

Population PK/PD Modeling of Lusutrombopag, Thrombopoietin Receptor Agonist, in Healthy Volunteers for Exploring PK/PD Covariates

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Objective

- Lusutrombopag (also known as S-888711) is a small-molecule orally active thrombopoietin (TPO) receptor agonist. Lusutrombopag acts on human TPO receptors expressing in megakaryocytes and leads to thrombocytopoiesis. Lusutrombopag may have potency for the treatment of thrombocytopenia.
- Phase 1 studies in Japan and US were conducted in the development program.
- The aim of this study is to develop a population pharmacokinetic (PK)/pharmacodynamic (PD) model to describe plasma lusutrombopag concentrations and platelet (PLT) counts following oral lusutrombopag doses and also to explore PK/PD covariates.

Method

- A sequential PK and PD modeling approach was applied.

PK/PD Data

- 2539 plasma concentration data and 1408 PLT count data in 78 healthy adult subjects following single or multiple (once daily for 14 days) doses of lusutrombopag.
 - 54 Japanese and 24 US healthy volunteers

PK modeling

- A 2-compartment model and a 3-compartment model were tested as a PK structural model.
- PK covariates were selected by screening using univariate regression ($p < 0.05$) to construct a full model, followed by backward deletion from the full model ($p < 0.01$).
 - Tested PK relation: body weight, (WT), age, sex and ethnicity (ETN, Japanese or non-Japanese) on CL/F and V2/F.
- In addition, effects of ethnicity on bioavailability (F1) and of WT on V3/F were finally tested.

PK/PD modeling

- A semi-physiological model with production, maturation and elimination processes of blood platelet [1] was used as a PD structural model.
- The optimal number of transit compartment model, the type of drug effect model (sigmoid $E_{\max}$ or linear), and the presence of feedback function were determined based on fitting results.
- PD covariates were selected by the same approach as for PK covariates.
 - Tested PD relation: age, sex and ETN on EC_{50}

