

Population Pharmacokinetics Modelling of Ibrexafungerp Using Data from Healthy Volunteers

A comprehensive popPK model to describe ibrexafungerp PK profile in HV, providing a foundation to understand ibrexafungerp exposure across varying population profiles and treatment settings



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Introduction

- Ibrexafungerp is a triterpenoid antifungal agent (BCS class 4) that is approved in US for the treatment of vulvovaginal candidiasis (VVC) and reduction in the incidence of recurrent VVC [1,2].
- Multiple routes (intravenous [IV] and oral), formulations, formulation strength as well as food effect were investigated during development of ibrexafungerp.

Aims

- The aims of this analysis were to develop a **comprehensive population pharmacokinetic (popPK) model** of ibrexafungerp to describe the pharmacokinetics (PK) of ibrexafungerp and to quantify the influence of covariates.

Methods

- Data from 12 Phase 1 studies where intensive PK data following IV and oral administration in healthy volunteers (HV) were used (Table 1).
- A **base structural model** was selected based on IV data. Oral data was then incorporated to explore extent and rate of absorption. Different absorption models were considered, e.g. first-order absorption with or without lag-time, and more complex transit models.
- Covariates** including demographic variables (Table 2), formulations and formulation strength, food effect (Table 1).
- NONMEM was used for modelbuilding. The first-order conditional estimation method with interaction (FOCE-I) was used for parameter estimation. Stepwise covariate model (SCM) was used to select the statistically significant and scientifically plausible covariates.
- Model performance was evaluated using goodness-of-fit plots and visual predictive checks.

Results

A total of 7283 observations from HV were included in the popPK model (n=1567 from IV, n=5716 from oral).

Table 1 Summary of study regimens, food effect, formulation and formulation strength, number of subjects, included in popPK analysis

Study number	Route	Regimen	Food effect	Formulation	Formulation strength	N subjects (samples)
SCY-078-106	IV infusion	• Single dose: 30, 60, 125, 250, 375 mg • 60 mg Day 1 (AM) 30 mg on Day 1 (PM), BID 30 mg Day 2,3; • 60 mg on Day 1, then 30 mg QD on Day 2,4	NA	SBECD	NA	28 (828)
SCY-078-101	IV infusion	Single dose: 2.5, 5, 12.5, 25, 50, 75, 100, 125, 150, 200 mg	NA	PEG400	NA	20 (656)
SCY-078-001	Oral	Single dose: 10, 20, 40, 80, 150, 300, 600, 800, 1600 mg	NA	PC	10 mg or 100 mg	16 (655)
SCY-078-002	Oral	QD 300, 600, 800 mg for 10 days QD 800 mg for 20 days	NA	PC	100 mg	24 (717)
SCY-078-003	Oral	Single dose: 500 mg	NA	PC	100 mg	13 (152)
SCY-078-014	Oral	Single dose of 1800 mg (600 mg TID) on Day 1 followed by multiple doses of 500 mg QD on Days 2-7	NA	PC	100 mg	6 (191)
SCY-078-015	Oral	Single dose of 500 mg	High fat meal vs fasted	PC CT	100 mg 250 mg	16 (499)
SCY-078-102	Oral	Single dose of 500 mg	High fat meal vs fasted	CT PT	250 mg 250 mg	23 (877)
SCY-078-103	Oral	• Day 1: 1250 mg QD ; Day 2-8: 750 mg QD • Day 1: 1250 mg QD; Day 2-3 750 mg QD	NA	CT	250 mg	35 (435)
SCY-078-104	Oral	Day 1: 1250 mg QD, day 2-8: 750 mg QD	NA	CT	250 mg	23 (205)
SCY-078-107	Oral	Single dose of 100, 300, 600 mg	Low fat vs high fat vs fasted	CT LT	150 mg 100 mg	32 (1580)
SCY-078-111	Oral	Day 1-2: 750 mg BID, Day 3-7: 750 mg QD	Standard meal*	CT	250 mg	16 (432)

Standard meal: not specified as low-fat or high-fat meal according to FDA guidance, including standard breakfast, lunch, dinner and snacks in-between. QD - once a day; BID - twice a day; TID: three time a day; CT: citrate tablet, LT: lipid dispersion tablet, PC: phosphate capsule, PT: phosphate tablet; SBECD: Sulfobutyl ether derivative of beta cyclodextrin; PEG400: Polyethylene glycol 400 IV diluent

