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ORIGINAL RESEARCH ARTICLE

Population Pharmacokinetic and Pharmacodynamic Modeling of Lusutrombopag, a Newly Developed Oral Thrombopoietin Receptor Agonist, in Healthy Subjects

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Abstract

Objectives The aim of this study was to develop a population pharmacokinetic (PK)/pharmacodynamic (PD) model for describing plasma lusutrombopag concentrations and platelet response following oral lusutrombopag dosing and for evaluating covariates in the PK/PD profiles.

Methods A population PK/PD model was developed using a total of 2539 plasma lusutrombopag concentration data and 1408 platelet count data from 78 healthy adult subjects following oral single and multiple (14-day once-daily) dosing. Covariates in PK and PK/PD models were explored for subject age, body weight, sex, and ethnicity.

Results A three-compartment model with first-order rate and lag time for absorption was selected as a PK model. A three-transit and one-platelet compartment model with a sigmoid E_{max} model for drug effect and feedback of platelet production was selected as the PD model. The PK and PK/PD models well described the plasma lusutrombopag concentrations and the platelet response, respectively. Body weight was a significant covariate in PK. The bioavailability of non-Japanese subjects (White and Black/African American subjects) was 13 % lower than that of Japanese subjects, while the simulated platelet response profiles using the PK/PD model were similar between Japanese and non-Japanese subjects. There were no significant covariates of the tested background data including age, sex, and ethnicity (Japanese or non-Japanese) for the PD sensitivity.

Conclusion A population PK/PD model was developed for lusutrombopag and shown to provide good prediction for the PK/PD profiles. The model could be used as a basic PK/PD model in the drug development of lusutrombopag.

Key Points

A population pharmacokinetic/pharmacodynamic (PK/PD) model was developed for lusutrombopag. The developed PK/PD model enables good prediction of PK/PD profiles following oral administration of lusutrombopag.

Body weight was suggested to have an effect on lusutrombopag PK, and platelet count profiles following oral administration of lusutrombopag were similar between Japanese and non-Japanese subject populations.

The effects of age, sex, and ethnicity seemed to be minimal on the PD sensitivity for lusutrombopag.

1 Introduction

Thrombopoietin (TPO) is a cytokine that stimulates the proliferation and differentiation of megakaryocytic progenitor cells from hematopoietic stem cells, as well as

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megakaryocyte maturation, and regulates platelet production by binding with the TPO receptor [1]. Lusutrombopag is a small-molecule, orally active, TPO receptor agonist discovered by Shionogi & Co., Ltd. Lusutrombopag acts on the transmembrane domain of human TPO receptors expressed in megakaryocytes, stimulates megakaryocytes to proliferate and differentiate via the same signal transduction system as that of endogenous TPO, and promotes thrombocytopoiesis. Lusutrombopag has been developed to treat thrombocytopenia in patients with chronic liver disease [2] or chronic immune thrombocytopenic purpura.

The clinical studies demonstrated the following. Lusutrombopag pharmacokinetics is linear in the range of the tested doses (0.25–50 mg). The time to maximum plasma lusutrombopag concentration was approximately 4 h and the elimination half-life approximately 20 h. After single oral doses of lusutrombopag from 1 to 50 mg, urine concentrations of unchanged lusutrombopag were below the lower limit of quantification, suggesting minimal contribution from renal elimination. Additionally, plasma concentrations of lusutrombopag metabolites (deshexyl and 5-keto) were notably lower than those of unchanged lusutrombopag.

Pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation can serve as a powerful tool to gain insight into drug action and disease state [3, 4]. Mechanistic PK/PD models to describe platelet response profiles following the administration of pegylated thrombopoietin mimetic peptide or pegylated recombinant megakaryocyte growth and development factor have been reported [5]. Additionally, the PK/PD model for eltrombopag, a small-molecule, orally active, TPO receptor agonist, has been reported [6, 7].

The aim of the present study was to develop a population PK/PD model for describing the plasma concentration profiles of lusutrombopag and the platelet response profiles following oral administration of lusutrombopag in healthy adult subjects and to evaluate the covariates influencing lustrombopag PK and PD profiles.

2 Methods

2.1 Clinical Study and Design

Plasma concentration data of lusutrombopag and platelet count data were collected from three phase I studies (Japanese single-dose study [M0611], Japanese multiple-dose study [M0613], and US multiple-dose study [M0615]). The M0611 study was a phase I, placebo-controlled, double-blinded, and single-dose study. The M0613 study was a phase I, placebo-controlled, double-blinded, and multiple-dose study. The M0615 study was a phase I, placebo-controlled, double-blinded, and multiple-dose study. The characteristics of the clinical trials are presented in Table 1 and the demographic data of the study populations in

Table 1 Summary of clinical studies

Study no.	Study description	Dosage regimen	Formulation and food condition	Subjects	PK sampling	PD sampling[a]
M0611	Phase I Japanese single-dose study	1-, 2-, 4-, 10-, 25-, and 50-mg single dosing	Solution in the fasted state	36 healthy male adults	Pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 144, 216, and 312 h post-dose	Days 1 (pre-dose), 2, 3, 4, 7, 10, and 14 after the initial dosing and at the discontinuation
M0613	Phase I Japanese multiple-dose study	0.25-, 0.5-, and 2-mg once-daily dosing for 14 days	0.25 and 0.5 mg: solution in the fed state 2 mg: 2-mg tablet in the fed state	18 healthy male adults	Days 1, 7, and 14: pre-dose, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 16 h post-dose; days 2–6, 8, and 10: pre-dose; days 15–20: 24, 48, 72, 96, 120, and 144 h post-dose	Days 1 (pre-dose) to 28 and 35 after the initial dosing and at the discontinuation
M0615	Phase I US multiple-dose study	0.25-, 0.5-, 0.75-, and 1-mg once-daily dosing for 14 days	0.25-mg tablet in the fed state	24 healthy male and female adults	Days 1, 7, and 14: pre-dose, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 16 h post-dose; days 2–6, 8, and 10: pre-dose; days 15–20: 24, 48, 72, 96, 120, and 144 h post-dose	Days 1 (pre-dose) to 28 and 35 after the initial dosing and at the discontinuation

