

OBJECTIVES

- Enavogliflozin is a selective sodium-glucose cotransporter 2 inhibitor developed for the treatment of type 2 diabetes mellitus (T2DM).
- This study aimed to develop a population pharmacokinetic (PK) model of enavogliflozin to characterize its PK profile, including in individuals with impaired hepatic or renal function. In addition, the study aimed to investigate covariate effects on enavogliflozin pharmacokinetics.

METHODS

- A prior-base model was developed using log-transformed plasma concentration-time data from seven clinical studies conducted in Korean participants with full PK data including five studies in healthy participants and one each in patients with hepatic or renal impairment (Table 1).
- A base model was further refined by incorporating sparse PK data from four additional studies involving Korean patients with T2DM (Table 1).
- The final model incorporated covariates that significantly affect the pharmacokinetics of enavogliflozin. Covariate selection was based on visual inspection followed by statistical testing using stepwise forward selection ($p < 0.05$) and backward elimination ($p < 0.01$), based on the criteria of the objective function value (OFV). Continuous covariate candidates included age, height, weight, body mass index, estimated glomerular filtration ratio (eGFR), aspartate transaminase, alanine transaminase, albumin, total bilirubin, and total protein, while categorical covariates included sex, food status (fasted/fed), T2DM status (T2DM patient/healthy participants), hepatic function (normal/Child-Pugh class A/Child-Pugh class B), and renal function (normal/mild/moderate/severe).
- Model evaluation included assessment of parameter plausibility, OFV comparison, goodness-of-fit (GOF) plots, and visual predictive checks (VPCs) with 1,000 simulations.
- Due to the relatively infrequent occurrence of plasma concentration values below the lower limit of quantitation, these values were regarded as missing values and excluded from the dataset (the M1 approach). Missing covariate values were imputed within each subject using the last observation carried forward method or, when possible, derived from other variables (e.g., eGFR calculated from serum creatinine and age).

RESULTS

- A total of 7,218 measurable plasma enavogliflozin concentration-time data from 446 participants were included in the population PK model development.
- Compared to healthy participants, T2DM patients were older and exhibited reduced renal function (Table 1)

Table 1. Baseline characteristics of the participants

Data type	Full PK dataset used for a prior-base model development							Sparse PK dataset used for a base model development			
	DW_DWP16001_001	DW_DWP306001_101	DW_DWP16001_102	DW_DWP16001_103**	DW_DWP16001_104	DW_DWP16001_105	DW_DWP16001_110**	DW_DWP16001_201	DW_DWP16001_301	DW_DWP16001_302	DW_DWP16001_303
Characteristics	(NCT03364985)	(NCT05321732)	(NCT04064073)	(NCT04221399)	(NCT04343547)	(NCT05414591)	(NCT05747664)	(NCT04014023)	(NCT04632862)	(NCT04634500)	(NCT04654390)
Number of T2DM patients / total participants	0 / 80	0 / 20	0 / 32	22 / 22	0 / 33	0 / 38	2 / 22	17 / 17	48 / 48	66 / 66	68 / 68
Number of PK samples	2,279	640	986	312	1,015	921	354	22	182	245	262
Food status	Fasted & Fed*	Fasted	Fasted	Fasted	Fasted	Fasted	Fasted	Fasted	Fasted	Fasted	Fasted
Age (year)	30.5 ± 6.0	29.3 ± 7.8	33.2 ± 6.2	60.4 ± 10.5	32.2 ± 6.9	33.2 ± 9.8	51.9 ± 7.6	60.8 ± 7.4	63.2 ± 10.7	59.5 ± 12.1	59.9 ± 9.7
Sex, n (%)											
Male	80 (100.0%)	20 (100.0%)	32 (100.0%)	12 (54.5%)	33 (100.0%)	38 (100.0%)	10 (45.5%)	10 (58.8%)	26 (54.2%)	39 (59.1%)	41 (60.3%)
Weight (kg)	70.9 ± 7.7	72.7 ± 10.5	69.5 ± 8.1	66.9 ± 10.7	71.9 ± 7.2	72.0 ± 8.1	64.5 ± 12.3	63.8 ± 8.7	67.4 ± 11.5	69.4 ± 11.0	67.7 ± 10.7
HbA1c (%)	NA	NA	NA	6.8 ± 0.8	NA	NA	NA	7.7 ± 1.0	7.7 ± 0.6	7.8 ± 0.7	7.8 ± 0.7
eGFR (mL/min/1.73 m ²)	101.9 ± 10.3	100.0 ± 7.8	111.6 ± 14.9	65.4 ± 32.5	109.4 ± 9.6	111.0 ± 17.5	96.2 ± 15.9	87.4 ± 9.6	84.8 ± 17.3	87.7 ± 18.8	87.7 ± 16.9

*In DW_DWP16001_001, 8 participants provided pharmacokinetic samples after enavogliflozin administration in both fed and fasted states, while the remaining 72 participants did so in the fasted state only.