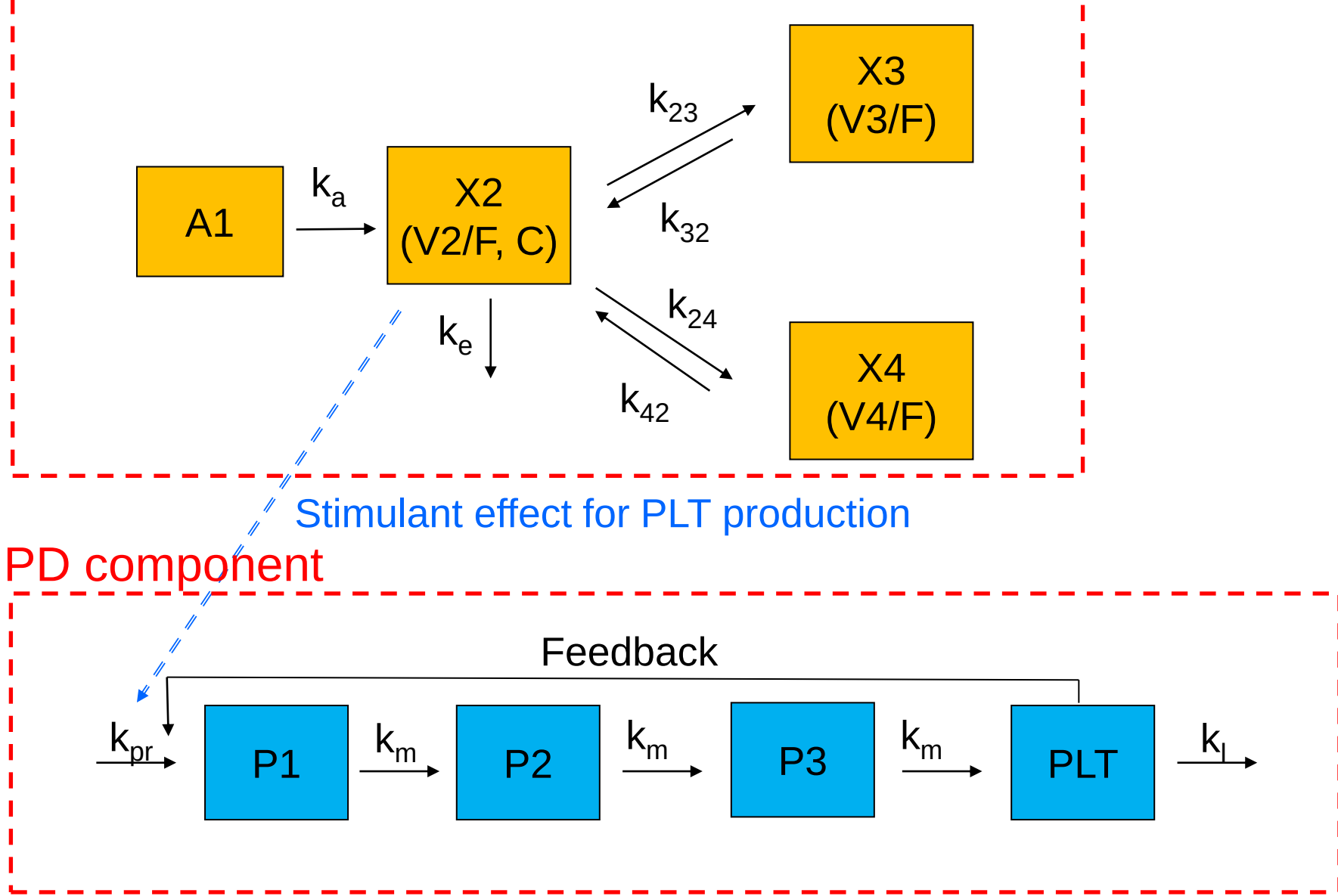
Software

- NONMEM ver. 7.2 [2] for parameter estimation and Perl-speaks NONMEM ver. 3.5.4 [3] for execution

Summary and Conclusion

- The population PK/PD model suggested the followings:
 - The difference in body weight between Japanese and non Japanese subjects results in the difference in lusutrombopag PK profile between the populations.
 - The PD sensitivity for PLT response with the lusutrombopag effect is similar between Japanese and non Japanese subjects.

PK component (conventional 3-compartment model)



PD model equation

$$\begin{aligned}\frac{dP1}{dt} &= k_{pr} \cdot (1 + E) \cdot FB - k_m \cdot P1 \\ \frac{dP2}{dt} &= k_m \cdot P1 - k_m \cdot P2 \\ \frac{dP3}{dt} &= k_m \cdot P2 - k_m \cdot P3 \\ \frac{dPLT}{dt} &= k_m \cdot P3 - k_l \cdot PLT \\ E &= \frac{E_{\max} \cdot C^h}{EC_{50}^h + C^h} \\ FB &= \left(\frac{PLT_0}{PLT} \right)^y\end{aligned}$$

Description for PD parameters

k_{pr} : 0-order rate for PLT production ($= PLT_0 \cdot k_l$), k_m : 1st-order rate constant for PLT maturation, k_l : 1st-order rate constant for PLT elimination, PLT_0 : baseline of PLT count, $E_{\max}$: maximum effect rate constant, EC_{50} : Michaelis-Menten constant, C: plasma lusutrombopag concentration, h: sigmoidicity constant for $E_{\max}$ model, y: sigmoidicity constant for the feedback function

Fig. 1 Scheme of the lusutrombopag PK/PD model for describing profiles of plasma concentrations and PLT counts.