PD pharmacodynamics, *PK* pharmacokinetics

[a] Sampling time for the PD data in the dataset

Table 2 Demographic data in the analysis population

	Mean (SD)	Median (range)
Total		
Age (years)	29.1 (8.2)	27 (20–54)
Body weight (kg)	67.6 (9.5)	66.2 (50.2–93.7)
Sex (male:female)	71:7	
Ethnicity (Japanese:White:Black)	54:21:3	
M0611 study		
Age (years)	24.8 (4.0)	23 (20–34)
Body weight (kg)	63.8 (7.4)	62.8 (50.2–77.0)
Sex (male:female)	36:0	
Ethnicity (Japanese:White:Black)	36:0:0	
M0613 study		
Age (years)	26.4 (4.3)	26 (20–37)
Body weight (kg)	63.8 (6.1)	65.1 (51.6–75.2)
Sex (male:female)	18:0	
Ethnicity (Japanese:White:Black)	18:0:0	
M0615 study		
Age (years)	37.5 (9.0)	36.5 (21–54)
Body weight (kg)	76.0 (9.0)	77.4 (57.6–93.7)
Sex (male:female)	17:7	
Ethnicity (Japanese:White:Black)	0:21:3	

SD standard deviation

Table 2. A total of 78 healthy adult subjects aged 20–54 years were included in the PK/PD analysis, 54 Japanese, 21 White, and 3 Black/African American subjects. A total of 2539 plasma concentration data of lusutrombopag and 1408 platelet count data were available.

All studies were conducted according to the principles of the Declaration of Helsinki and in accordance with the Guideline of Good Clinical Practice. These studies were approved by independent ethics committees, and signed informed consent forms were obtained from all subjects.

2.2 Bioanalytical Methods

The plasma samples were deproteinized by adding acetonitrile. Lusutrombopag in the extract obtained by the deproteinization was assayed by validated high-performance liquid chromatography-tandem mass spectrometry. The lower limit of quantification was set at 1.00, 0.100, and 0.100 ng/mL in the M0611, M0613, and M0615 studies, respectively.

2.3 PK Modeling

A two- and a three-compartment model with a first-order absorption rate with or without lag time for absorption were tested to describe the plasma concentration data of lusutrombopag. Bioavailability was found to be dependent on the combination of the formulation (solution, 0.25-mg tablet or 2-mg tablet) and the food condition (fasted or fed). In other clinical studies (relative bioavailability and food effect studies), relative bioavailability was 0.857 and 0.820 for the 2-mg tablet in the fed state compared with the solution in the fasted state and for the 0.25-mg tablet in the fed state compared with the solution in the fed state, respectively, based on ratios of area under the plasma concentration curve (AUC) estimated by non-compartmental analyses. F1, which is a parameter to describe bioavailability, for the solution in the fasted state, was fixed at 1 as a reference value. F1 values for the 2- and 0.25-mg tablet in the fed state were fixed at 0.857 and 0.820, respectively. After fixing these F1 values, F1 for the solution in the fed state was estimated in the modeling. Furthermore, as the absorption phase for the solution in the fed state appeared to be different from that for other combinations of formulations and food state, parameters related to absorption (i.e., first-order absorption rate constant [KA] and lag time for absorption [ALAG1]) were estimated for the solution in the fed state and the others. Inter-individual variability (IIV) was assumed to be log-normally distributed. A proportional residual error model and a combination residual error model (proportional residual error + additive residual error) were tested. In the covariate modeling, relations of age, body weight, sex, and ethnicity (Japanese subjects or non-Japanese subjects) on apparent total clearance (CL/F) and apparent volume of distribution in the central compartment (V2/F) and the effect of body weight on apparent volume of distribution in peripheral compartment (V3/F) were tested by screening using univariate regression analysis based on the objective function value (OFV) in NONMEM with $p < 0.05$ (3.84 at a difference with one degree of freedom). Because IIV for apparent inter-compartmental clearances could not be estimated owing to being close to 0, it was concluded that covariate modeling could not be conducted on apparent inter-compartmental clearances. Covariates were normalized to the median values for the continuous covariates (age and body weight) and modeled using the following equation:

$$\theta_i = \theta_{pop} \times (COV_i/COV_{med})^{\theta COV}, \quad (1)$$

where θ_i is the individual predicted parameter for the individual covariate value COV_i, θ_{pop} is a population mean parameter, θ_{COV} is an estimate for the covariate effect, and COV_{med} is median value of the covariate as a reference value.

The following equation was used for the categorical covariates (sex and ethnicity [Japanese subjects or non-Japanese subjects]):

$$\theta_i = \theta_{pop} \times \theta_{COV}^{COV_i}, \quad (2)$$

where θ_i is the individual predicted parameter for individual covariate value COV_i, θ_{pop} is a population mean parameter, and θ_{COV} is an estimate for the covariate effect.

In the screening, as the effects of ethnicity on CL/F and V2/F were significant, the effect of ethnicity on F1 was also tested. Significant relationships were incorporated into the base model to construct a full model. Next, backward deletion based on the OFV with $p < 0.01$ (6.63 at a difference with one degree of freedom) was performed to develop the final model.