**DW_DWP16001_103 was conducted in patients with renal impairment, DW_DWP16001_110 in patients with hepatic impairment.

Data are expressed as the number of participants (percentage) or mean ± standard deviation.

Abbreviations: T2DM, type 2 diabetes mellitus; PK, pharmacokinetic, HbA1c, Hemoglobin A1c; eGFR, estimated glomerular filtration rate using MDRD formula; NA, not available

- A three-compartment model with zero-order absorption and first-order elimination adequately described the pharmacokinetics of enavogliflozin (Figure 1). Age was identified as a significant covariate for apparent clearance (CL/F), and food status for duration of zero-order absorption (D1).

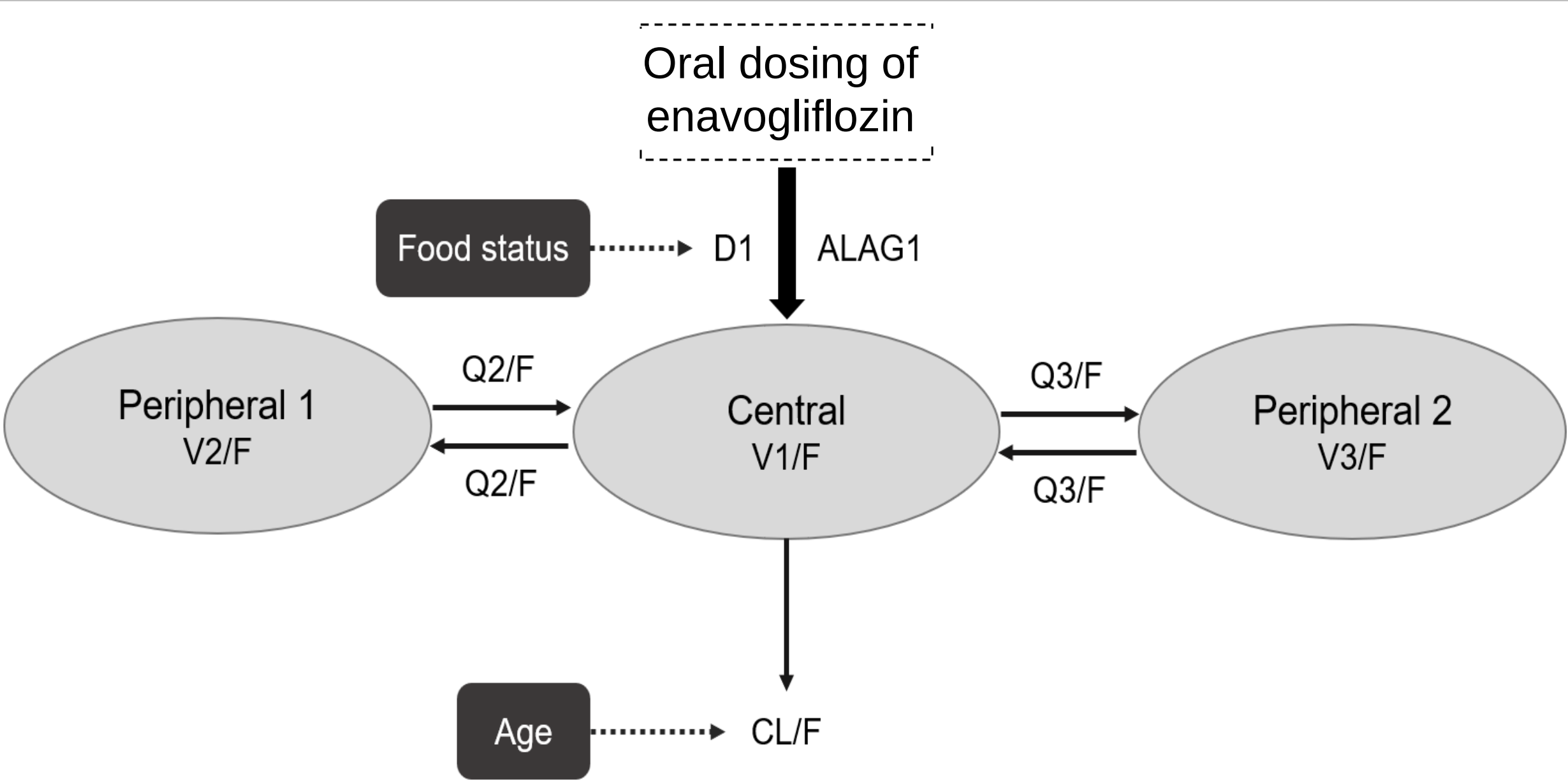


Figure 1. A structure of the final population pharmacokinetic model of enavogliflozin

