

POPULATION PHARMACOKINETIC MODELING OF VVZ-149 AND ITS ACTIVE METABOLITE IN HEALTHY VOLUNTEERS

BACKGROUND & OBJECTIVE

- **VVZ-149, a dual antagonist on GlyT2 and 5HT_{2A}, is an investigational analgesic product targeted for post-operative pain.**
- **The clinical therapeutic concentration range of VVZ-149 including its active metabolite (VVZ-368) was expected to be 600 – 1900 µg/L, according to the preclinical study results.**
- **The aim of this study was to develop a population PK model for VVZ-149 and VVZ-368.**

DATASET

Data from a Phase I study of VVZ-149 was used for population pharmacokinetic analysis.

Demographic characteristics

Healthy Korean male subjects were enrolled the study. The demographic characteristics of subjects were within the range of 20 to 40 years (age), 1.63 to 1.86 m (height), 54.7 to 87.6 kg (body weight), and 19.1 to 26.1 kg/m² (BMI).

Extent of exposure

	Single dose study						Multiple dose study	
Dose of VVZ-149	0.25 mg/kg	0.5 mg/kg	1 mg/kg	2 mg/kg	4 mg/kg	6 mg/kg	8 mg/kg	
Number of subjects	3	3	6	6	6	6	6	7

Blood samples

Serial blood samples were collected to analyze plasma concentration of VVZ-149 and VVZ-368. A total of 2,042 plasma concentrations were pooled to develop a population PK model.

METHOD

- **Software**
: Nonlinear mixed-effects method in NONMEM (ver. 7.3).
- **Estimation**
: First-order Conditional Estimation method with Interaction (FOCE-I).
- **Model selection criteria**
: Likelihood Ratio Test (LRT), Akaike Information Criterion (AIC).
- **Model evaluation**
: bootstrap method (resampling 1000 times), visual predictive check (VPC).

RESULTS

- The final model consisted of 3 compartments: central (1) and peripheral (2) for VVZ-149 and central for VVZ-368 (3). All transfers were described with first-order processes.
- The central volume of distribution of VVZ-368 was set equal to that of VVZ-149.
- The creatinine clearance was the only selected covariate in the model and it had positive relationship with CL.
- Model evaluation by bootstrapping and VPC suggested that the proposed model was adequate, robust, and stable, and the parameters were estimated with good precision.
- From the simulation of multiple intermittent IV infusion regimen, administering total daily dose divide by more than 3 times a day had higher probability to maintain target therapeutic concentration of VVZ-149.
- The continuous IV infusion of VVZ-149 was the most appropriate regimen to maintain target therapeutic concentration, but the required total daily dose was higher than the intermittent IV infusion regimens.

