

A Population Pharmacokinetic-Pharmacodynamic Analysis of Fimasartan in Patients with Mild to Moderate Essential Hypertension



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Abstract

OBJECTIVES

- Fimasartan is a novel nonpeptide angiotensin II receptor antagonist with a selective AT₁ receptor blockade effect. The objective of this study was to develop a population pharmacokinetic-pharmacodynamic (PK-PD) model, which can adequately describe and predict the PK-PD profiles of fimasartan in patients with mild to moderate hypertension.

METHODS

- A total of 1,438 fimasartan plasma concentrations and 759 blood pressure measurements from 42 healthy subjects and 59 patients with mild to moderate essential hypertension (assigned to one of the following dose groups: placebo, 20 mg, 60 mg and 180 mg) were pooled to develop a population PK-PD model using the nonlinear mixed-effects method in NONMEM (ver. VI).

RESULTS

- A two-compartment linear model with mixed zero- and first-order absorption and first-order elimination was chosen as the final PK model. The typical values of apparent clearance (CL/F), apparent central volume of distribution (V₂/F) and fraction absorbed via first-order process (F₁) were 176 L/h, 371 L and 56.4%, respectively.
- The final PK-PD model was a random baseline effect compartment model with placebo response. The equilibrium rate constants for the effect compartment were 0.052 and 0.0263 hr⁻¹ for DBP and SBP, respectively. The maximum blood pressure reduction effects were estimated to be 20.9 and 38.8 mmHg for DBP and SBP, respectively. The plasma concentrations at 50% of maximum effect were 23.3 and 30.2 ng/mL for DBP and SBP, respectively.

CONCLUSION

- The final PK-PD model of fimasartan adequately described the observed blood pressure profiles in patients with mild to moderate hypertension. The model developed in this study could be applied in guiding further clinical development of fimasartan.

Background

- Fimasartan (BR-A-657) is a novel nonpeptide angiotensin II receptor antagonist with a selective AT₁ receptor blockade effect, currently being developed as an antihypertensive agent by Boryung Pharm.

Study Objectives

- To develop a population pharmacokinetic-pharmacodynamic (PK-PD) model, which can adequately describe and predict the PK-PD profiles of fimasartan in patients with mild to moderate hypertension.

Methods

Data for PK model building

PK data from Study 51055A, 56413A, A657-BR-CT-201

Data for PD model building

Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) data from A657-BR-CT-201

- Study 51055A:** A double-blind, placebo-controlled, ascending single oral dose, sequential group study in healthy subjects. Five dose levels of fimasartan (20, 60, 120, 240 and 480 mg) were studied in eight subjects (placebo: 2, active: 6) per each dose group.
- Study 56413A:** A double-blind, placebo-controlled, ascending multiple oral dose (7 dose), sequential group study in healthy subjects. Two dose levels of fimasartan (120 and 360 mg) were studied in eight subjects (placebo = 2, active = 6) per each dose group.
- Study A657-BR-CT-201:** A 4-week, randomized, double-blind, placebo-controlled, parallel, dose-response study in mild to moderate essential hypertension patients. Three dose groups of fimasartan (20, 60 and 180 mg) with a placebo group were studied. (N=16, 15, 15 and 15 respectively)

Software

Nonlinear mixed-effects method in NONMEM(ver. VI).

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 PK model

: A two-compartment linear model with mixed zero- and first-order absorption and first-order elimination