Table 2. Parameter estimates for the final population pharmacokinetic model of enavogliflozin

Parameter	Unit	Estimate	RSE (%)	IIV (%)	IIV RSE (%)
Duration of zero-order absorption (D1)	h	0.939 FIX	-	-	-
- Food status on D1*		10.3 FIX	-	-	-
Absorption lag-time (ALAG1)	h	0.206 FIX	-	42.8 FIX	-
Apparent clearance (CL/F)	L/h	7.11	2	28.1	6
- Age on CL/F**		-0.0053	4	-	-
Apparent central volume of distribution (V1/F)	L	46.4	23	37.7	5
Apparent inter-compartmental clearance between central and peripheral 1 compartment (Q2/F)	L/h	1.3 FIX	-	-	-
Apparent peripheral 1 volume of distribution (V2/F)	L	41.4	22	63.1 FIX	-
Apparent inter-compartmental clearance between central and peripheral 2 compartment (Q3/F)	L/h	7.35 FIX	-	-	-
Apparent peripheral 2 volume of distribution (V3/F)	L	44.4 FIX	-	32.3 FIX	-
Correlation between CL/F and V1/F	-	67	-	-	-
Additive error for full pharmacokinetic data	-	0.272	9	-	-
Additive error for trough pharmacokinetic data	-	0.425	8	-	-

* D1 (h) = 0.939 · (1 + 10.3 · FOOD), FOOD=0 (fasted) or 1 (fed)

** CL/F (L/h) = 7.11 · (AGE / 46.89)^{-0.0053}

Abbreviations: RSE, relative standard error; IIV, interindividual variability

- The GOF plots showed that the model-predicted concentrations were generally in agreement with the observed concentrations (Figure 2). And the prediction-corrected VPC plots showed that the median, 5th and 95th percentiles of the observed data were well captured by the 95% confidence intervals for the corresponding percentiles of the simulated data (Figure 3).

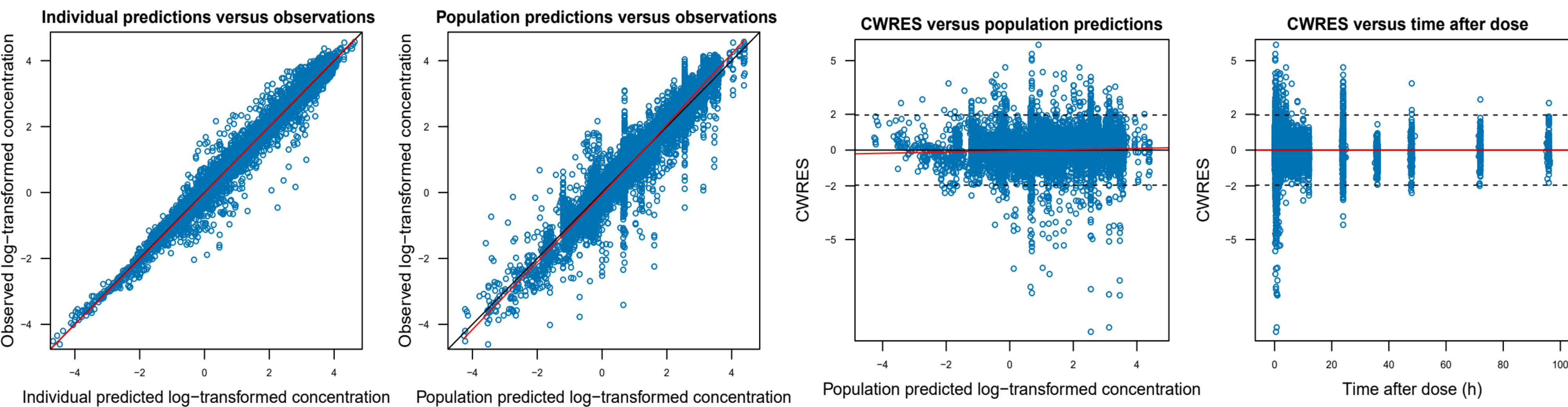


Figure 2. Goodness of fit plots for the final population pharmacokinetic model of enavogliflozin

