Population Pharmacokinetic Analyses of Vimseltinib in Healthy Volunteers and Patients With Solid Tumors or Tenosynovial Giant Cell Tumor

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Introduction

- Tenosynovial giant cell tumor (TGCT) is a locally aggressive neoplasm caused by the dysregulation of the colony-stimulating factor 1 *(CSF1)* gene leading to overproduction of CSF1[1]
  - The disease is not always amenable to surgery, and these patients require systemic therapies[1]
- Vimseltinib is an oral, switch-control tyrosine kinase inhibitor designed to selectively and potently inhibit the CSF1 receptor[2]
  - Vimseltinib was approved in February 2025 by the US Food and Drug Administration for the treatment of adult patients with symptomatic TGCT for which surgical resection will potentially cause worsening functional limitation or severe morbidity[3]
  - In September 2025, vimseltinib was also approved by the European Commission for the treatment of TGCT in a similar patient population[4]
- The pharmacokinetics (PK) of vimseltinib were investigated across several clinical trials that used varying dose levels and schedules and included different study populations (healthy participants and patients with malignant solid tumors [MSTs] or TGCT)[5-8]
- This analysis characterizes vimseltinib PK, including the effects of intrinsic and extrinsic factors, in a pooled population of healthy participants and patients with MST or TGCT

Methods

- This study pooled data from 3 clinical trials of vimseltinib (**Table 1**)
- NONMEM v7.5 was used to conduct the population PK (popPK) analysis
- The popPK analysis included exploratory graphical analysis of observations and covariates and the development of a base model
- Body weight was included as a mechanistic covariate; structural and exploratory covariate-parameter relationships were evaluated using the stepwise covariate model building procedure with adaptive scope reduction
- Evaluated covariates included participant characteristics, biomarkers for liver and renal function, dosing regimen, study population (healthy participants, MST, TGCT), and food status (fasted or fed)
- Model performance was assessed by precision of parameter estimates and visual predictive checks (VPCs); the effect of covariates on PK parameters are illustrated by forest plots
- The final PK model was used to simulate vimseltinib plasma concentrations for the different dosing regimens in clinical studies

Table 1. Summary of studies included in the vimseltinib popPK analysis

	Vimseltinib study details	Number of PK samples	Vimseltinib dose regimens
Phase 1/2 DCC-3014-01-001 NCT03069469	Dose escalation and dose expansion in patients with MST and TGCT	2256	50 mg QD (3 days) followed by 20 mg QD 10 mg QD 10 mg QD (5 days) followed by 10 mg BIW 20 mg QD (3 days) followed by 6 mg QD 20 mg QD (5 days) followed by 20 mg BIW 20 mg QD (5 days) followed by 20 mg QW 30 mg BIW 30 mg QD (3 days) followed by 10 mg QD 30 mg QD (5 days) followed by 30 mg BIW 40 mg QD (5 days) followed by 40 mg BIW
Phase 1 DCC-3014-01-002	PK in healthy participants	2967	6 mg single dose 10 mg single dose 30 mg single dose (fasted or fed) 40 mg QD (5 days) 50 mg QD (2 days)
Phase 3 (MOTION) DCC-3014-03-001 NCT05059262	Safety and efficacy in patients with TGCT	976	30 mg BIW

Data cutoff for DCC-3014-01-001: June 27, 2023; data cutoff for DCC-3014-01-002 and DCC-3014-03-001: August 22, 2023.
BIW, twice weekly; MST, malignant solid tumor; PK, pharmacokinetics; popPK, population PK; QD, once daily; TGCT, tenosynovial giant cell tumor.

Results

Demographics and Baseline Characteristics

- The pooled population included 6199 PK observations from 349 adult participants (healthy participants and patients with MST or TGCT), with an average of 17.8 observations per participant
- Baseline characteristics are shown in **Table 2**