Table 1 PK/PD parameters of lusutrombopag

PK			PD		
Parameter	Population mean	%RSE	Parameter	Population mean	%RSE
CL/F (L/hr)	0.778	2.6	k_m (hr ⁻¹)	0.0302	7.9
V2/F (L)	14.2	3.6	k_l (hr ⁻¹)	0.00648 ($= \ln(2)/107$)	Fixed
Q3/F (L/hr)	0.656	9.0	$E_{\max}$ (hr ⁻¹)	4.52	13.8
V3/F (L)	8.08	5.2	EC_{50} (ng/mL)	80.1	19.2
Q4/F (L/hr)	0.0189	10.2	h	1.65	12.7
V4/F (L)	3.40	27.4	y	0.275	37.1
k_a (hr ⁻¹)	0.309	5.4	PLT_0 (*10 ⁴ μ L)	20.3	2.1
$k_{a-sol, fed}$ (hr ⁻¹)	0.144	6.4	ω^2 for k_m (CV%)	40.6	45.2
Lag time (hr)	0.195	3.2	ω^2 for EC_{50} (CV%)	52.1	20.0
F1~sol, fast	1.00	Fixed	ω^2 for PLT_0 (CV%)	17.6	16.5
F1~sol, fed	0.906	3.3	σ^2 for residual: exponential (CV%)	4.9	19.1
F1~2-mg tab	0.857	Fixed	σ^2 for residual: additive (*10 ⁴ μ L)	0.609	62.8
F1~0.25-mg tab	0.761	Fixed			
Effect of WT on CL/F	0.750	Fixed			
Effect of WT on V2/F	1.00	Fixed			
Effect of WT on V3/F	1.00	Fixed			
Effect of ETN on F1	0.870	3.5			
ω^2 for CL/F (CV%)	17.5	19.4			
ω^2 for V2/F (CV%)	12.4	37.6			
Cor. for CL/F and V2/F	0.859	29.2			
ω^2 for V3/F (CV%)	13.6	48.5			
ω^2 for k_a (CV%)	32.6	18.7			
σ^2 for residual: exponential (CV%)	18.4	10.0			

%RSE: relative standard error in percent

F1 = 0.870^{ETN} * [effect of formulation and food condition]
ETN = 0 for Japanese and ETN = 1 for non Japanese

CL/F = 0.778*(WT/66.2)^{0.75}

V2/F = 14.2*WT/66.2

V3/F = 8.08*WT/66.2

Sol: solution, tab: tablet, fast: fasted state, fed: fed state

ω^2 : variance for inter-individual variability

σ^2 : variance for residual error

Cor.: correlation (R)

Result – PK Modeling

- The scheme of PK/PD model and the parameters are shown in Fig. 1 and Table 1, respectively.
- The 3-compartment model with 1st-order rate and lag time for absorption was selected as a base PK model.
- From the screening, the relations, CL/F-WT, V2/F-WT, V2/F-ETN and V2/F-age, were significant (Fig. 2 for visual inspection).
- The final population PK model was constructed as follows:
 - The empirical allometric relations for the effects of WT on CL/F and V2/F were applied since the effect of ethnicity may be confounded with the effect of WT.
 - After the backward deletion, CL/F-WT and V2/F-WT were remained in the final model. Moreover, ETN-F1 and V3/F-WT were added into the model as significant relations ($p < 0.01$).
- The final population PK model suggested WT was the most influential PK, while the ethnicity was not clinically significant (13% higher in Japanese than in non Japanese).
- The prediction-corrected VPC [4] indicated the final model well described time courses for plasma lusutrombopag concentrations (Fig. 3).

