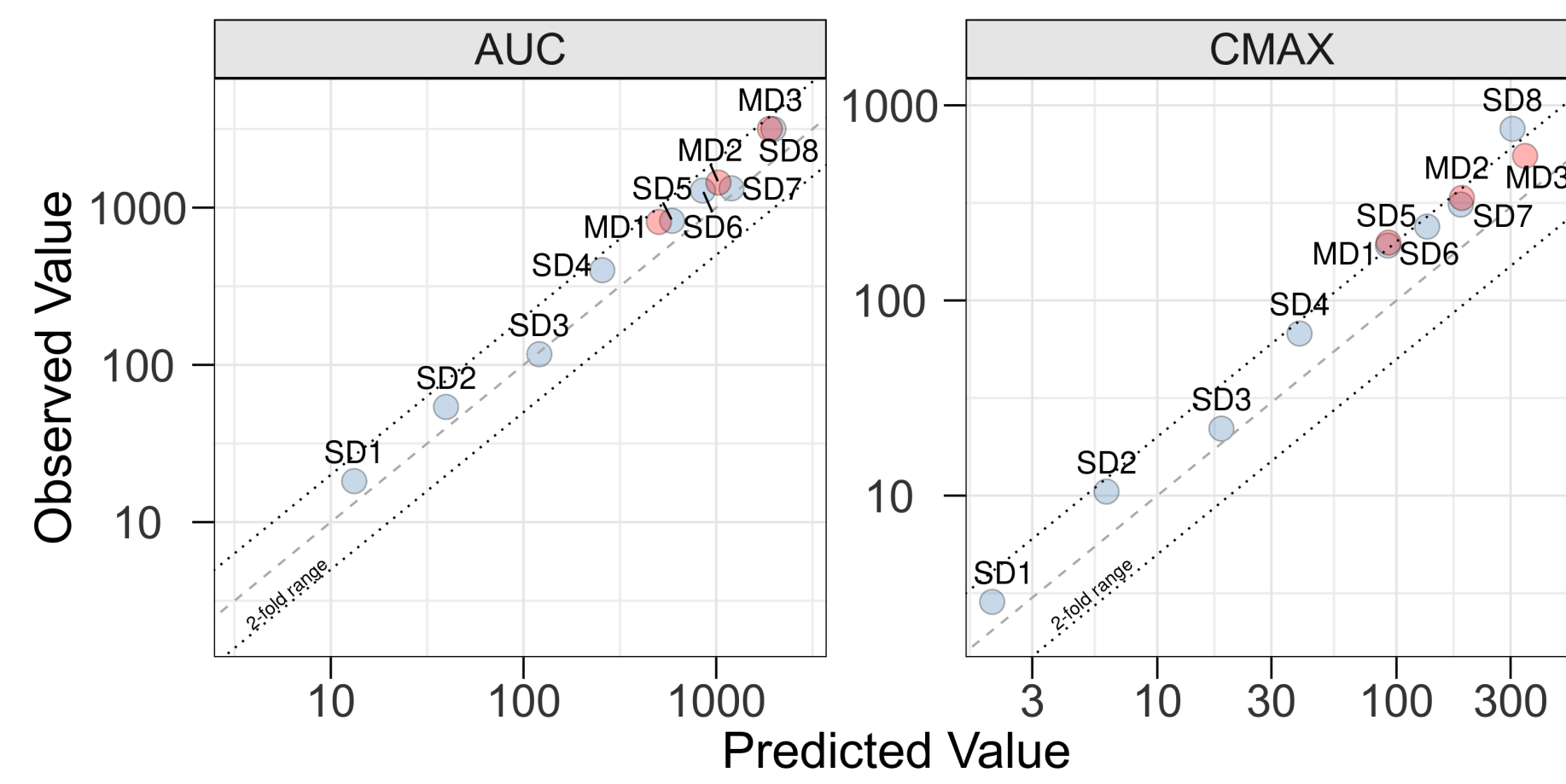


Figure 5. Comparison of “pre-trial predicted” and observed mean values for AUC and C_{max} across all SAD/MAD cohorts – assumed human oral F =35%

Table 3. Observed key exposure metrics and prediction accuracy for GRT6018 across the FIH trial SAD and MAD Cohorts

SAD	Dose (mg)	C_{max} (ng/ml)			AUC_{inf} (h* ng/ml)		
		Mean OBS	PE 1 (%)	PE 2 (%)	Mean OBS	PE 1 (%)	PE 2 (%)
SAD Cohort 1	1	2.9	-28.5	-8.1	18.2	-27.4	-6.6
SAD Cohort 2	3	10.5	-41.5	-24.8	54	-26.7	-5.7
SAD Cohort 3	9	22	-15.9	8.2	116.9	3.4	32.9
SAD Cohort 4	20	67.7	-41.9	-25.3	400	-36	-17.7
SAD Cohort 5	45	191.2	-51.8	-38	824.6	-28.4	-7.9
SAD Cohort 6	65	239	-43.8	-27.7	1283	-33.6	-14.6
SAD Cohort 7	90	310	-40.1	-23	1326.8	-9.5	16.3
SAD Cohort 8	150	757.5	-58.9	-48.1	3153.6	-37.2	-19.2

MAD	Dose (mg)	C_{max} (ng/ml)			AUC_{inf} (h* ng/ml)		
		Mean OBS	PE 1 (%)	PE 2 (%)	Mean OBS	PE 1 (%)	PE 2 (%)
MAD1	40	197	-53.2	-39.8	811	-37.8	-20.1
MAD2	80	335	-44	-27.9	1443	-28.8	-8.5
MAD3	150	550	-37.3	-19.4	3170	-40.1	-23

C_{max} = Maximum plasma concentration; AUC: Area under the plasma concentration-time curve extrapolated to infinity (inf) or within the dosing interval (tau); PE1= prediction error of the ‘pre-trial’ model simulations unadjusted (i.e., assumed F of 35%); PE2= prediction errors of the ‘pre-trial’ simulations adjusted for an assumed F value of 45% (instead of the standard 35%).

The calculated absolute prediction error (APE) for mean C_{max} across all SAD cohorts (Table 3) ranged from 16% to 59% (average 40%) and from 3% to 37% for mean AUC_{inf} (average 25%). Based on interim PK data for the first dose escalation meeting, adjusting assumed F value from 35% to 45% in the simulations improved the prediction accuracy, reducing average APE from 40% to 25% for mean C_{max} and from 25% to 15% for mean AUC_{inf} . Overall, No adjustment to the planned doses for any cohort was required during the trial conduct.

Conclusions

Allometric scaling, combined with popPK modeling and CTS, enables robust translation of preclinical PK data into human PK and dose predictions for FIH trials. This case highlighted the value of allometric popPK modeling for a Biopharmaceutics Classification System Class I compound. Accurate assumptions of oral bioavailability are critical for optimal exposure predictions, suggesting that physiologically based PK modeling may be required to support FIH predictions for drugs with more complex PK profiles, such as those with solubility-limited or non-linear absorption.

References

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- Davies, Michael, et al. Trends in pharmacological sciences 41.6 (2020): 390-408.
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