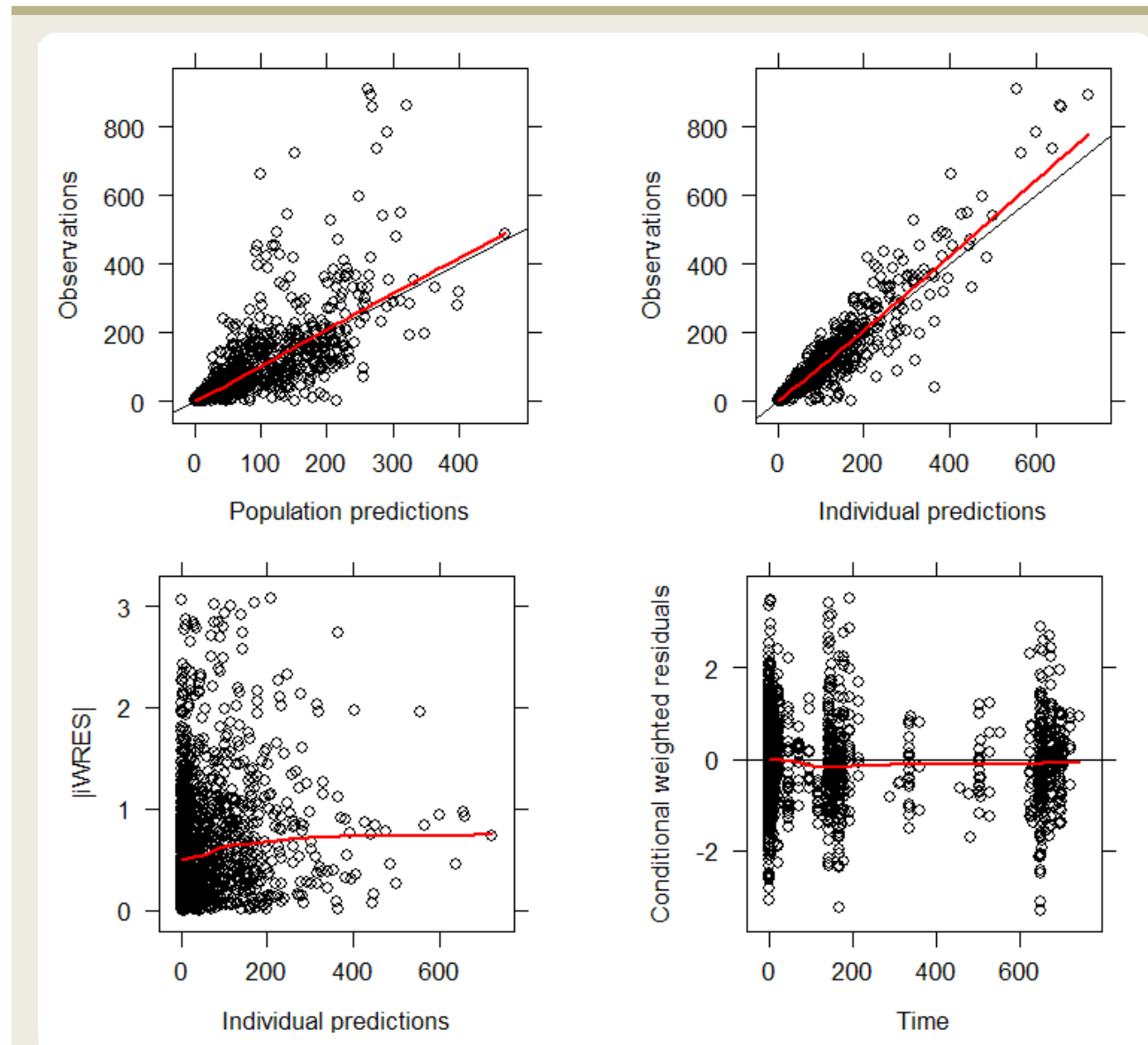


Figure 1. Basic goodness-of-fit plot for the final PK model

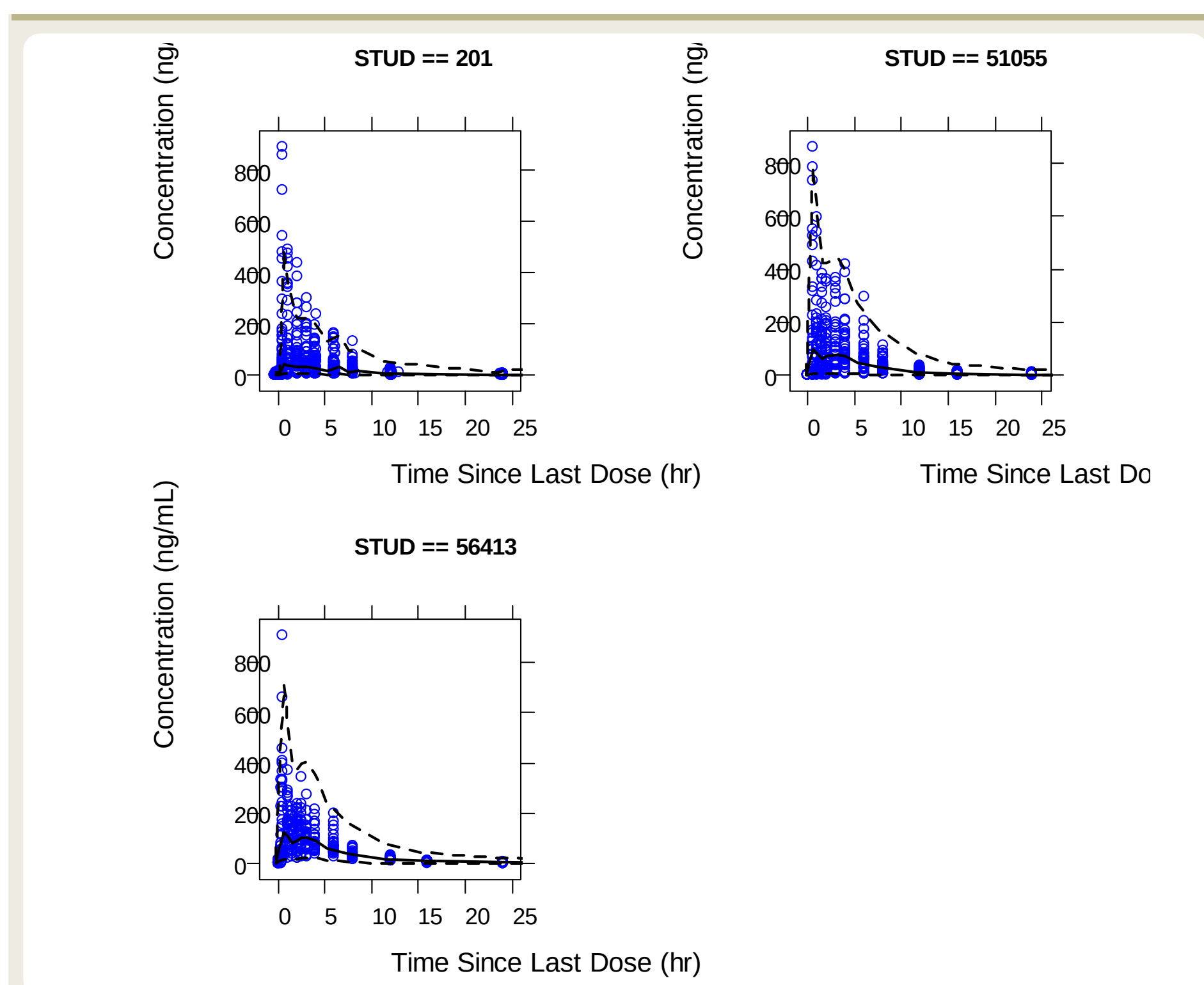


Figure 2. Visual predictive check of the final PK model classified by study

Table 1. Summary of parameters: the final pooled PK model				
Parameters	Population estimate	Median [95% CI]	BSV (CV%) [median,95%CI]	IOV (CV%) [median,95%CI]
CL/F (L/hr)	176	176[164, 189]	26.9 [26.3,20.8-31.4]	10.5 [10.9,6.2-15.5]
Body weight on CL/F	0.657	0.651[0.198, 1.0170]		
Total bilirubin on CL/F	-0.15	-0.17[-0.29, -0.05]		
V2/F (L)	371	357[207, 459]	56.4 [57.5,44.9-76.7]	NE
Body weight on V2/F	1.65	1.68[0.71, 2.64]		
Q/F (L/hr)	37.6	37.9[31.8, 44.5]	41.1 [43.2,32.4-53.1]	NE
Body weight on Q/F	1.28	1.41[0.48, 2.26]		
V3/F (L)	565	601[505, 747]	48.8 [53.2,39.2,70.4]	NE
Body weight on V3/F	1.88	2.02[1.17, 2.95]		
Ka (hr ⁻¹)	0.308	0.301[0.242, 0.358]	24.4 [21.2,3.5-31.9]	NE
Age on Ka	-0.358	-0.324[-0.622, -0.049]		
D2 (hr)	0.566	0.579[0.500, 0.726]	NE	NE
F1	0.596	0.607[0.540, 0.744]	NE	81.4 [82.2,61.9-102.0]
ALAG1 (hr)	1.63	1.63[1.24, 1.76]	NE	NE
Proportional residual variability(CV%)	32.6	33.1[30.3, 35.5]		

Population PK-PD model:

A random baseline effect compartment model with placebo response

$$BIBP(t) = MBP + \frac{\theta_{P_{max}} \times day}{\theta_{PD50} + day} \cdot \frac{\theta}{\theta + 1}$$
$$\frac{dC_e}{dt} = k_{eo}(C_p - C_e)$$
$$BP(t) = \theta_{BIBP}(t) - \frac{E_{max} \times C_e}{EC_{50} + C_e} + e_{BP}$$