Table 2. Baseline characteristics of the pooled population

Characteristic	DCC-3014-01-001 n = 134	DCC-3014-01-002 n = 98	MOTION n = 117[a]	Overall N = 349
Age, years, median (range)	52 (21–91)	38 (20–60)	44 (20–78)	45 (20–91)
Female sex, n (%)	82 (61)	53 (54)	69 (59)	204 (58)
Race, n (%)				
Asian	3 (2)	6 (6)	4 (3)	13 (4)
Black or African American	2 (1)	13 (13)	4 (3)	19 (5)
Multiple or other	10 (7)	1 (1)	0 (0)	11 (3)
Missing	3 (2)	0 (0)	0 (0)	3 (1)
Native Hawaiian or other Pacific Islander	1 (1)	0 (0)	0 (0)	1 (0.3)
White	115 (86)	78 (80)	79 (68)	272 (78)
Unknown or not reported	0 (0)	0 (0)	30 (26)	30 (9)
Study population, n (%)				
Healthy	0 (0)	98 (100)	0 (0)	98 (28)
MST	37 (28)	0 (0)	0 (0)	37 (11)
TGCT	97 (72)	0 (0)	117 (100)	214 (61)
Body weight, kg, median (range)	78.0 (44.0–150)	72.2 (46.1–110)	78.0 (43.0–142)	76.0 (43.0–150)
Albumin, g/L, median (range)	42.3 (29.0–51.0)	45.0 (39.0–51.0)	45.0 (37.0–52.0)	44.0 (29.0–52.0)
ALT, U/L, median (range)	18.5 (5.00–91.0)	16.5 (4.00–54.0)	15.0 (6.00–48.0)	17.0 (4.00–91.0)
AST, U/L, median (range)	20.0 (8.00–66.0)	18.0 (9.00–34.0)	18.0 (8.00–61.0)	18.0 (8.00–66.0)
Total bilirubin, µmol/L, median (range)	7.45 (3.00–21.0)	8.55 (3.40–20.5)	7.00 (3.00–22.0)	7.00 (3.00–22.0)
eGFR, mL/min/1.73 m², median (range)[b]	99.3 (37.7–134)[c]	105 (63.8–144)	103 (58.2–138)	103 (37.7–144)[c]

[a]Patients from MOTION who received at least 1 dose of vimseltinib and had an evaluable PK sample. [b]Calculated using CKD-EPI formula. [c]Three participants had missing values.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MST, malignant solid tumor; PK, pharmacokinetic; TGCT, tenosynovial giant cell tumor.

PopPK Analysis

- Individual observed vimseltinib plasma concentrations up to 7 days after the last dose were included in the PK analysis data set to provide the most representative PK profile for data visualization (**Figure 1**)
  - Profiles of individual observations vs time suggest a relatively rapid absorption followed by slower distribution and elimination
- A 2-compartment with sequential zero and first-order absorption model adequately described the data (**Figure 2**)
- Parameter estimates of the final vimseltinib PK model are presented in **Table 3**