Abbreviations: CWRES, Conditional weighted residuals

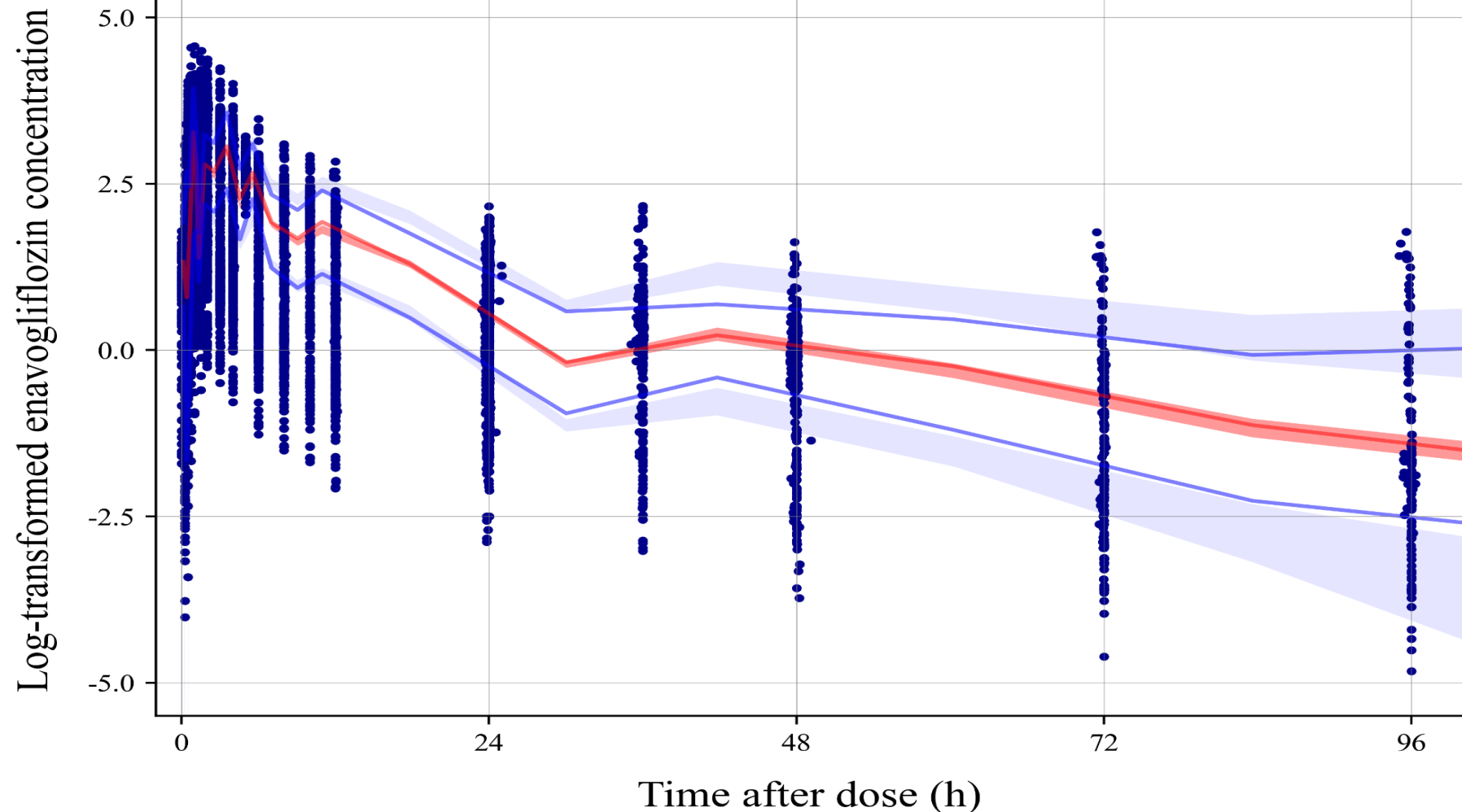


Figure 3. Prediction-corrected visual predictive check plots for the final population pharmacokinetic model of enavogliflozin

The circles represent the observed log-transformed plasma concentrations of enavogliflozin. Red and blue lines show the observed 50th, 5th, and 95th percentiles; shaded areas indicate the 95% confidence intervals of simulated percentiles.

CONCLUSION

- Enavogliflozin pharmacokinetics were adequately described by a three-compartment model with zero-order absorption and first-order elimination. Age significantly affected CL/F, and food status influenced D1. Model evaluation confirmed the reliability of the final population PK model.
- This model will be used to provide a scientific basis for dose optimization and personalized treatment strategies in patients with impaired renal or hepatic function. In addition, as the model was developed using data from Korean subjects, it may serve as a basis for future bridging studies that consider ethnic factors, supporting global regulatory strategies in line with the ICH E5 guideline.