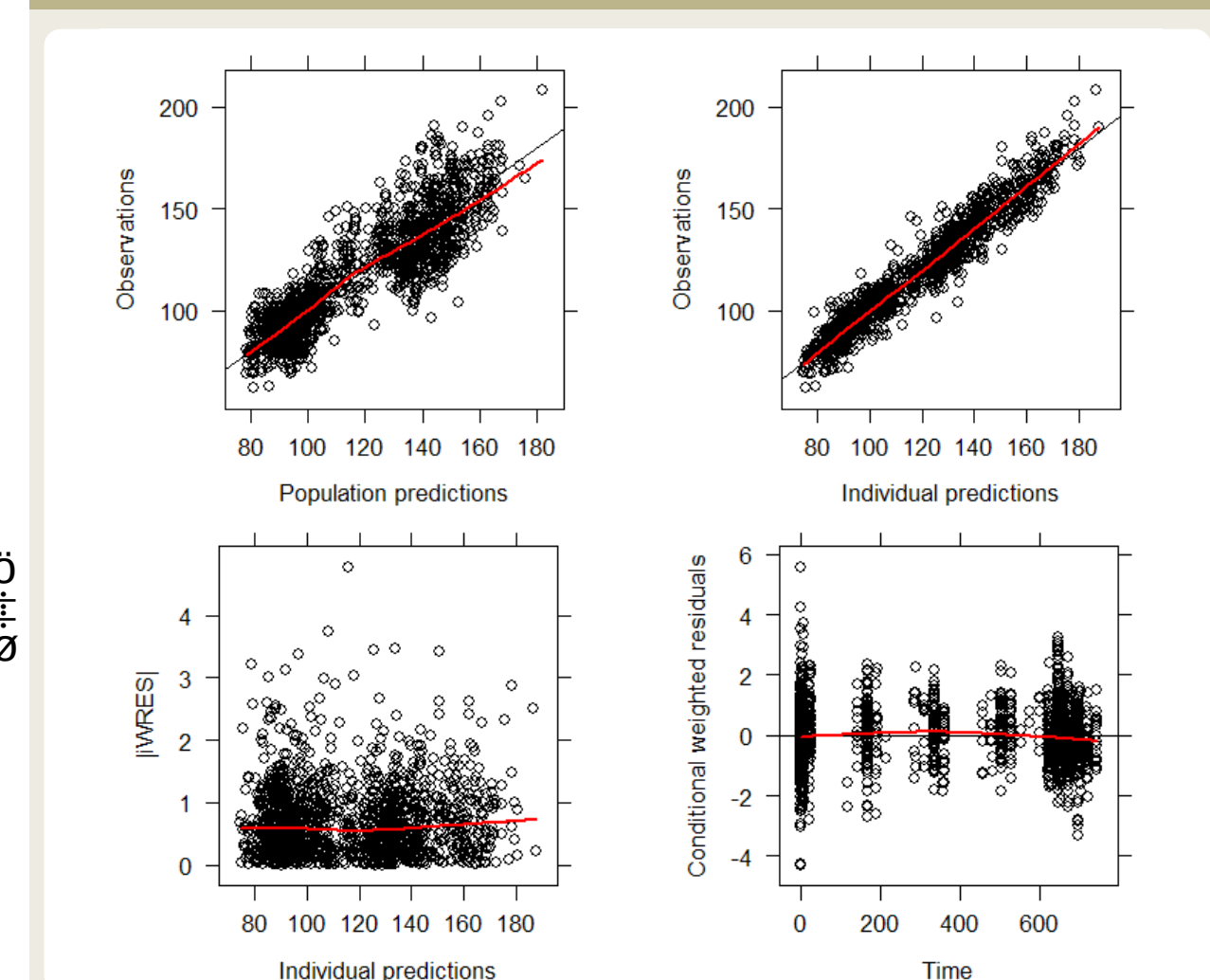


Figure 3. Basic goodness-of-fit for the final PK-DBP-SBP model

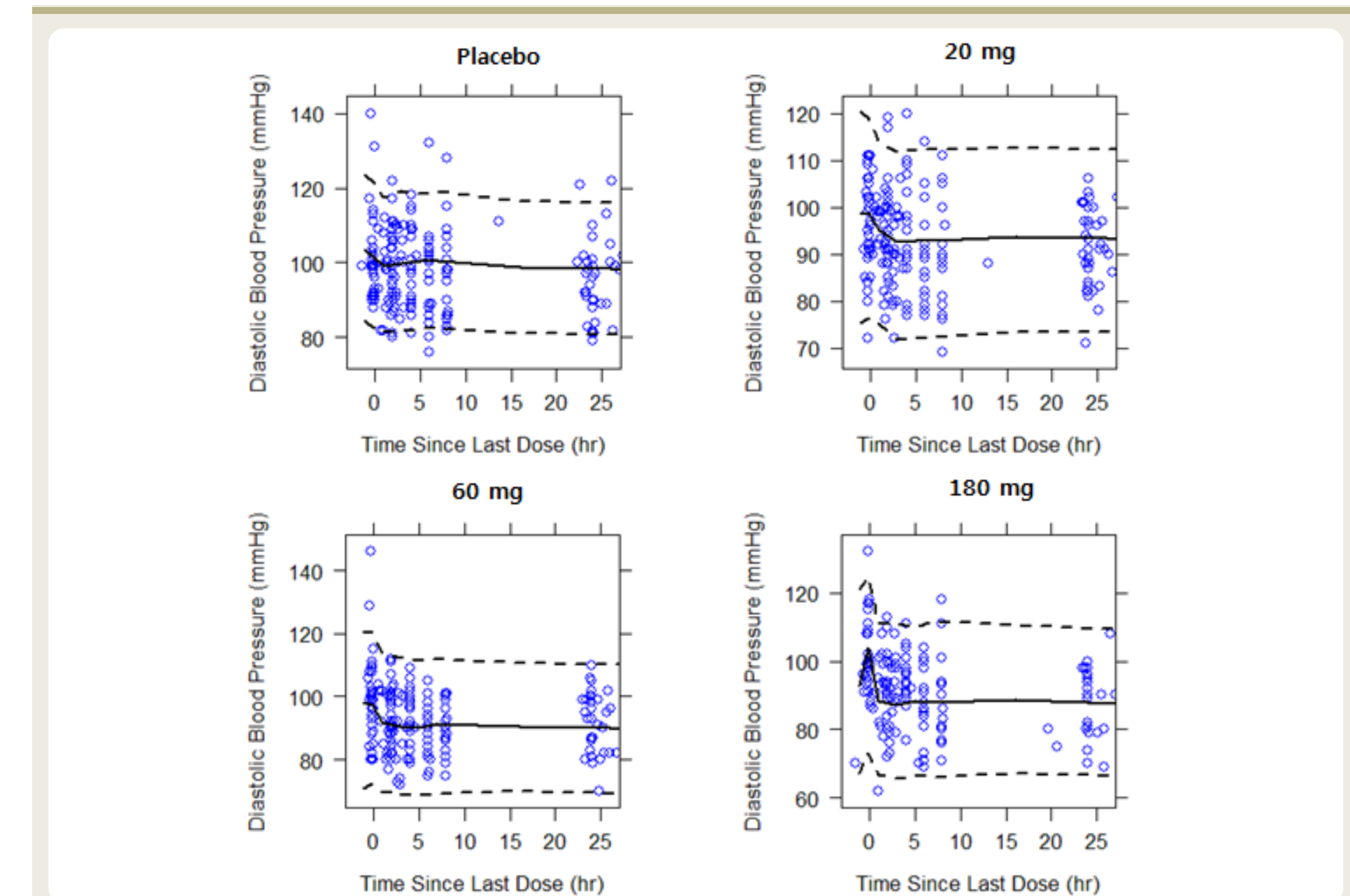


Figure 4. Visual predictive check of the final PK-SBP-DBP model, DBP

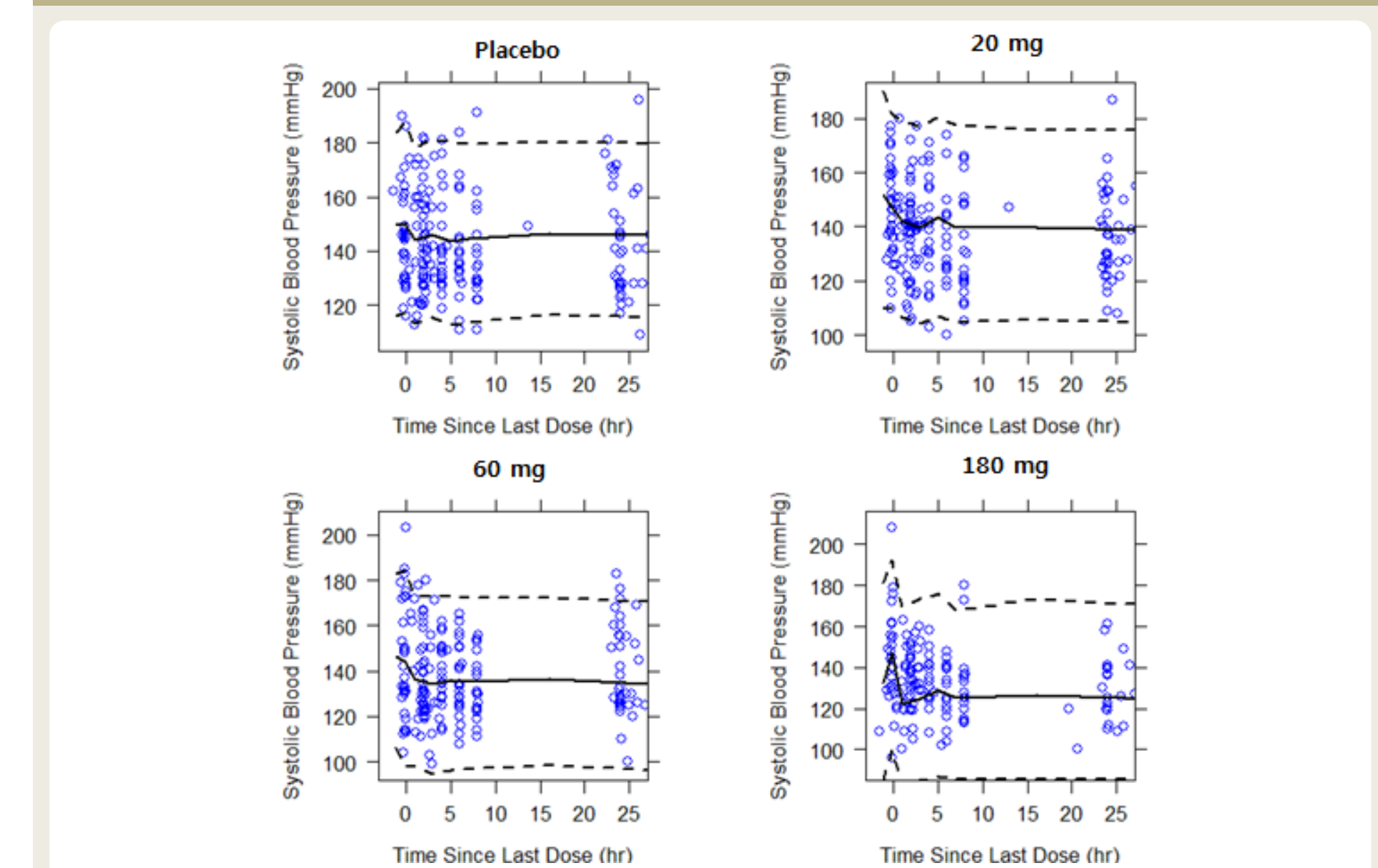


Figure 5. Visual predictive check of the final PK-SBP-DBP model, SBP

Table 2. Summary of parameters: the final pooled PK-DBP-SBP model

Parameters	Symbol	Diastolic BP		Systolic BP	
