



Pharmacokinetic/Pharmacodynamic Modelling and Simulation of Lusutrombopag, a Novel Thrombopoietin Receptor Agonist, for the Treatment of Thrombocytopenia in Patients with Chronic Liver Disease Undergoing Invasive Procedures

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Abstract

Background Patients with thrombocytopenia associated with chronic liver disease (CLD) are at greater risk of bleeding during invasive procedures. This study characterized the pharmacokinetic/pharmacodynamic (PK/PD) profile of lusutrombopag, a novel thrombopoietin-receptor agonist, using modelling and simulation, and evaluated the appropriate dose regimen for treatment of thrombocytopenia in CLD patients undergoing invasive procedures.

Methods A population PK/PD model was developed using plasma lusutrombopag concentrations from 78 healthy subjects and 349 CLD patients, as well as platelet counts from 347 of these 349 patients. Covariates were explored from subject characteristics. Monte-Carlo simulations were performed to assess a dose response for efficacy (platelet counts $\geq 50,000/\mu\text{L}$) and a risk for platelet overshooting (platelet counts $> 200,000/\mu\text{L}$).

Results Visual predictive checks indicated the developed models described the PK/PD profile of lusutrombopag well. In the simulations, without stopping criteria, lusutrombopag 3 mg once daily for 7 days before scheduled invasive procedures provided effective platelet response (85.2% probability for efficacy). The probability of platelet overshooting was 1.2%, indicating that platelet monitoring is not necessary. Although body weight was an influential covariate on the pharmacokinetics of lusutrombopag, individually estimated peak platelet counts overlapped among the body weight groups, suggesting no clinically significant effect on body weight.

Conclusion The modelling and simulation support lusutrombopag 3 mg once daily for 7 days without platelet monitoring.

The results of this study were partially presented at the United European Gastroenterology (UEG) Week (Vienna, 20–24 October 2018) and the American Association for the Study of Liver Diseases (AASLD) Liver Meeting® (San Francisco, 9–13 November 2018).

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Key Points

The pharmacokinetic/pharmacodynamic (PK/PD) profile of lusutrombopag in thrombocytopenic chronic liver disease patients was characterized with modelling and simulation, followed by evaluation of an appropriate dose regimen for the treatment of thrombocytopenia based on the developed model.

The PK/PD profile of lusutrombopag was predictable using the developed model. The PK/PD simulations support that lusutrombopag 3 mg once daily for 7 days provides efficacy with no ethnic difference. The risk for platelet overshooting is likely to be low with a fixed 7-day dosing of lusutrombopag (i.e. no platelet monitoring for stopping the dose).

1 Introduction

Thrombocytopenia commonly develops in patients with chronic liver disease (CLD) regardless of the etiology of the disease [1]. CLD patients with severe thrombocytopenia (platelet count of $< 50,000/\mu\text{L}$) [1] are at greater risk of bleeding in the procedure and postprocedure periods. Platelet transfusion is the current standard of care to reduce bleeding risk in these patients; however, platelet transfusion has complications, including risk of allergic and febrile non-haemolytic transfusion reactions, refractoriness, and infection, as well as treatment limitations such as unpredictable increases in haemostatic platelet levels, short duration of effect, and requirement for hospitalization [2, 3].

Lusutrombopag (S-888711, Mulpleta[®]; Shionogi & Co., Ltd, Osaka, Japan) is a small-molecule, orally active thrombopoietin (TPO) receptor agonist (TPO-RA) that acts on the transmembrane domain of human TPO receptors expressed in megakaryocytes. Lusutrombopag stimulates megakaryocytes to proliferate and differentiate via the same signal transduction system as that of endogenous TPO, and promotes thrombocytopoiesis [4]. Lusutrombopag exhibits linear pharmacokinetics (PK), and the recovery of lusutrombopag in urine was $< 1\%$ of the dose [5]. Lusutrombopag was approved for the treatment of thrombocytopenia in adult CLD patients undergoing procedures in Japan, the US and the EU [4–6]. The lusutrombopag treatment scheme for thrombocytopenic CLD patients is shown in electronic supplementary Fig. S1.

Excessive platelet increase is the major concern during treatment with TPO-RAs. In a clinical study of another TPO-RA—eltrombopag—in patients with cirrhosis and severe thrombocytopenia, the risk of thrombotic events increased above a platelet count of $200,000/\mu\text{L}$, although the causality has not been established [7]. Therefore, the therapeutic window of platelet counts is considered to be $50,000$ – $200,000/\mu\text{L}$ for the treatment of thrombocytopenia in CLD patients, which is relatively narrow given that the haemostatic balance in CLD patients is known to be fragile and the patients may easily become either hypo- or hypercoagulable [8]. As there is a time lag between the PK profile of lusutrombopag and the pharmacodynamic (PD) effect of increased platelets [9], pharmacokinetic/pharmacodynamic (PK/PD) modelling and simulation would be useful for evaluating appropriate dose regimens.