Table 2 Summary of subject demographic included in popPK analysis

Characteristic	IV	Oral	Total
Sex			
Male (n)	41	169	210
Female (n)	7	35	42
Race			
White (n)	18	126	144
Black/African American (n)	29	71	100
Asian (n)	0	1	1
Others (n)	1	6	7
Weight (kg)*	82.5 (55.1-107.2)	78.1 (41.8-104.8)	79 (41.8-107.2)
Age (yrs)*	41.5 (21-50)	32 (18-76)	33 (18-76)

* Data shown as median (min-max)

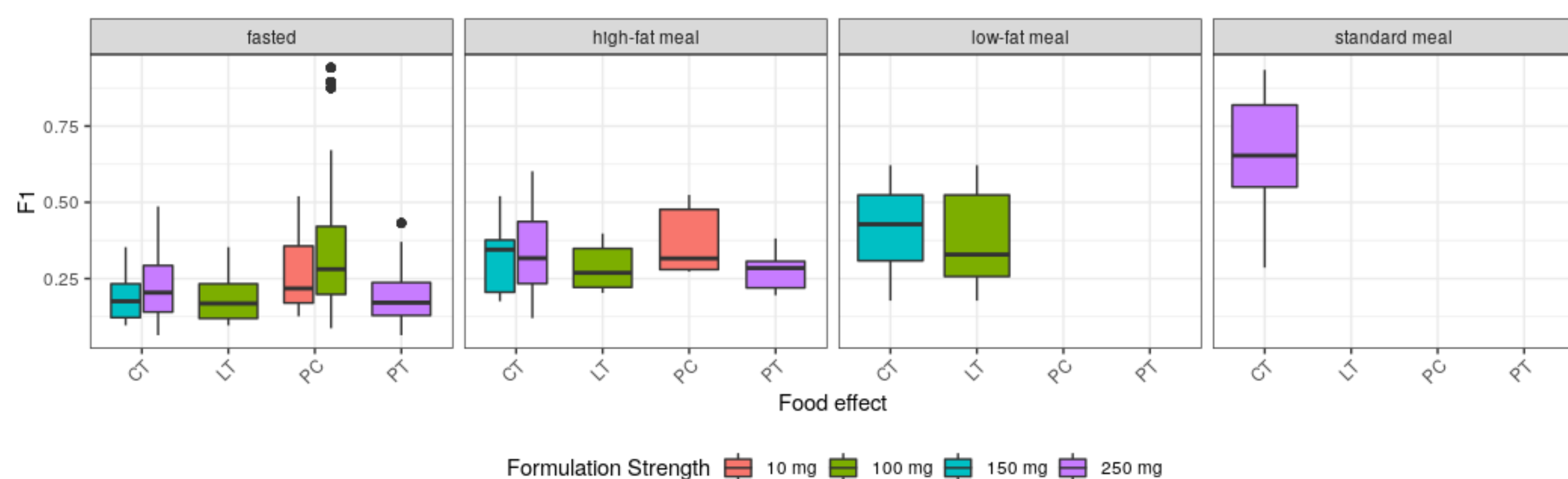


Figure 3 Impact of formulation, formulation strength and food effect on bioavailability of orally administered ibrexafungerp.

Conclusions

- The developed popPK model well described ibrexafungerp PK profile in HV, providing a foundation to understand ibrexafungerp exposure across varying population profiles and treatment settings.
- The impact of covariates on ibrexafungerp was quantified, among which formulation and food effect were significant covariates on both rate and extent of absorption after oral administration of ibrexafungerp

Next Steps

- The underlying mechanisms driving the complex impact of covariates on FI and MTT could be: micelle-mediated solubilization and permeability, effect of pH and ionization of BCS4 compound, it may be addressed by using a Physiologically Based Biopharmaceutic Model [3].
- Sparse PK collected in patients will be added to the model, to understand the impact of disease population on exposure of ibrexafungerp.