Figure 1. Observed plasma vimseltinib concentration up to 7 days after last dose

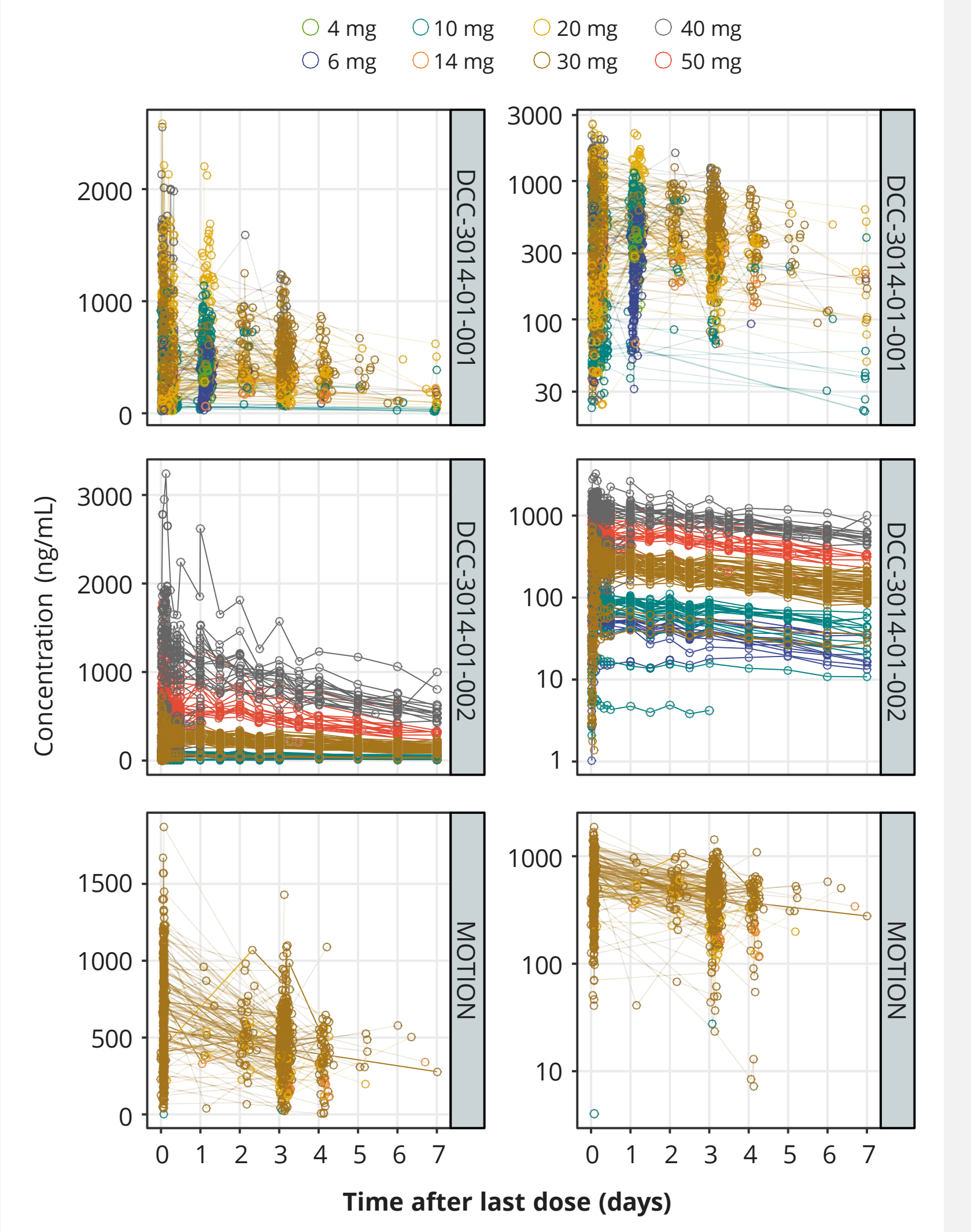
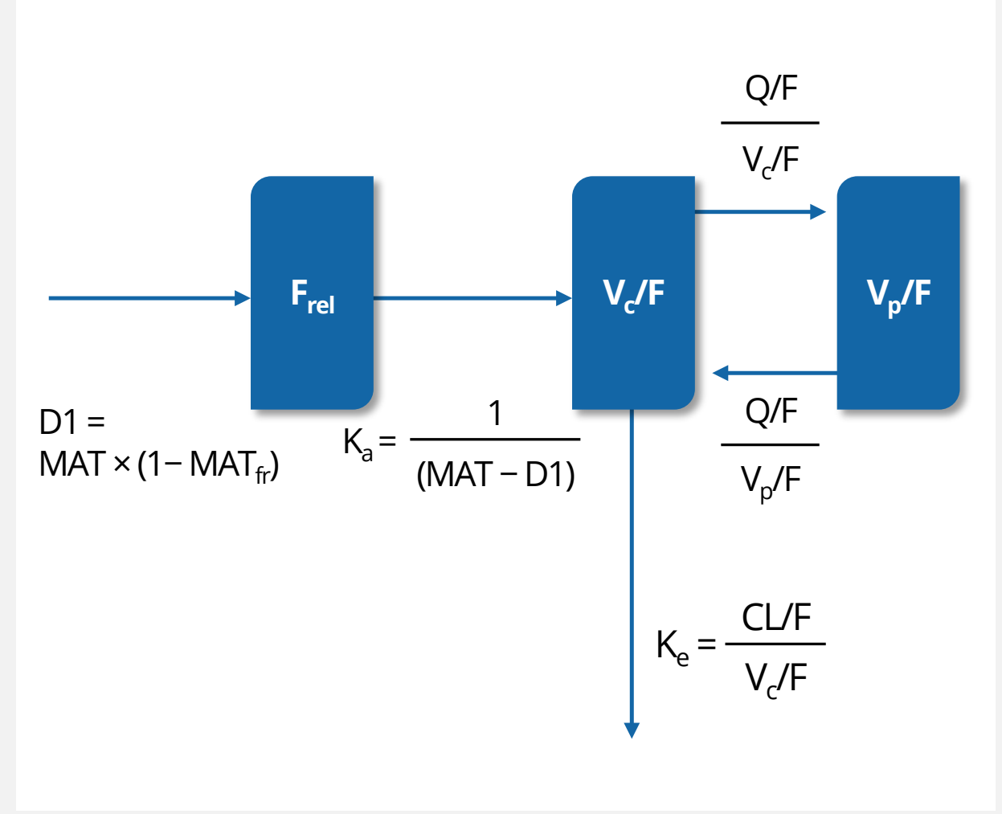