2.4 PK/PD Modeling

A semi-physiological model incorporating the platelet production process in bone marrow and the degradation process in circulating blood was used as a PD structural model, composed of a transit compartment and a platelet compartment [7], to describe platelet count data following lusutrombopag dosing. In the model, lusutrombopag was assumed to stimulate the zero-order production rate of platelet precursors in a manner dependent on plasma lusutrombopag concentration. Lusutrombopag, as well as endogenous TPO [8], activates the signal transduction at all stages of thrombopoiesis. However, it was difficult to consider the response at each stage of thrombopoiesis into the model as only the platelet count data were used as a PD index. The final PD structural model was a four-compartment model (three-transit and one-platelet compartment model) with the feedback model as given in Eqs. 3–7:

$$\mathrm{dP1}/\mathrm{d}t = \mathrm{KPR} \cdot (1 + E) \cdot \mathrm{FB} - \mathrm{KM} \cdot \mathrm{P1}, \quad (3)$$

$$\mathrm{dP2}/\mathrm{d}t = \mathrm{KM} \cdot \mathrm{P1} - \mathrm{KM} \cdot \mathrm{P2}, \quad (4)$$

$$\mathrm{dP3}/\mathrm{d}t = \mathrm{KM} \cdot \mathrm{P2} - \mathrm{KM} \cdot \mathrm{P3}, \quad (5)$$

$$\mathrm{dPLT}/\mathrm{d}t = \mathrm{KM} \cdot \mathrm{P3} - \mathrm{KL} \cdot \mathrm{PLT}, \quad (6)$$

$$\mathrm{FB} = (\mathrm{PLT0}/\mathrm{PLT})^{\gamma}, \quad (7)$$

where KPR is a zero-order rate for the production of platelet precursors, KM is a first-order rate constant for the maturation of platelet precursors, and KL is a first-order rate constant for the elimination of platelets. P1–P3 are platelet precursor counts, PLT is the observation variable of platelet counts, and γ is an exponent to describe feedback based on PLT. KM, KL, PLT0, and γ were the parameters to be estimated. The initial conditions at a steady state of platelet precursor counts and platelet counts were: P1(0) to P3(0) = KPR/KM, PLT(0) = PLT0, and KPR = PLT0 × KL. The PD model was linked with the PPK model developed in the PK modeling. The KL was fixed at 0.00648 h^{-1} based on a physiological value reported previously [9].

A linear model and a sigmoid $E_{\max}$ model given in Eqs. 8 and 9, respectively, were tested to explain the drug effect (E in Eq. 3):

$$E = \mathrm{SLOP} \times C, \quad (8)$$

$$E = \mathrm{E}_{\max} \times C^{\mathrm{H}} / \left(\mathrm{EC}_{50}^{\mathrm{H}} + C^{\mathrm{H}}\right), \quad (9)$$

where SLOP is the slope related to plasma lusutrombopag concentrations, C is the plasma lusutrombopag concentration, $E_{\max}$ is the maximum effect constant, EC_{50} is the plasma lusutrombopag concentration achieving 50 % of $E_{\max}$, and H is the Hill coefficient.

IIV for the parameters was assumed to be log-normally distributed. A proportional residual error model and a combination residual error model (proportional residual error + additive residual error) were tested. The optimal number (integer) of transit compartments, the presence of feedback model, the drug effect model, and the type of residual error model (proportional or combination) were determined based on OFV with $p < 0.01$.

In the covariate modeling, effect of age, sex, and ethnicity (Japanese subject or non-Japanese subject) on EC_{50}, which is a parameter for PD sensitivity with estimable IIV, were tested by the screening followed by the stepwise backward deletion similar to the PK modeling.

2.5 Parameter Estimation

A sequential PK and PD modeling approach was applied, i.e., first the PK modeling was conducted and then PK/PD modeling was conducted using empirical Bayes-estimated PK parameters from the final PK model to provide individual plasma lusutrombopag concentrations. The parameters were estimated from the data with the first-order conditional estimation using the interaction method. ADVAN4 (two-compartment PK model) and ADVAN12 (three-compartment PK model) were used for the PK modeling and ADVAN6 for the PK/PD modeling in NONMEM. The data included that for two Japanese subjects and seven non-Japanese subjects who did not complete the 14-day dosing. Data below the limit of quantification (BLQ) were excluded from the estimation. The BLQ data of plasma concentrations except for BLQ at pre-dose were 13 data points, which were much smaller than the observed data (2539 plasma concentrations). Therefore, the method for exclusion of BLQ data was not likely to affect the results of modeling. In addition, the plasma lusutrombopag concentration data (trough concentration data) on Day 10 in the multiple-dose study (M0613) were excluded to avoid any bias in the analysis because, for reasons unknown, the plasma concentrations in all dose groups were on average 1.3- to 1.5-fold higher compared with other trough concentration data.

2.6 Model Evaluation

Prediction-corrected visual predictive checks (VPC) [10] were performed to assess the final PK and PK/PD models. In the VPC, the prediction interval based on the individual predicted data corrected for population prediction was compared with the observed data corrected for population prediction. Five-hundred data sets were simulated using the final model parameters. The simulated data were evaluated by graphical comparisons between the model predicted median and 90 % prediction interval, and the individual observed data.

A nonparametric bootstrap (500 replicates) was employed to calculate 95 % confidence intervals of parameter estimates.

2.7 Evaluation of the Impact of Covariate Effect

Ratios of CL/F and V2/F with body weight of 50–90 kg relative to the reference value (CL/F and V2/F with 70 kg) and the 95 % confidence intervals (CIs) were calculated based on the parameter estimates using the non-parametric bootstrap and compared for a clinically significant range, 0.8–1.2, to evaluate the impact of the effect of body weight on lusutrombopag PK. AUC at steady state for 1.5-mg multiple dosing was also calculated with individual CL/F using an empirical Bayes estimation in case of F1 = 1 and summarized by ethnicity.