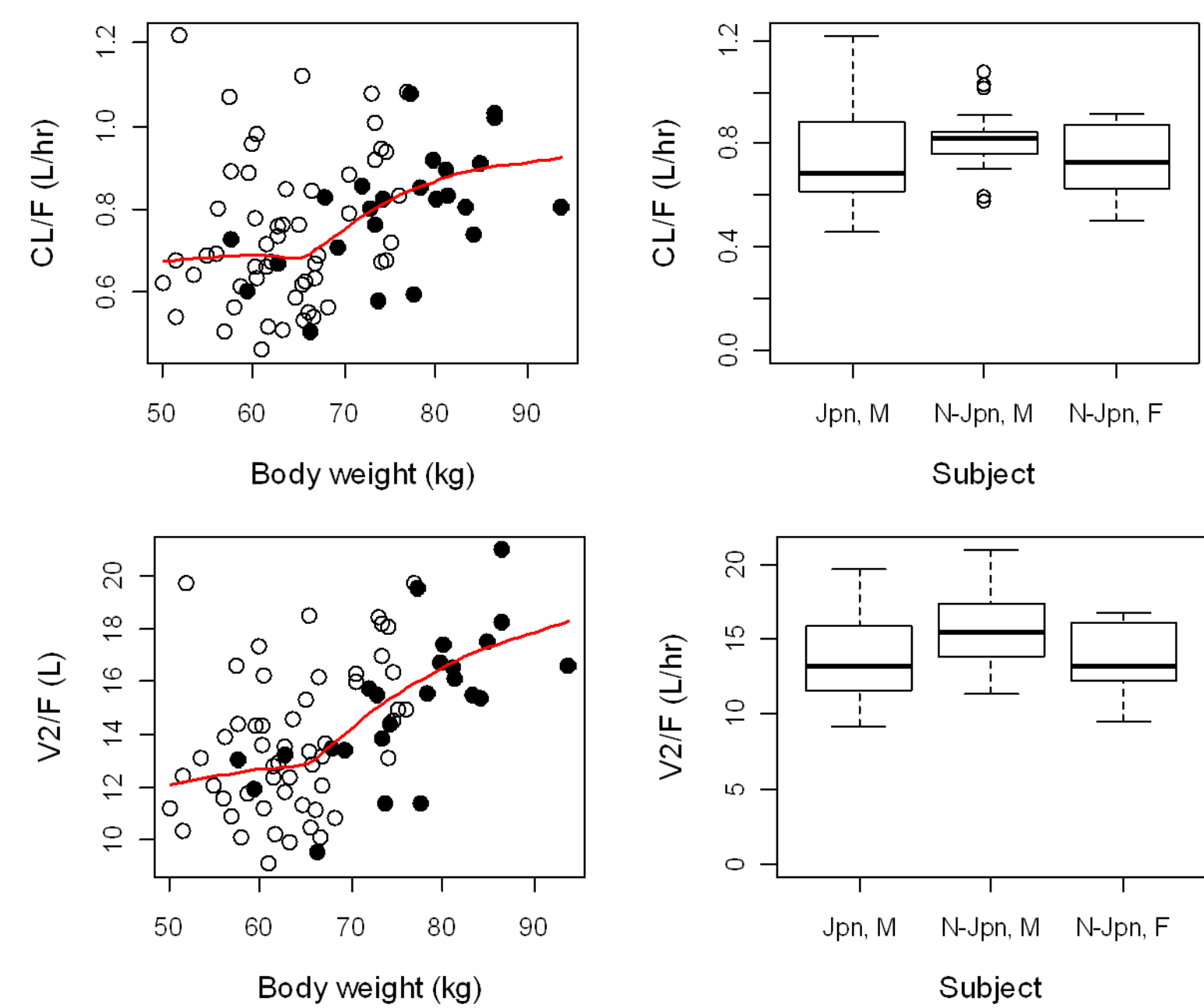


Fig. 2 Relationships between PK parameters (CL/F and V2/F) of base PK model and covariate candidates.

Upper: CL/F. Lower: V2/F. Open circles or Jpn: Japanese subjects. Closed circle or N-Jpn: non Japanese subjects. M: male. F: female.