References

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Disclosures

QW, AN and SY are employees of GSK and hold financial equities in GSK. This above-study analysis is funded by GSK

- A two-compartment model with first-order elimination, and a transit absorption model best characterised the PK profile (Table 3, Figure 1&2)
- Body weight was a significant covariate on Q and V3, age was a significant covariate on Q.
- Food effect was a significant covariate on FI, formulation and food effect were significant covariates on MTT, formulation strength had no effect on rate and extent of absorption (Figure 3)

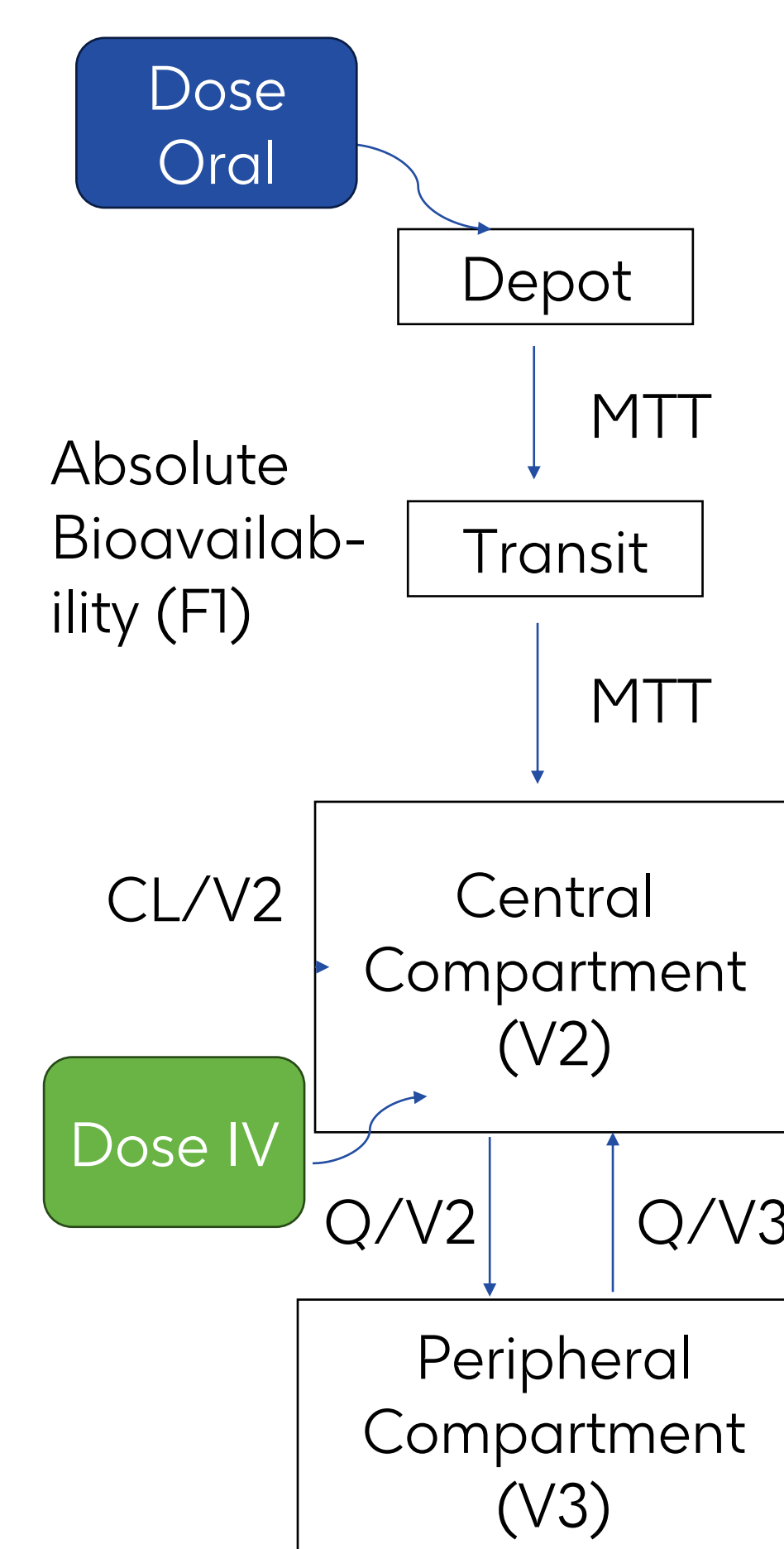


Figure 1 Schematic overview of ibrexafungerp popPK base model

Table 3 PK parameters of final model

PK parameters	Final model		
	Parameter estimates (RSE%)	Interindividual variability (RSE%)	
MTT (1/hr)	θMTT~Phosphate capsule#	0.134 (5%)	29.5% (8%)
	θMTT~Citrate tablet#	-0.245 (20%)	