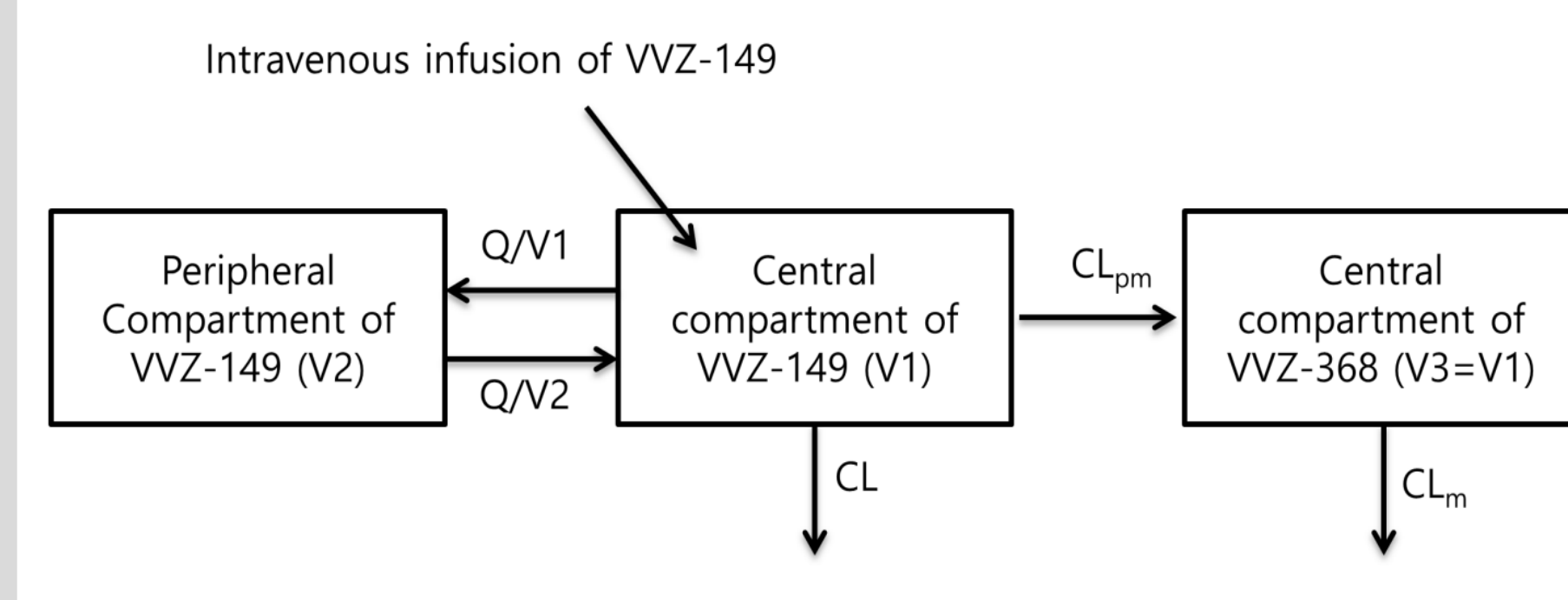


Figure 1. Final model scheme for compartmental pharmacokinetic analysis.

Parameters	Final model		Bootstrap result	
	Estimate (RSE%)	IIV (RSE%)	Median [95% CI]	IIV [95% CI]
CL	48.8 (2.8%)	18.6% (10.1%)	49 [46.5 - 52]	18.1% [14.2% - 22%]
V1	19 (15.4%)	34.7% (14.5%)	18.9 [0.9 - 24.8]	34.1% [23.9% - 44.6%]
V2	78.5 (5.1%)	22.1% (8.6%)	79.1 [70.7 - 97.8]	21.8% [17.8% - 25.4%]
Q	88.5 (10.1%)	.	88.7 [73.8 - 139.9]	.
CL _m	2.73 (15.6%)	.	2.73 [0.14 - 3.55]	.
CL _{pm}	1.01 (16.7%)	46.8% (10.7%)	1 [0.05 - 1.34]	45.8% [35.3% - 56.6%]
CL _{CR} on CL	0.51 (34.3%)	.	0.52 [0.16 - 0.85]	.
Proportional residual error of VVZ-149	16% (5.8%)	.	16% [0.14% - 0.18%]	.
Proportional residual error of VVZ-368	20.8% (6.5%)	.	21% [0.18% - 0.23%]	.

RSE, relative standard error (%); IIV, inter-individual variability (coefficient of variation, %); CL, clearance of VVZ-149 (L/h); V1, central volume of distribution (L); Q, inter-compartmental clearance (L/h); V2, peripheral volume of distribution (L); CL_{pm}, metabolic clearance of VVZ-149 converted into VVZ-368 (L/h); CL_m, clearance of VVZ-368 (L/h); CL_{CR}, creatinine clearance. The relationship of CL_{CR} with CL were modeled using power model and the CL_{CR} was centered at the median values.

Table 2. Model parameter estimates and bootstrapping results.