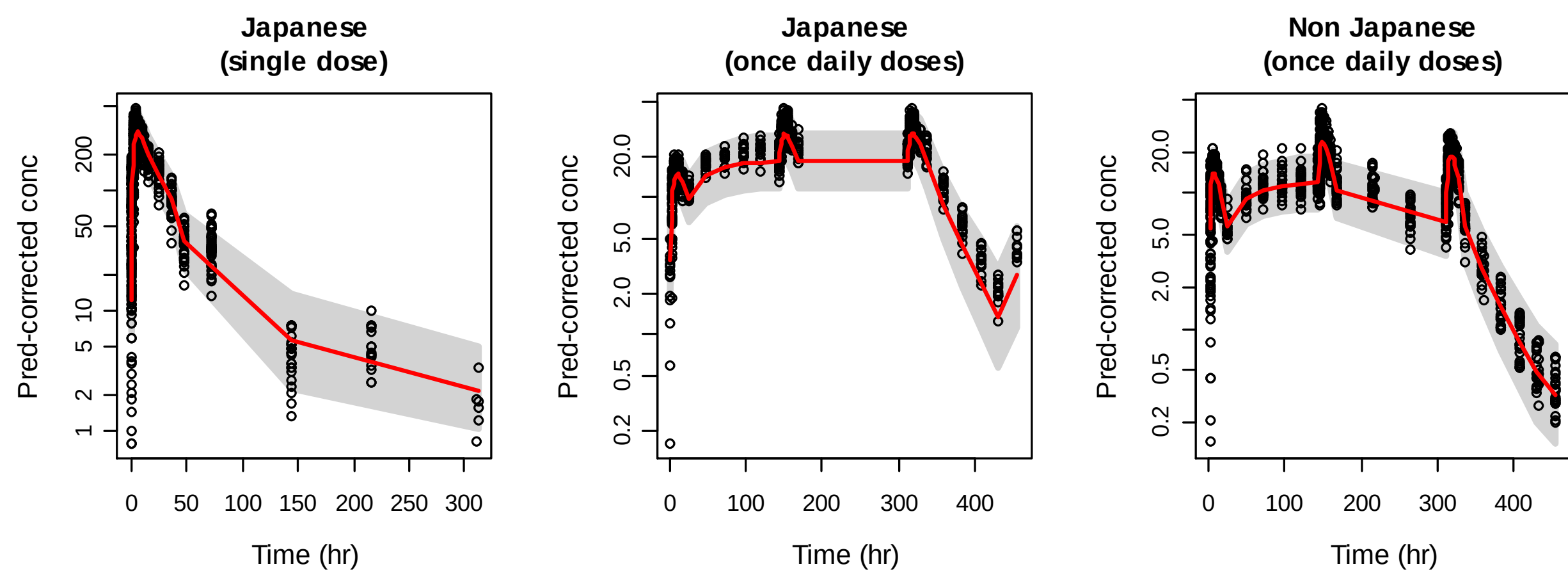


Fig. 3 Prediction-corrected VPC for plasma lusutrombopag concentration profiles by regimen and ethnicity. Semi-log scale. Red line: median prediction. Grey area: 90% prediction interval. Open circle: observed data.

Result – PK/PD Modeling

- k_l was calculated using the reported half-life of PLT count (107 hours) [5].
- The 3 transit compartment model with the sigmoid $E_{\max}$ model and the feedback was selected for describing PLT count change with drug effect (Fig. 1).
- After the backward deletion, any significant covariates for EC_{50} were not found.
- The prediction-corrected VPC indicated the final model well described time courses for PLT count following lusutrombopag dosing (Fig. 4).
- PK and PD profiles in typical Japanese and non Japanese subjects were predicted (Fig. 5).