Figure 2. Schema of the final vimseltinib popPK model



Absorption model: sequential zero- and first-order absorption

Disposition model: first-order elimination from the central compartment

Inter-individual model: exponential on CL/F, V_c/F, V_p/F, and MAT; as well as η correlations between the CL/F and V_c/F parameters

RUV model: proportional RUV (implemented as additive on the log-scale) with an exponential inter-individual variability term

CL/F, apparent clearance; D1, duration of zero order input; Frel, relative bioavailability; k_a, first-order absorption rate constant; k_e, first-order elimination rate constant from the central compartment; MAT, mean absorption time; MAT_{fr}, fraction of MAT associated with first order absorption; popPK, population pharmacokinetics; Q/F, apparent intercompartmental clearance; RUV, residual unexplained variability; V_c/F, apparent central volume of distribution; V_p/F, apparent peripheral volume of distribution.

Table 3. Parameter estimates of the final vimseltinib popPK model

Category	Estimate	RSE (%)	SHR (%)
Parameter estimates			
CL/F, L/h	0.612	2.41	
V_c/F, L	88.0	2.25	
V_p/F, L	28.9	4.36	
MAT[a], h	0.713	1.56	
Q/F, L/h	17.1	4.98	
MAT_{fr}[a]	0.434	2.25	
Estimated covariate effects			
Fed food status on MAT[a]	4.77	2.62	
Baseline albumin on V_c/F	−0.0261	18.6	
Healthy participants on V_c/F	−0.293	10.9	
Healthy participants on V_p/F	1.15	8.49	
Black or African American race on V_p/F	0.334	23.6	
Body weight on CL/F	0.750		
Body weight on V_c/F	1.00		
Body weight on V_p/F	1.00		
Body weight on Q/F	0.750		
F_{rel}	1.00		
Interindividual variability			
RUV, CV	0.451	4.04	1.15
CL/F, CV	0.440	3.18	1.83
V_c/F, CV	0.430	3.74	8.34
Correlation CL/F – V_c/F	0.637	4.80	
V_p/F, CV	0.150	18.3	62.6
MAT, CV	1.17	5.09	30.7
RUV, CV	0.240	2.16	1.11

[a]The point estimate for this parameter was fixed in the final model.
CL/F, apparent oral clearance; CV, coefficient of variation; F_{rel}, relative bioavailability; MAT, mean absorption time; MAT_{fr}, fraction of MAT associated with first order absorption; popPK, population pharmacokinetics; Q/F, apparent intercompartmental clearance; RSE, relative standard error; RUV, residual unexplained variability; SHR, shrinkage; V_c/F, apparent volume of distribution of central compartment; V_p/F, apparent volume of distribution of peripheral compartment.

Equation. Final vimseltinib popPK covariates model

Final Covariate model: Body weight on CL/F, V_c/F, V_p/F, and Q/F, food status on MAT, baseline albumin on V_c/F, study population on V_c/F and V_p/F, and race on V_p/F

$$CL/F\ (L/h) = 0.612\ (L/h) \times \left(\frac{WT}{75\ (kg)}\right)^{0.75}$$

$$V_c/F\ (L) = 88.0\ (L) \times \left(\frac{WT}{75\ (kg)}\right)^{1} \times e^{-0.0261 \times (\text{albumin}-44\ (g/L))} \times \begin{cases} 1 & \text{if not healthy participants} \\ 1 - 0.293 & \text{if healthy participants} \end{cases}$$

$$V_p/F\ (L) = 28.9\ (L) \times \left(\frac{WT}{75\ (kg)}\right)^{1} \times \begin{cases} 1 & \text{if not healthy participants} \\ 1 + 1.15 & \text{if healthy participants} \end{cases} \times \begin{cases} 1 & \text{if not Black or African American} \\ 1 + 0.334 & \text{if Black or African American} \end{cases}$$