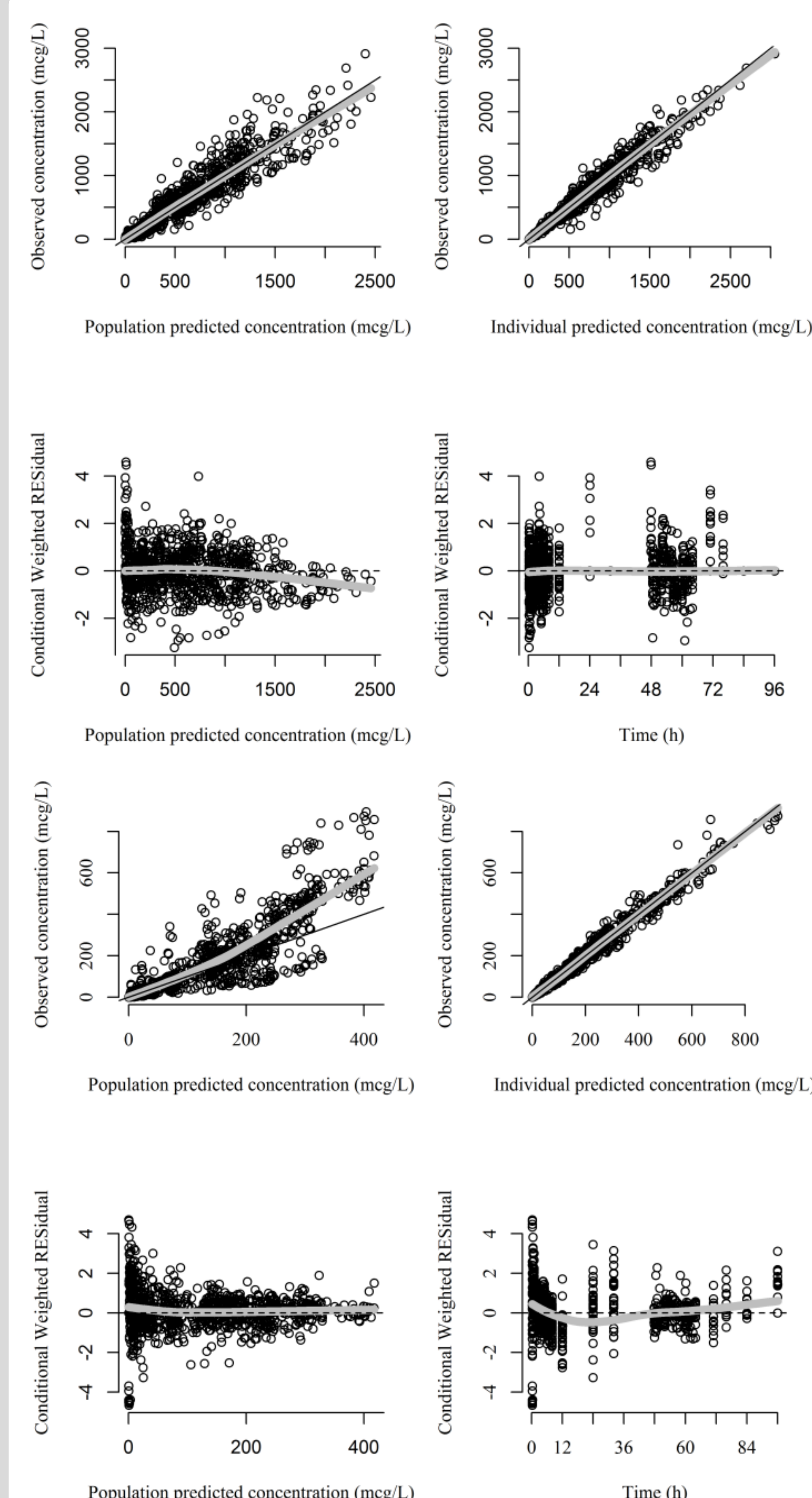


Figure 2. Basic goodness-of-fit plots of the VVZ-149 and VVZ-368 (upper and lower, respectively).