2.8 Simulation for Platelet Response Profile

Seventy-eight virtual subjects were generated by resampling the body weight, which was the influential covariate on PK, from the dataset. The baseline of platelet count in the virtual subject was randomly generated based on the estimates of PLT0 and IIV for PLT0. Platelet counts of virtual subjects following 1.5-mg dosing once daily for 7 days were simulated every 24 h from 0 to 696 h with 200 replicates. Median platelet counts and the 90 % prediction interval were calculated using the simulated platelet count data.

2.9 Software

NONMEM version 7.3 (ICON Development Solutions, Ellicott City, MD, USA) was used [11]. Perl-speaks NONMEM version 3.4.2 [12] was used to execute a NONMEM run and a non-parametric bootstrap method for calculating 95 % CIs of parameter estimates.

3 Results

Figure 1 shows the scheme of the final PK/PD model. The three-compartment model with the first-order absorption rate, lag time, and proportional residual error model was selected as the base model. The estimation of KA and ALAG1 for the solution in the fed state and the others improved the result of model fitting (OFV from 10976.049 to 10896.185). Supplemental Fig. S1 shows the plots of relationships of empirical Bayes-estimated parameters for CL/F and V2/F of the base model to the background data. Clear relationships appeared between CL/F or V2/F and body weight or ethnicity. Table 3 shows population PK parameters of the final model. The lower limit of 95 % CI for parameter estimates based on the standard error did not reach zero (relative standard error <50 %) except for IIV for V3/F. Median values of

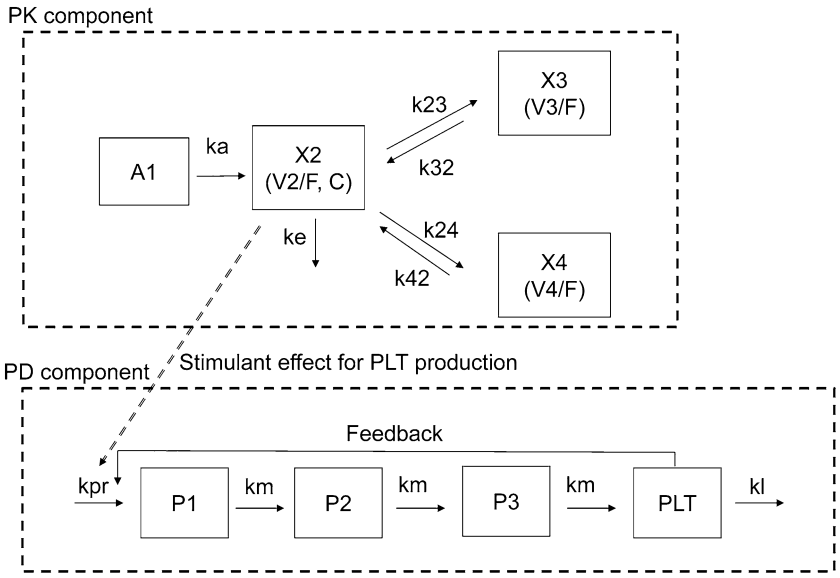

Fig. 1 Scheme of PK/PD model for lusutrombopag. *PK/PD* pharmacokinetic/pharmacodynamic

Table 3 Population PK parameters of the final model

	Estimate	%RSE	Bootstrap[a]
CL/F (L/h)	0.775	2.7	0.774 (0.733–0.818)
V2/F (L)	13.7	5.2	13.6 (12.4–15.0)
Q3/F (L/h)	0.732	10.7	0.740 (0.592–0.879)
V3/F (L)	8.41	7.0	8.37 (7.36–9.53)
Q4/F (L/h)	0.0195	10.3	0.0202 (0.0162–0.0237)
V4/F (L)	3.32	22.9	3.34 (2.42–5.92)
F1 relative to solution in the fasted state			
Solution, fasted	1	Fixed	Fixed
Solution, fed	0.874	3.2	0.873 (0.813–0.933)
2-mg tablet, fed	0.857	Fixed	Fixed
0.25-mg tablet, fed	0.820 × 0.906	Fixed	Fixed
KA (h^{-1})			
Solution, fed	0.167	8.9	0.168 (0.139–0.199)
Other	0.299	6.3	0.298 (0.269–0.334)
ALAG1 (h)			
Solution, fed	0.552	6.7	0.552 (0.490–0.660)
Other	0.194	3.3	0.195 (0.183–0.209)
F1 relative to JPN	0.905	4.4	0.906 (0.822–1.02)
Effect of WT on CL/F	0.710	27.0	0.692 (0.330–1.11)
Effect of WT on V2/F	1.02	19.1	1.02 (0.636–1.45)
Effect of WT on V3/F	1.06	18.9	1.06 (0.675–1.48)
IIV for CL/F (CV %)	17.9	18.9	17.4 (14.2–20.8)
IIV for V2/F (CV %)	12.9	37.8	12.75 (8.1–17.6)
Correlation between CL/F and V2/F	0.861	31.1	0.0188 (0.00935–0.0331)[b]
IIV for V3/F (CV %)	12.8	50.6	11.6 (3.9–18.8)
IIV for KA (CV %)	32.1	21.8	31.7 (25.4–38.5)
Proportional residual error (CV %)	18.2	10.3	18.0 (16.4–20.1)

$CL/F = 0.775 \times (WT/66.2)^{0.710}$, $V2/F = 13.7 \times (WT/66.2)^{1.02}$, $V3/F = 8.41 \times (WT/66.2)^{1.06}$, $F1 = 0.905^{ETH}$, if Japanese, then ETH = 0, otherwise ETH = 1. η shrinkage for CL/F, V2/F, V3/F, and KA was 1.9, 13.1, 34.2, and 5.3 %. ε shrinkage was 3.6 %