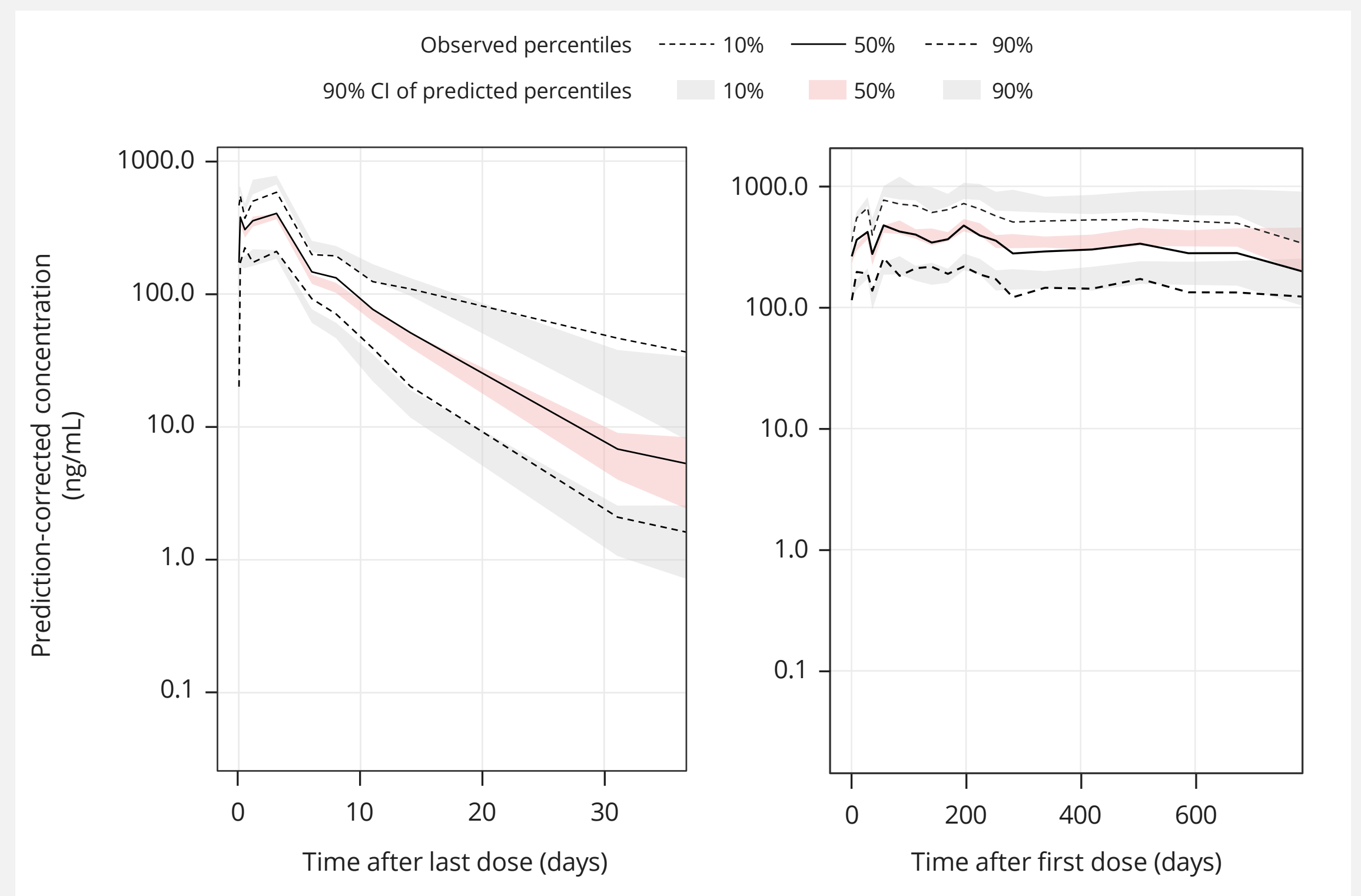
$$MAT = 0.713 \times \begin{cases} 1 & \text{if fasted or missing} \\ 1 + 4.77 & \text{if fed} \end{cases}$$

$$Q/F\ (L/h) = 17.1\ (L/h) \times \left(\frac{WT}{75\ (kg)}\right)^{0.75}$$

CL/F, apparent clearance; MAT, mean absorption time; popPK, population pharmacokinetics; Q/F, apparent intercompartmental clearance; V_c/F, apparent central volume of distribution; V_p/F, apparent peripheral volume of distribution; WT, body weight.