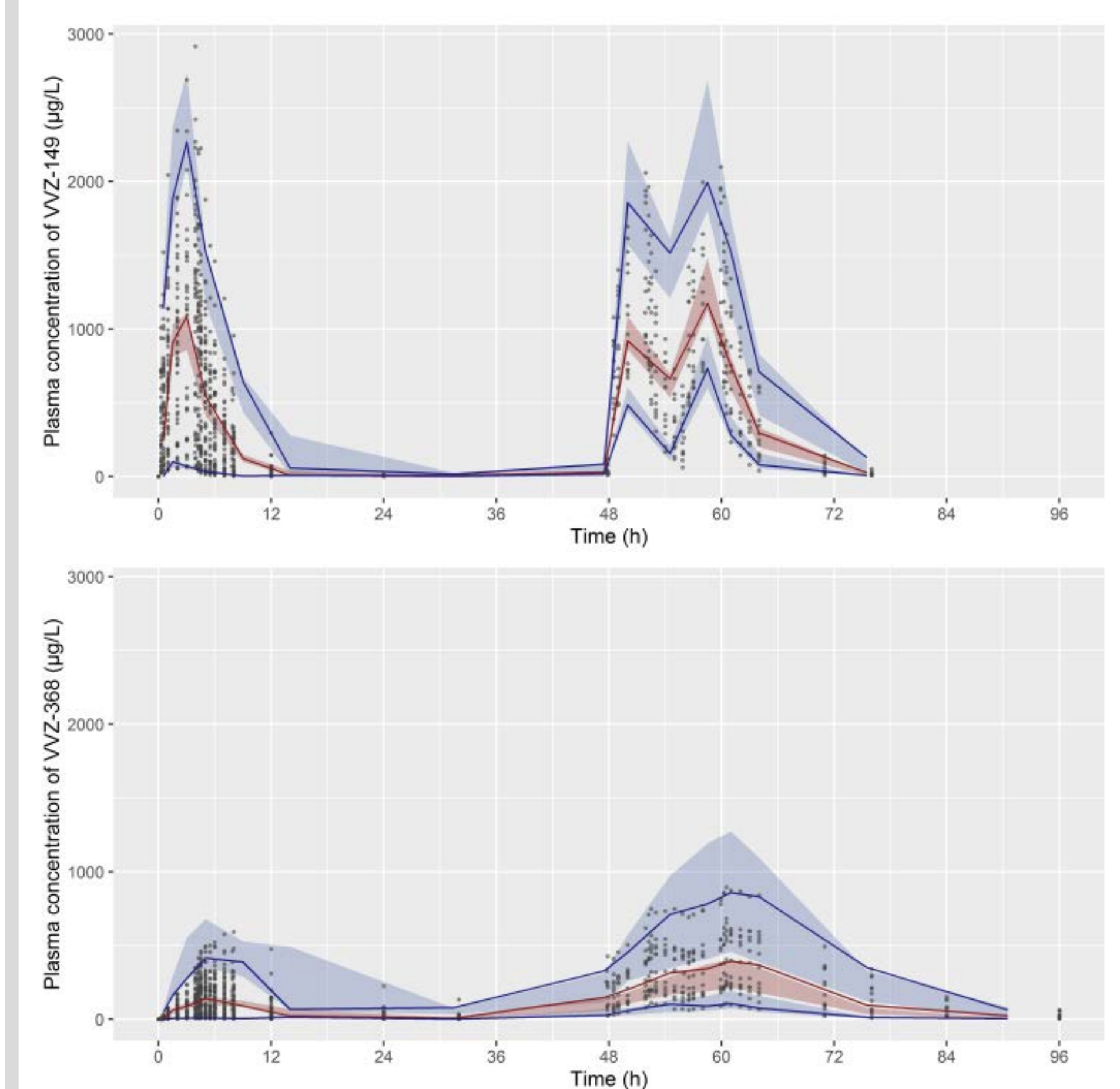


Figure 3. Visual predictive check of the final PK model. Filled circles represent observed concentrations. The lines represent the median (red), 5th and 95th percentiles (blue) of observed concentration. The shaded areas represent the 95% confidence intervals for the median (red), 5th and 95th percentiles (blue) of the simulated concentrations.