		Estimate	[95% CI]	Estimate	[95% CI]
Equilibrium constant for effect compartment (hr ⁻¹)	θ_{keo}	.052	[.017, .087]	.0263	[.0051, .0475]
Maximum effect for blood pressure reduction (mmHg)	θ_{Emax}	20.9	[8.1, 33.7]	38.8	[0, 80.8]
Concentration at 50% of E _{max} (ng/mL)	θ_{EC50}	23.3	[0, 57.0]	30.2	[0, 93.3]
Between subject variability for EC ₅₀ (CV %)	η_{EC50}	140.4	[0, 228.5]	130.8	[0, 220.3]
Maximum placebo effect (mmHg)	θ_{Pmax}	-8.35	[-5.37, -11.33]	-11.1	[-5.2, -17.0]
Day at 50% P _{max} (day)	θ_{PD50}	0.139	[0, .313]	.0535	[0, .1764]
Mean blood pressure, random baseline (mmHg)	θ_{MBP}	105	[102, 108]	154	[149, 159]
Power term for standardized screening BP on MBP	θ_{MBP_power}	.77	[.27, 1.27]	.791	[.459, 1.123]
Between subject variability for MBP (CV %)	η_{MBP}	5.1	[0, 7.8]	6.5	[0, 10.0]
Interoccasion variability for MBP (SD, mmHg)	K_{MBP}	2.16	[0, 5.08]	5.23	[2.05, 8.41]
Residual variability (SD, mmHg)	ϵ_{BP}	6.28	[5.75, 6.81]	8.59	[7.83, 9.35]
Correlation coefficient between BSV terms for MBP's		0.77			

Conclusion

- The final PK-PD model of fimasartan adequately described the observed blood pressure profiles in patients with mild to moderate hypertension. The model developed in this study could be applied in guiding further clinical development of fimasartan.

Conflict of Interest

- The authors declare no conflict of interest to disclose.