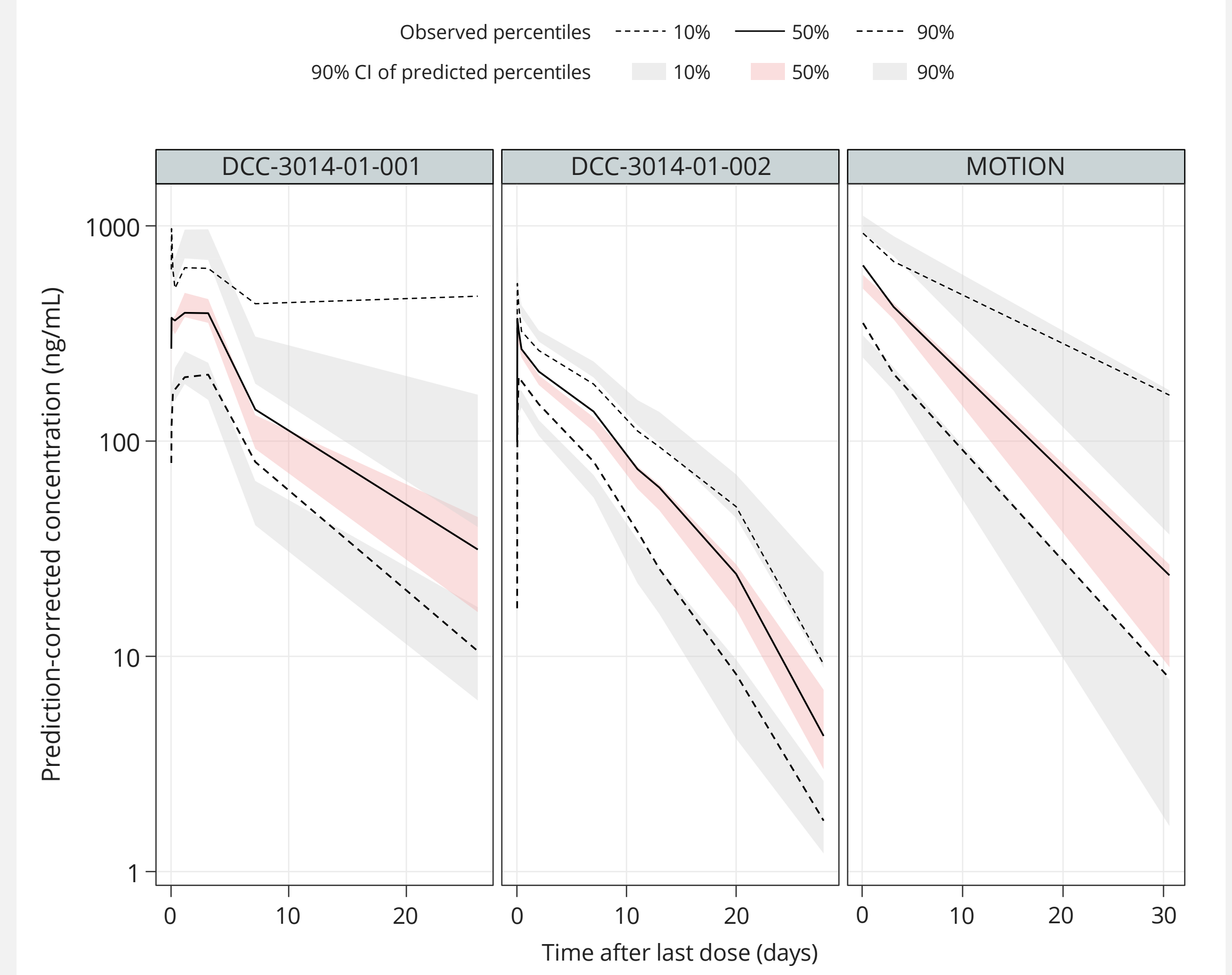
- Prediction-corrected VPCs of vimseltinib plasma concentrations by time after first and last dose indicated the model provided a good description of the observed data (**Figure 3**)
- The final model resulted in robust prediction of vimseltinib exposure across the different dosing regimens administered in the 3 clinical trials (**Figure 4**)

Figure 3. Prediction-corrected visual predictive checks of vimseltinib plasma concentrations



CI, confidence interval.