%RSE relative standard error in percent, *WT* body weight, *F1* bioavailability, *CL/F* apparent total clearance, *V2/F* apparent central volume, *Q3/F and Q4/F* apparent inter-compartmental clearance, *V3/F and V4/F* apparent peripheral distribution volume, *KA* first-order absorption rate constant, *lag time* lag time for absorption, *ALAG1* lag time for absorption, *JPN* Japanese, CV coefficient of variation, *PK* pharmacokinetics

[a] Median (95 % confidence interval) from 377 successfully completed bootstrap runs

[b] Values as covariance

estimates based on the bootstrap approach were close to point estimates for all parameters and the CIs did not include null values. Estimates of IIV for parameters were small (coefficient of variation [CV %] <20 %) except for that for KA. The IIV for V4/F, Q3/F, and Q4/F was excluded because it was close to zero. The screening followed by stepwise backward deletion showed body weight to be a significant covariate for CL/F, V2/F, and V3/F. The exponents of body weight on the parameters were similar to the theoretical exponent of allometric scaling (i.e., 0.75 for CL/F and 1 for V2/F and V3/F). Ethnicity was also a significant covariate of F1 (ΔOFV of −39.064 in the screening), with an approximately 10 % lower bioavailability in non-Japanese subjects (white and black/African American subjects) relative to Japanese subjects. In addition, the 95 % CI for the difference in bioavailability between Japanese and non-Japanese subjects included the null value and was within 0.8–1.2. Although the effects of ethnicity on CL/F and V2/F were significant in the screening (ΔOFV of −5.014 and −11.118 for CL/F and V2/F, respectively), the significance of ethnicity on CL/F and V2/F was not observed after including the relation of ethnicity on F1. Supplemental Fig. S2 shows goodness-of-fit plots of the final PK model for plasma lusutrombopag

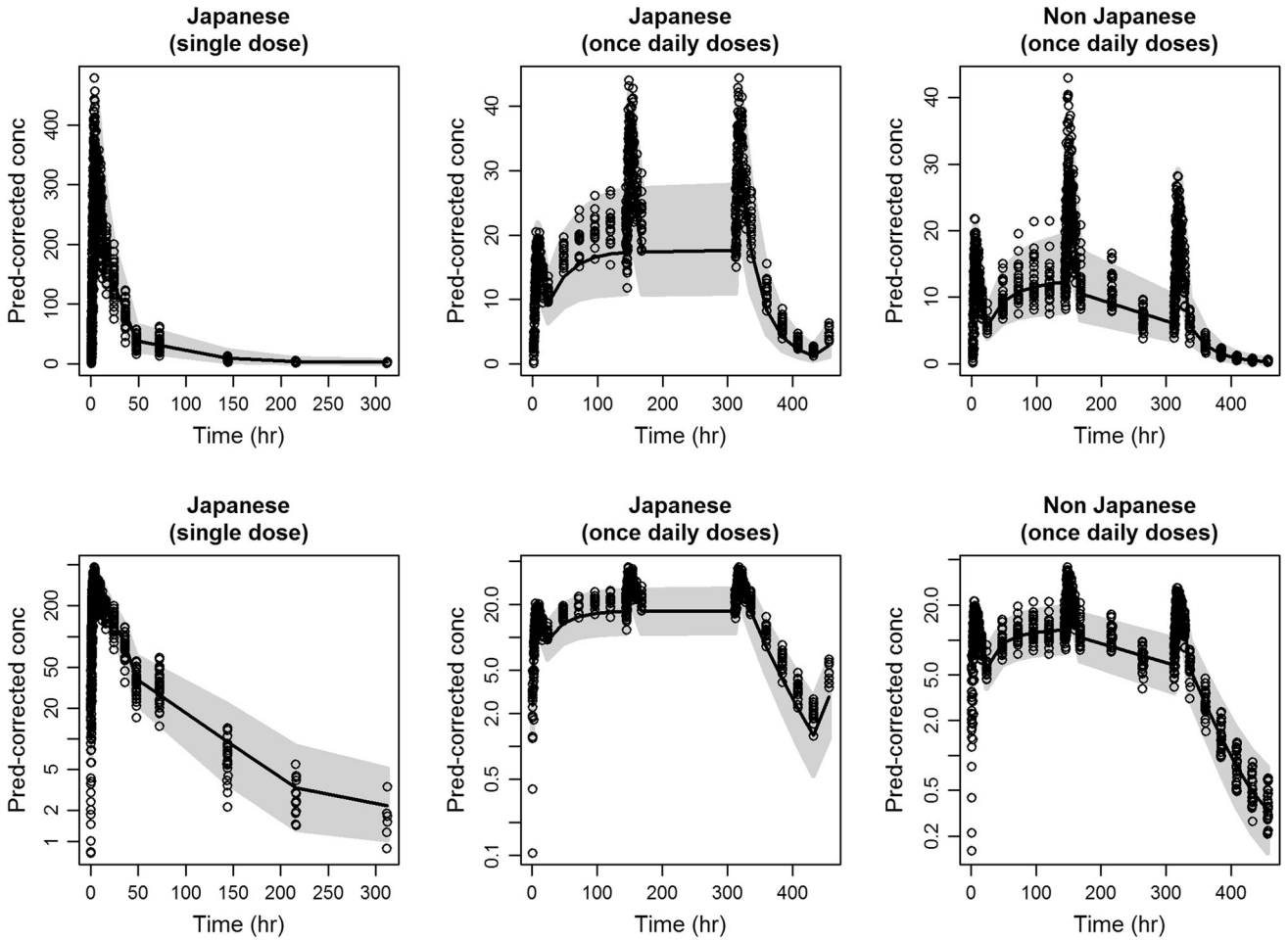

Fig. 2 Prediction-corrected VPC for the final PK model by ethnicity and dosage regimen. *Open circles*: observed data. *Solid lines*: simulated median data. *Shaded area*: 90 % prediction interval. *Upper*: linear scale. *Lower*: semi-logarithmic scale. The data of two Japanese subjects and seven non-Japanese subjects who did not complete the 14-day dosing were included. *Pred-corrected conc* prediction-corrected plasma lusutrombopag concentration, *PK* pharmacokinetic, *VPC* visual predictive checks