	θMTT~Phosphate tablet#	-0.679 (28%)	
	θMTT~lipid dispersion tablet#	-0.225 (21%)	
	θMTT~fasted#	0.134 (5%)	
	θMTT~high-fat#	-0.245 (20%)	
	θMTT~standard-meal#	-0.679 (3%)	
CL (L/hr)†		16.6 (4%)	29.1%(15%)
	V2 (L)†	19.8 (4%)	
	Q (1/hr)†	75.9 (3%)	
V3 (L)†	θQ~Age#	-0.301 (27%)	87.6%(11%)*
	θQ~Weight#	0.0104 (13%)	
	θV3~Weight#	0.0105 (19%)	
Flogit	θFlogit~standard-meal#	-1.75 (14%)	0.23
	θFlogit~food#\$	-0.565 (14%)	
FI	FI (Fasted)	0.23	0.367
	FI (standard-meal)	0.714	
	FI (food#\$)	0.367	
Proportional residue error		0.337 (8%)	
Additive residue error (ng/mL)		64.9 (7%)	

#Linear relationship *logit function: FI=exp(FIlogit+ETA)/(1+exp(FIlogit+ETA)) † Parameter evaluated using IV data then fixed with addition of Oral data; \$food effect including both low-fat and high-fat meal.

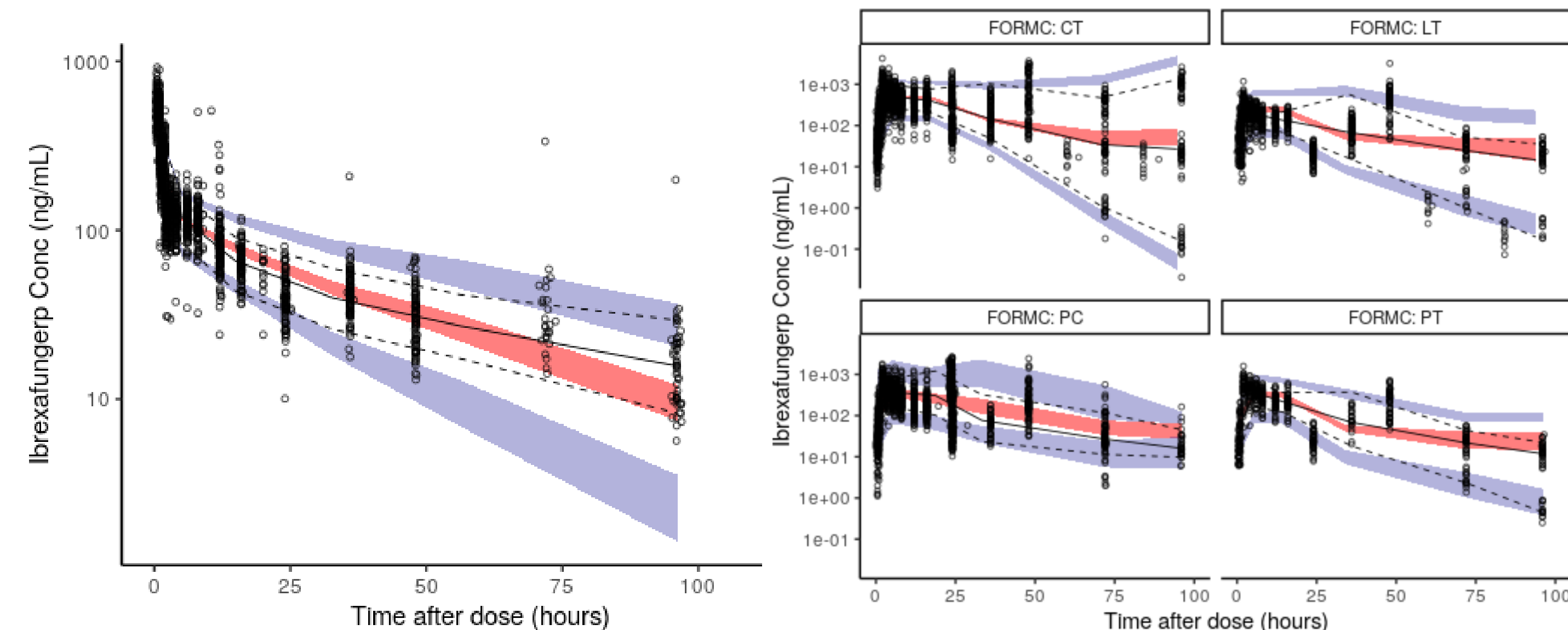


Figure 2 Prediction corrected VPC of final popPK model via IV (left panel) and oral (right panel) stratified by formulation