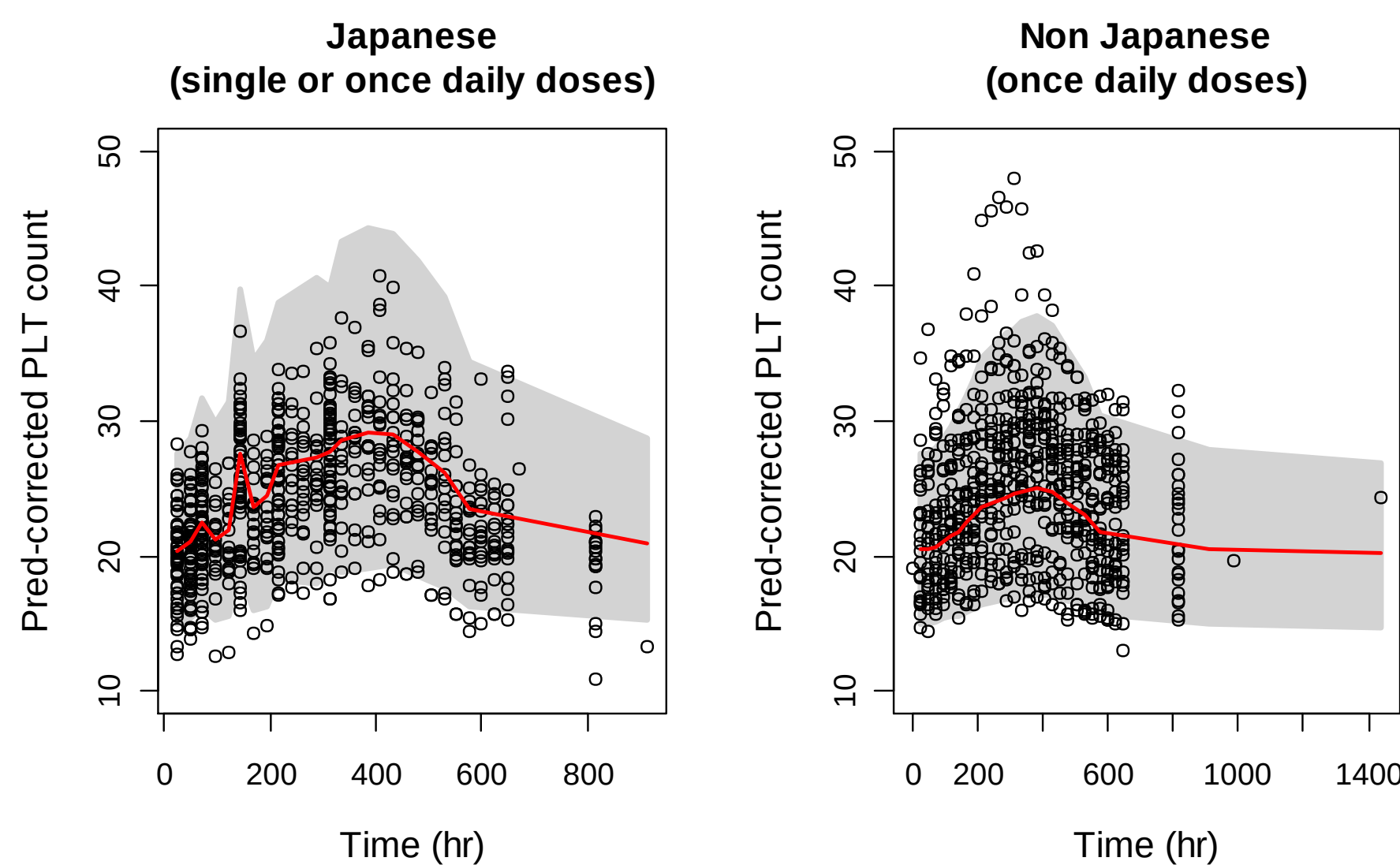


Fig. 4 Prediction-corrected VPC for platelet count profiles following lusutrombopag dosing by ethnicity. Red line: median prediction. Grey area: 90% prediction interval. Open circle: observed data.