concentrations. The population prediction and the individual-predicted prediction corresponded to the observations. There was a lack of bias of the conditional weighted residuals against population prediction or time. Figure 2 shows the prediction-corrected VPC for the PK profiles. The median plasma concentration profile following multiple dosing for Japanese subjects was slightly lower than the observed data. However, overall, the final PK model provided good predictions for single and multiple dosing in Japanese and non-Japanese subjects.

Supplemental Table S1 shows the model development process for the PD structural model. The three-transit compartment model was the best of the tested transit compartment models (two- to four-transit compartment models) based on OFV. The sigmoid E_{max} model was better than the linear model for describing the drug effect of lusutrombopag (ΔOFV of 56.957 for linear model relative to sigmoid E_{max} model). Incorporation of the feedback of platelet production improved the OFV (ΔOFV of −44.128). The proportional residual error model was selected. Supplemental Fig. S3 shows the plots for the relationships of empirical Bayes-estimated parameters for EC_{50} to the background data. No clear relationships between EC_{50} and any background data were suggested. The screening followed by the stepwise backward deletion showed no significant covariate for EC_{50}. Table 4 shows the population PD parameters of the final model. The lower limit of 95 % CI for parameter estimates based on the standard error did not reach zero for all parameters. Furthermore, median values of estimates based on the bootstrap approach were close to point estimates for all parameters and the CIs did not include a null value. IIV values for EC_{50} and KM were 52.2 and 41.8 %, respectively, suggesting large variability for the PD sensitivity

Table 4 Population PD parameters of the final model

Parameter	Estimate	%RSE	Bootstrap[a]
KM (h^{-1})	0.0302	7.6	0.0302 (0.0264–0.0358)
KL (h^{-1})[b]	0.00648	Fixed	Fixed
E_{max}	4.52	20.6	4.48 (3.37–6.35)
EC_{50} (ng/mL)	80.9	33.4	79.4 (53.0–141)
h	1.61	16.9	1.61 (1.18–2.06)
γ	0.286	38.1	0.289 (0.117–0.534)
PLT0 ($\times 10^4/\mu L$)	20.2	2.1	20.3 (19.4–21.1)
IIV for KM (CV %)	41.8	44.6	41.3 (26.1–65.3)
IIV for EC_{50} (CV %)	52.2	20.6	52.1 (40.4–65.2)
IIV for PLT0 (CV %)	17.7	16.4	17.5 (14.9–20.3)
Proportional residual error (CV %)	5.6	8.7	5.6 (5.1–6.1)

η shrinkage for KM, EC_{50}, and PLT0 was 12.0, 7.5 and 0.5 %. ε shrinkage was 7.4 %

%RSE relative standard error in percent, *EC_{50}* plasma S-888711 concentration achieving 50 % of E_{max}, *E_{max}* maximum effect, *h* a sigmoidicity factor, *KL* first-order rate constant for the elimination of platelets, *KM* first-order rate constant for the maturation of platelets, *PLT0* baseline platelet count, γ an exponent of feedback model

[a] Median (95 % confidence interval) from 494 successfully completed bootstrap runs

[b] KL was calculated based on the half-life of platelet (107 h) reported in [9]

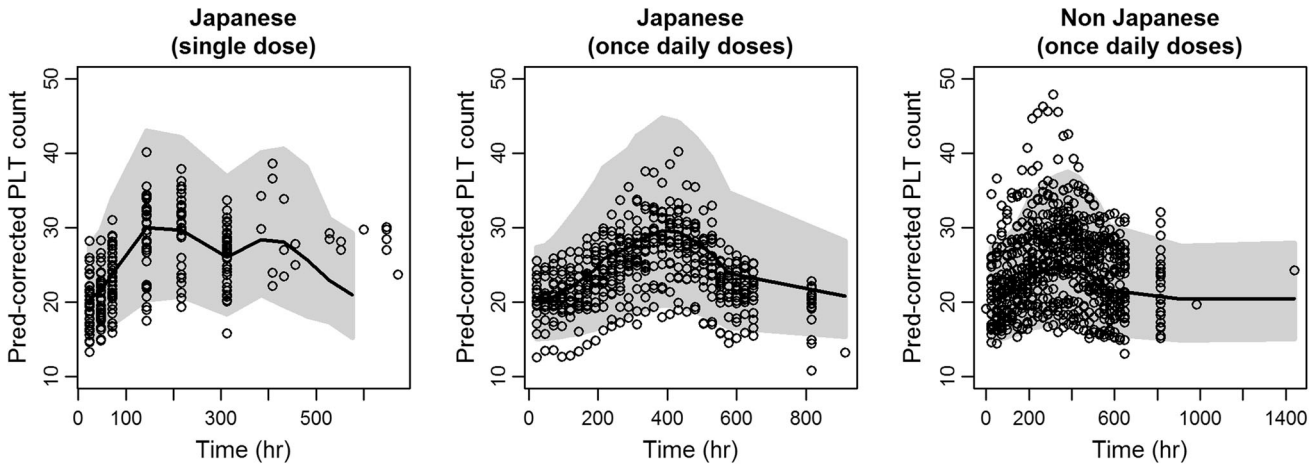

Fig. 3 Prediction-corrected VPC for the final PK/PD model by ethnicity and dosage regimen. *Open circles*: observed data. *Solid lines*: simulated median data. *Shaded area*: 90 % prediction interval. *PK/PD* pharmacokinetic/pharmacodynamic, *PLT* observation variable of platelet counts, *VPC* visual predictive checks, *Pred-corrected PLT count* prediction-corrected platelet count