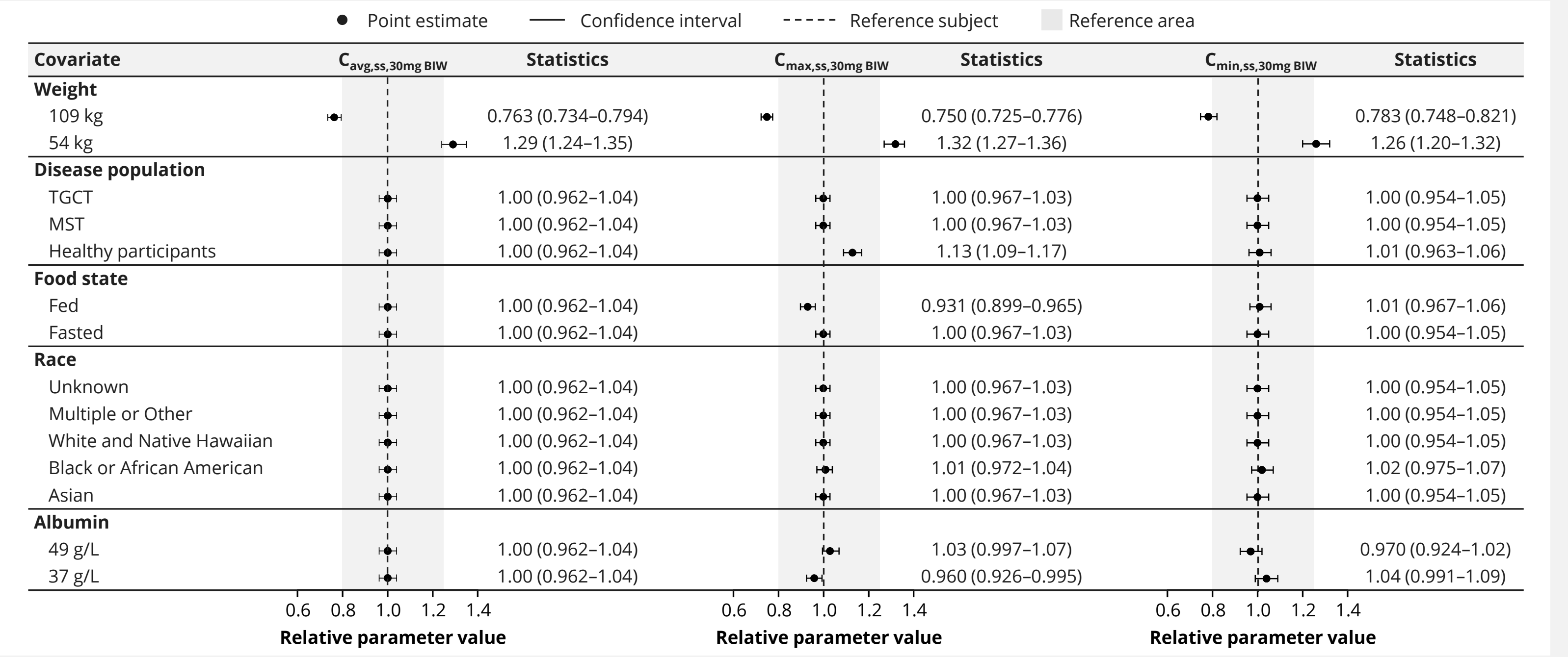
Figure 4. Prediction-corrected visual predictive checks of vimseltinib plasma concentrations, stratified by study



CI, confidence interval.

- Compared with a participant of typical body weight (76 kg), steady-state exposures at the 5th and 95th body weight percentiles slightly exceeded the 80%–125% range (**Figure 5**)
  - Dose adjustments are not warranted based on results of clinical studies and exposure-response analyses
- Food status had a limited effect on steady-state exposure
  - Fed participants had ~6-fold longer mean absorption time than fasted participants
- Other statistically significant covariates had no clinically meaningful effects, with <20% change in steady-state exposures

Figure 5. Forest plots for the effects of covariates on vimseltinib PK parameters at steady state based on the final PK model