To mitigate the risk of platelet overshooting (platelet counts $> 200,000/\mu\text{L}$), platelet monitoring and a treatment completion criterion were used in the initial clinical trials [10–12]. In these trials, the treatment completion criterion was as follows: administration of lusutrombopag was stopped on days 5, 6, or 7, if the platelet count had reached $\geq 50,000/\mu\text{L}$ and an increase of $\geq 20,000/\mu\text{L}$ from baseline. In a subsequent open-label study (1338M0633, JapicCTI-153023),

the study design decreased the frequency of monitoring (no or 1-day monitoring) for completing lusutrombopag dosing and explored the overall need for monitoring. In addition, modelling and simulation would be useful to address the risk for platelet overshooting with or without the treatment completion criterion.

The aim of the current study was to describe plasma lusutrombopag concentrations in healthy subjects and thrombocytopenic CLD patients, as well as platelet counts in the CLD patients, by developing a population PK/PD model, and assess the dose regimen (2, 3, and 4 mg once daily for 7 days) with or without the treatment completion criterion using the simulations. We also used the model to explore the effects on the PK/PD of covariates that included age, body weight, sex, ethnicity (Japanese vs. non-Japanese), creatinine clearance, and liver dysfunction.

2 Methods

2.1 Data

For PK modelling, 4196 plasma lusutrombopag concentration data from 427 subjects (78 healthy subjects and 349 thrombocytopenic CLD patients) were used. For PK/PD modelling, 3526 platelet counts from 347 of the above 349 patients were used. The study design is summarized in electronic supplementary Table S1. The 46 samples with plasma concentrations below the lower limit of quantification (LLOQ) after the initial dosing were treated as missing in the analyses. Four plasma concentrations from one patient were excluded due to unidentified sampling times, and 17 plasma concentrations taken on day 10 from 17 subjects in a multiple-dose study were also excluded because these concentrations were anomalously higher, as previously reported [9]. The 20 platelet counts from two patients were excluded because these platelet count profiles were anomalous due to concomitant treatment with interactive drugs.

All clinical 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.

Plasma concentrations of lusutrombopag were measured by a validated high-performance liquid chromatography-tandem mass spectrometry with an LLOQ of 0.100 ng/mL (1.00 ng/mL only in Study 0713M0611). The precision of the bioanalytical method was 0.8–12.7%.

2.2 Pharmacokinetic Modelling

A three-compartment model with the first-order absorption and lag time, which was the same structural model as in

healthy subjects [9], was used as a PK starting base model. PK parameters were estimated from data in both healthy subjects and patients with CLD. Since the bioavailability of lusutrombopag was dependent on formulations and food conditions [9], a relative bioavailability, F1, was parameterized for the formulation (solution, 0.25 mg, 1 mg, 2 mg, or 3 mg tablet) in the food condition (fasted or fed). F1 in the fasted state of the solution was set to 1 as a reference value. F1 values in the fed state of the solution, the 1 mg tablet, and the 3 mg tablet were estimated. Based on the results in the relative bioavailability/food effect studies, F1 in the fed state of the 2 mg tablet was fixed at 0.857, and F1 in the fed state of the 0.25 mg tablet was calculated from 0.820 multiplied by F1 in the fed state of the solution. The resulting F1 for the dose regimen used was determined based on

F1 of the formulation in the food condition, considering the proportions of different tablets used. In addition, as a visual inspection suggests, different plasma concentration profiles between the solution in the fed state and the other conditions, the parameters related to absorption (i.e. first-order absorption rate constant [KA] and lag time for absorption [ALAG1]) for the solution in the fed state were estimated separately. The interindividual variability (IIV) was assumed to be log-normally distributed for apparent total clearance (CL/F), apparent volume of distribution in the central compartment (V2/F) or peripheral compartment (V3/F and V4/F), apparent intercompartmental clearance (Q3/F and Q4/F), and KA. A proportional residual error model and a combination residual error model (proportional residual error + additive residual error) were tested. In the covariate