and the platelet maturation process. Supplemental Fig. S4 shows goodness-of-fit plots of the final PK/PD model for platelet counts, and Fig. 3 shows the prediction-corrected VPC for platelet counts, suggesting that the final PK/PD model provided good predictions for platelet counts in both Japanese and non-Japanese subjects, although there seems to be over-prediction for the Japanese multiple doses.

Figure 4 shows plots for assessment of the effect of body weight on CL/F and V2/F using ratios of CL/F and V2/F relative to the reference value. The CI of the ratio for CL/F and V2/F in subjects with body weight 50 and 90 kg to 70 kg did not include 1 and were outside the range of 0.8–1.2.

Median post hoc AUC values (90 % prediction intervals) using individual CL/F estimates were 2046 (1389–2554) and 1692 (1339–2372) ng·h/mL in Japanese and non-Japanese subjects, respectively, being typically 17 % higher for Japanese subjects than non-Japanese subjects.

Figure 5 shows the simulated median platelet count profiles and the 90 % prediction interval following 24-mg single dosing or 1.5-mg once-daily regimens for 7 days for

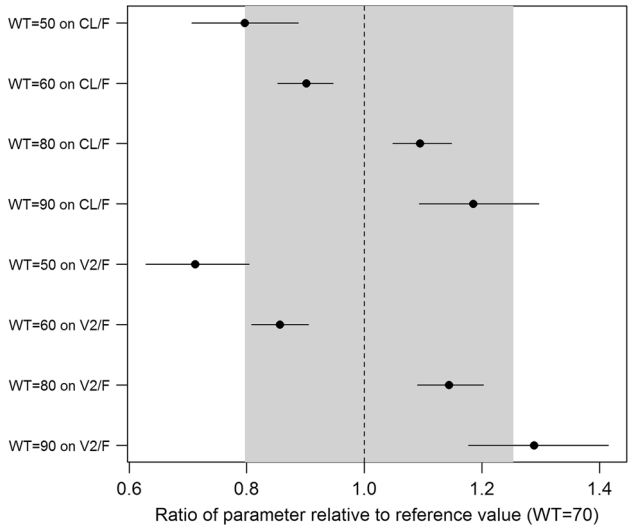

Fig. 4 Plots for assessment of effect of body weight on CL/F or V2/F. *Shaded area*: 20 % difference of ratio relative to the reference value. *Closed circle with error bar*: median with 95 % confidence interval. Ratios of parameters with the range of body weight from 50 to 90 kg relative to those with 70 kg and the 95 % confidence intervals were calculated based on parameter estimates using the non-parametric bootstrap. *CL/F* apparent total clearance, *V2/F* apparent central volume, *WT* body weight

Japanese and non-Japanese subjects. The platelet response profiles were similar between the subject populations. Median (90 % prediction interval (PI)) peak platelet counts for Japanese and non-Japanese subjects were 43.6 (30.1–62.6) and 41.8 (28.9–60.4) $\times$ 10^4/μL for 24-mg single dosing and 41.7 (26.2–64.3) and 37.6 (24.0–59.8) $\times$ 10^4/μL for 1.5-mg multiple dosing, respectively, suggesting that the peak platelet counts were comparable between these subject populations.

4 Discussion

The final PK and PK/PD model well described the data and offered good prediction. The typical plasma concentration profile following multiple dosing for Japanese subjects was slightly lower than the observed data in the VPC. This was probably owing to the complexity of absorption and a resulting accumulation. Consideration of this absorption should enable better prediction.

The time required for megakaryocytes to transform from their progenitors to fully mature cells, which shed platelets, has been reported in the literature as 3.5–5 days [13]. The simulated platelet counts typically began increasing at 3–4 days after initial administration of lusutrombopag and the time delay was consistent with the time for platelet maturation. The maximum response time was predicted to be 9 days after single administration of lusutrombopag in the simulations and corresponded to the sum of reported megakaryocyte (4 days) and platelet cell life span (5 days) [13].

Feedback from platelet production improved the model fitting (ΔOFV of −44.128). The same structure of the feedback model was reported previously for neutrophil counts [14]. In this study, the feedback phenomenon was considered to relate to the process of platelet production as well as neutrophils. The homeostasis of platelet counts in the blood is maintained by a negative feedback, which requires the clearance of TPO from the plasma by megakaryocytes and platelets [15]. This report would support the presence of feedback for platelet response in our PD model.

The difference in lusutrombopag pharmacokinetics between Japanese and non-Japanese subject populations would be minimal based on the results of this study. Eltrombopag, which is an oral TPO receptor agonist, showed steady-state post hoc AUC in healthy East Asian subjects that was approximately 50 % higher than that in healthy non-Asian subjects [6]. These results suggested a difference in PK properties between lusutrombopag and eltrombopag.