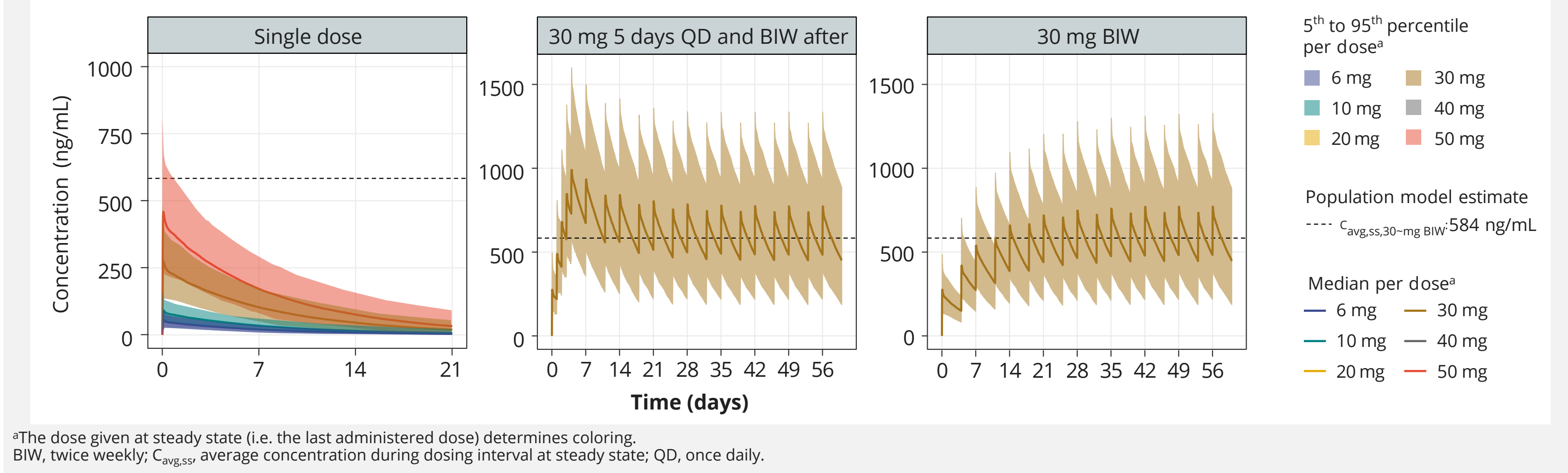


Covariate	$C_{avg,ss,30mg\ BIW}$ Statistics	$C_{max,ss,30mg\ BIW}$ Statistics	$C_{min,ss,30mg\ BIW}$ Statistics
Weight			
109 kg	0.763 (0.734–0.794)	0.750 (0.725–0.776)	0.783 (0.748–0.821)
54 kg	1.29 (1.24–1.35)	1.32 (1.27–1.36)	1.26 (1.20–1.32)
Disease population			
TGCT	1.00 (0.962–1.04)	1.00 (0.967–1.03)	1.00 (0.954–1.05)
MST	1.00 (0.962–1.04)	1.00 (0.967–1.03)	1.00 (0.954–1.05)
Healthy participants	1.00 (0.962–1.04)	1.13 (1.09–1.17)	1.01 (0.963–1.06)
Food state			
Fed	1.00 (0.962–1.04)	0.931 (0.899–0.965)	1.01 (0.967–1.06)
Fasted	1.00 (0.962–1.04)	1.00 (0.967–1.03)	1.00 (0.954–1.05)
Race			
Unknown	1.00 (0.962–1.04)	1.00 (0.967–1.03)	1.00 (0.954–1.05)
Multiple or Other	1.00 (0.962–1.04)	1.00 (0.967–1.03)	1.00 (0.954–1.05)
White and Native Hawaiian	1.00 (0.962–1.04)	1.00 (0.967–1.03)	1.00 (0.954–1.05)
Black or African American	1.00 (0.962–1.04)	1.01 (0.972–1.04)	1.02 (0.975–1.07)
Asian	1.00 (0.962–1.04)	1.00 (0.967–1.03)	1.00 (0.954–1.05)
Albumin			
49 g/L	1.00 (0.962–1.04)	1.03 (0.997–1.07)	0.970 (0.924–1.02)
37 g/L	1.00 (0.962–1.04)	0.960 (0.926–0.995)	1.04 (0.991–1.09)

Reference: 76 kg, albumin 44 g/L, fasted, non-Black or African American, patient with TGCT The 5th and 95th percentiles for body weight are represented by 54 and 109 kg, respectively.
BIW, twice weekly; $C_{avg,ss}$, average concentration during dosing interval at steady state; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum concentration at steady state; PK, pharmacokinetic; TGCT, tenosynovial giant cell tumor.

- Based on simulations using empirical Bayesian estimates, the median effective half-life of the vimseltinib 30-mg twice weekly (BIW) regimen was 124 hours for patients with TGCT from the MOTION trial (**Figure 6**)
  - Simulations based on the full analysis population showed that the approved vimseltinib dosing regimen (30 mg BIW) resulted in a median accumulation ratio of 2.59

Figure 6. Simulated vimseltinib plasma concentrations based on empirical Bayesian estimates



[a]The dose given at steady state (i.e. the last administered dose) determines coloring.
BIW, twice weekly; $C_{avg,ss}$, average concentration during dosing interval at steady state; QD, once daily.

CONCLUSIONS

- The final popPK model adequately described vimseltinib PK in patients with TGCT and enabled robust prediction of individual patient exposure
- Graphical exploration and model diagnostics did not indicate any time-dependent PK effects, and the model was considered appropriate to be used for further exposure-response analysis
- Body weight exerted a noticeable effect and may explain the variability in vimseltinib PK, but dose adjustment for weight is not warranted based on results from clinical studies and exposure-response analyses
- Food decreased the rate of vimseltinib absorption but had minimal effect on steady-state exposures

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DISCLOSURES

All authors are employees of Deciphera Pharmaceuticals, LLC.