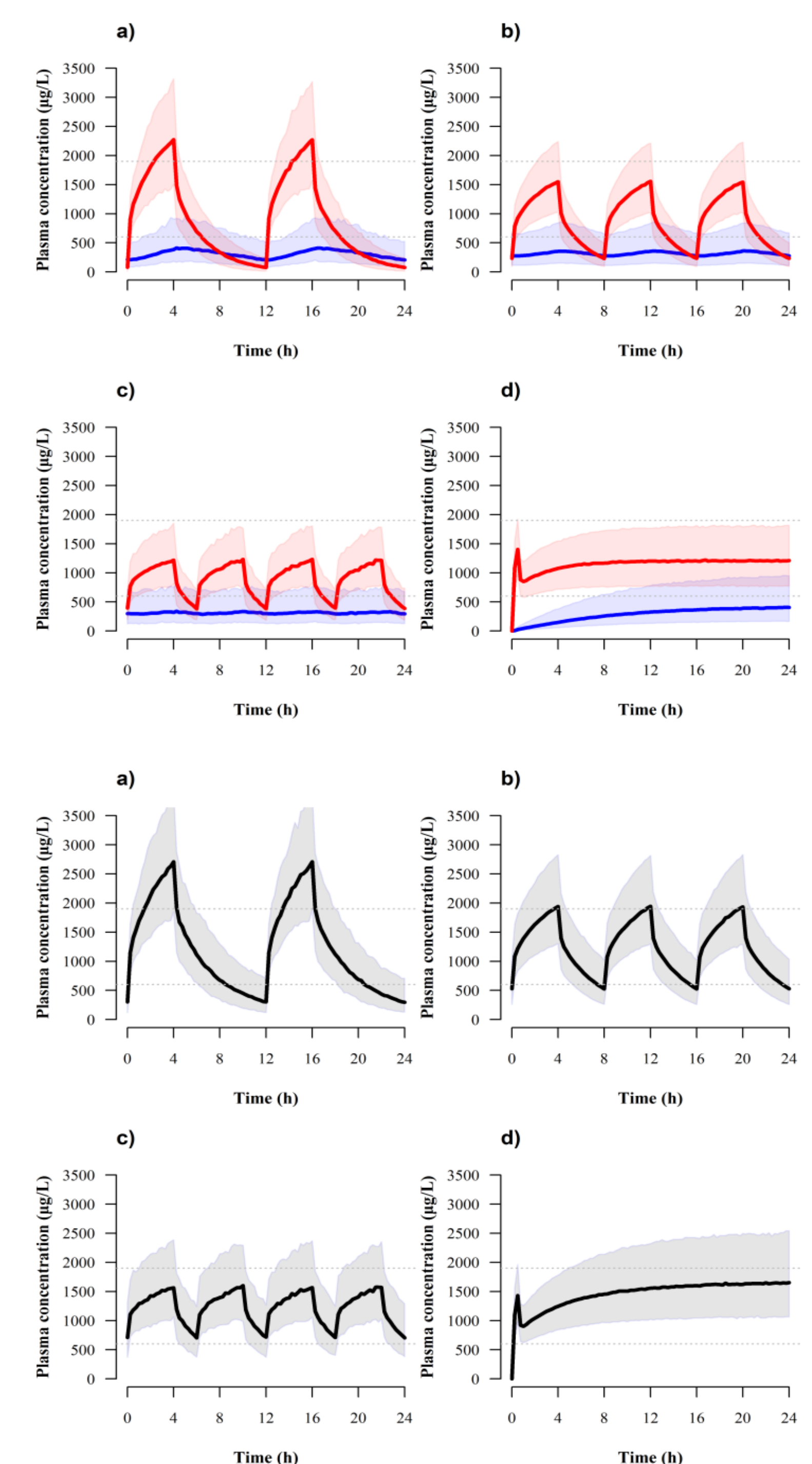


Figure 4. Simulation result of various dosing scenarios. Figure a, b and c is steady-state plasma concentration of VVZ-149 and VVZ-368 after multiple intermittent IV infusion of VVZ-149 for 4 hours. A total 16mg/kg/day dose of VVZ-149 were administered divided by 2, 3 and 4 times (a, b and c, respectively). Figure d is proposed loading-maintenance dose scenario (loading dose: 2.6 mg/kg/h for 0.5 h; maintenance dose: 0.9 mg/kg/h). Red: VVZ-149, blue: VVZ-368, grey: VVZ-149 + VVZ-368, line: median prediction, area: 95% prediction interval, hair line: expected effective concentration range based on non-clinical study result.

CONCLUSION

- The final model adequately described the observed plasma concentrations of VVZ-149 and VVZ-368 in healthy male subjects. The simulated dose regimen can be applied in further drug development.