The effects of body weight on CL/F, V2/F, and V3/F were significant. The exponents were close to those for allometric scaling. Assessment of the effect of body weight on CL/F and V2/F suggested that they would be modest for body weight of $\leq$50 kg or $\geq$90 kg. The PD sensitivity was higher for the patients with thrombocytopenia than the healthy subjects based in a report on eltrombopag [7]. The efficacy (platelet count profiles) for lusutrombopag in target patients could be predicted based on the PK/PD model of lusutrombopag for healthy subjects, considering differences in the distribution of body weight and differences in the PD sensitivity for eltrombopag between the patients and the healthy subjects.

There were no significant covariates for EC_{50}, which is a parameter to describe PD sensitivity. The PD sensitivity for eltrombopag (SLOP) was statistically significant for sex and age, with the female subjects having a 36 % lower SLOP estimate than male subjects and the SLOP increasing with age [7]. Although the number of female subjects (7 of 78 subjects) and the range of age (20–54 years) were limited in this study, the effects of sex and age on PD sensitivity for lusutrombopag were not suggested from the plots of Bayes-estimated EC_{50} (Supplemental Fig. S3) and they were not selected as significant covariates in the modeling.

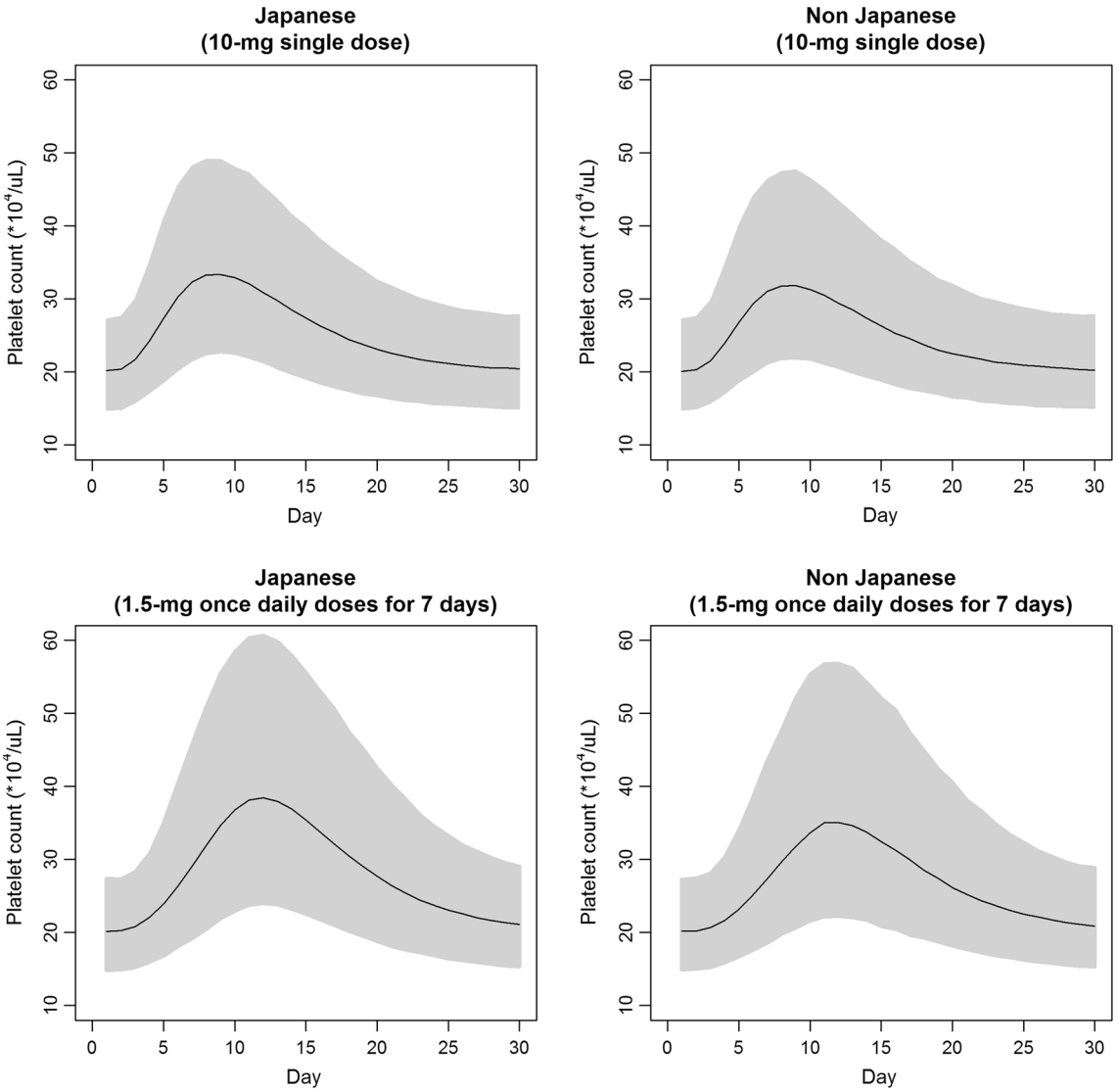

Fig. 5 Simulated platelet response profiles following 24-mg single dosing or 1.5-mg once daily dosing for 7 days in Japanese and non-Japanese subjects. *Solid line*: median platelet count profile. *Shaded area*: 90 % prediction interval

5 Conclusion

A population PK/PD model was developed for lusutrombopag PK/PD. The model well described plasma concentration profiles and platelet count profiles following single and multiple dosing of lusutrombopag. Covariate modeling for the PK model suggested that body weight was an influential covariate on lusutrombopag PK. The simulation for platelet response profiles suggested minimal difference in the PD profiles between Japanese and non-Japanese subject populations. The model could be used as a basic PK/PD model in the drug development of lusutrombopag

Compliance with Ethical Standards

Conflict of interest The authors, Takayuki Katsube, Toru Ishibashi, Takeshi Kano, and Toshihiro Wajima, are all employees of Shionogi & Co., Ltd.

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