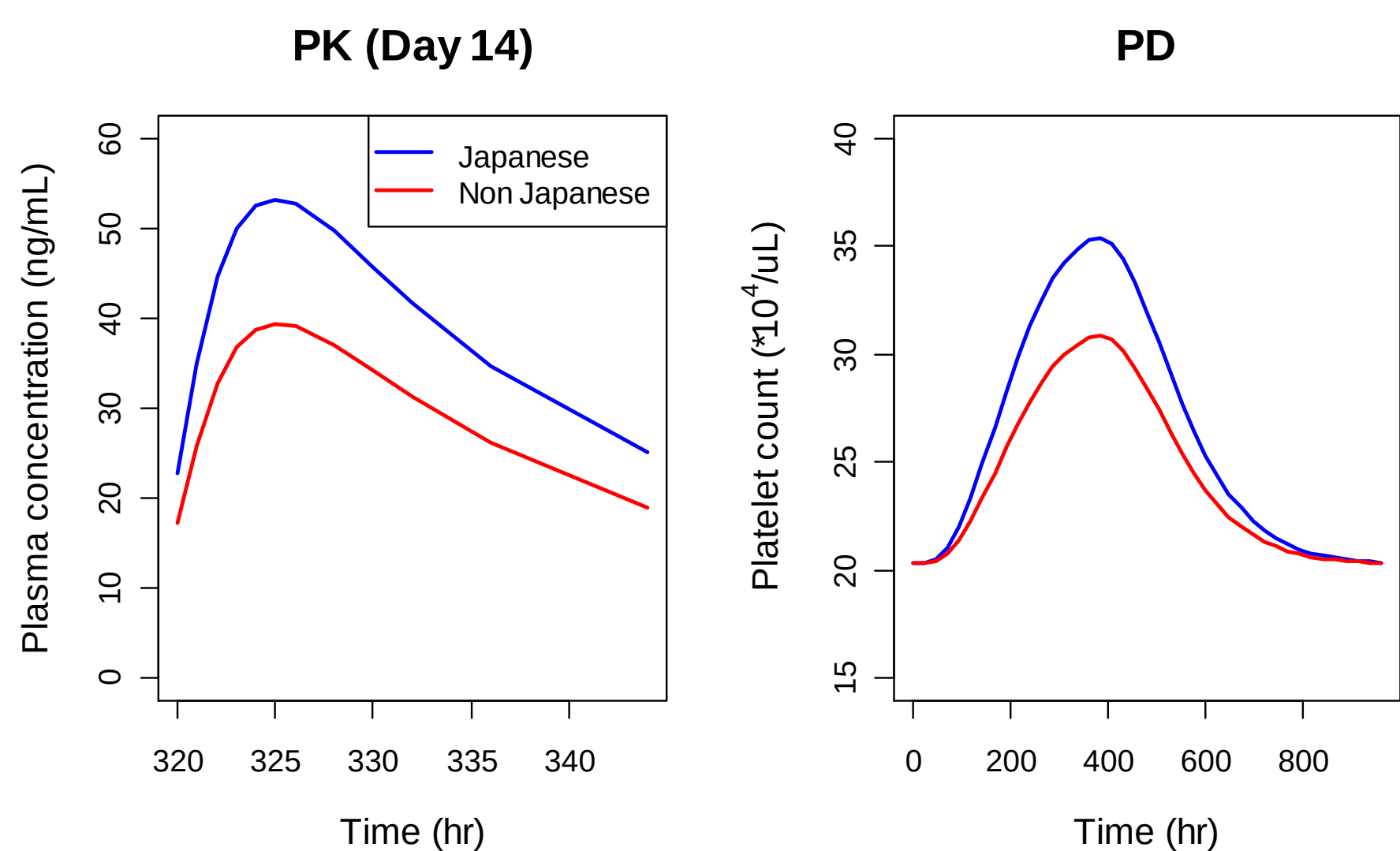


Fig. 5 Predicted PK and PD profiles in the typical subject following 1-mg once daily dosing for 14 days. Typical subject: a Japanese subject with 63.2 kg of WT and a non Japanese subject with 77.4 kg of WT.

Reference

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