Table 1 Demographics of the analysis population

Subject	Background data	Mean (SD)	Median (range)
All subjects [<i>N</i> = 427]	Age, years	58.0 (17.3)	63.0 (19.0–84.0)
	Body weight, kg	65.9 (14.6)	64.0 (34.9–142.0)
	CLcr, mL/min	96.71 (37.21)	90.16 (10.73–246.64)
	Sex, male/female [<i>n</i> (%)]	263 (61.6)/164 (38.4)	
	Child–Pugh class, normal/A/B/C [<i>n</i> (%)]	78 (18.3)/207 (48.5)/135 (31.6)/7 (1.6)	
	Japanese/non-Japanese [<i>n</i> (%)]	302 (70.7)/125 (29.3)	
	Race, White/Asian/Black or African American/American Indian or Alaska Native/other/not provided [<i>n</i> (%)]	99 (23.2)/317 (74.2)/4 (0.9)/2 (0.5)/3 (0.7)/2 (0.5)	
Japanese healthy subjects [<i>n</i> = 54]	Age, years	25.3 (4.1)	24.0 (20.0–37.0)
	Body weight, kg	63.8 (7.0)	63.2 (50.2–77.0)
	CLcr, mL/min	140.01 (21.60)	138.84 (99.54–195.87)
	Sex, male/female [<i>n</i> (%)]	54 (100.0)/0 (0.0)	
Non-Japanese healthy subjects [<i>n</i> = 24]	Age, years	37.5 (9.0)	36.5 (21.0–54.0)
	Body weight, kg	76.0 (9.0)	77.4 (57.6–93.7)
	CLcr, mL/min	108.03 (18.58)	114.73 (73.56–138.28)
	Sex, male/female [<i>n</i> (%)]	17 (70.8)/7 (29.2)	
Japanese CLD patients [<i>n</i> = 248]	Age, years	68.1 (8.2)	69.0 (49.0–84.0)
	Body weight, kg	60.7 (11.4)	60.2 (34.9–96.7)
	CLcr, mL/min	80.97 (29.94)	75.00 (31.82–246.64)
	Sex, male/female [<i>n</i> (%)]	134 (54.0)/114 (46.0)	
	Child–Pugh class, normal/A/B/C [<i>n</i> (%)]	0 (0.0)/141 (56.9)/103 (41.5%)/4 (1.6)	
Non-Japanese CLD patients [<i>n</i> = 101]	Age, years	55.2 (11.6)	55.0 (19.0–81.0)
	Body weight, kg	77.3 (17.9)	74.0 (39.0–142.0)
	CLcr, mL/min	109.52 (39.17)	110.04 (10.73–239.33)
	Sex, male/female [<i>n</i> (%)]	58 (57.4)/43 (42.6)	
	Child–Pugh class, normal/A/B/C [<i>n</i> (%)]	0 (0.0)/66 (65.4)/32 (31.7)/3 (3.0)	
	Race, White/Asian/Black or African American/American Indian or Alaska Native/other/not provided [<i>n</i> (%)]	78 (77.2)/15 (14.9)/1 (1.0)/2 (2.0)/3 (3.0)/2 (2.0)	

CLcr creatinine clearance, CLD chronic liver disease, SD standard deviation

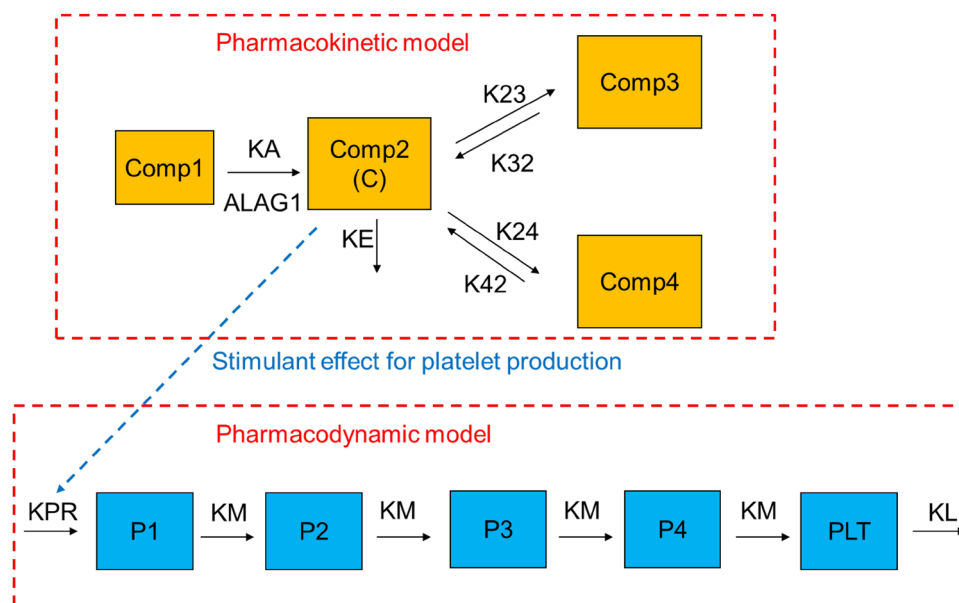


Fig. 1 Scheme of the pharmacokinetic/pharmacodynamic model for lusutrombopag. *Comp1* absorption compartment, *Comp2* central compartment, *Comp3* and *Comp4* peripheral compartment, *P1*, *P2*, *P3* and *P4* hypothetical platelet precursor compartment, *PLT* platelet compartment, *KA* first-order rate constant of absorption, *K23*, *K32*, *K24* and *K42* first-order transfer rate constant between compartments,

KE first-order rate constant of elimination, *ALAG1* lag time for absorption, *C* plasma lusutrombopag concentration, *KPR* zero-order rate for the production of platelet precursors, *KM* first-order rate constant for maturation of platelet, *KL* first-order rate constant for elimination of platelets

modelling, the following effects were tested: age, body weight, sex, Child–Pugh classification (A, B or C) [13], creatinine clearance estimated using the Cockcroft–Gault equation [14], ethnicity (Japanese or non-Japanese subjects), and subject population (healthy subjects or CLD patients) on CL/F; age, body weight, sex, ethnicity, and subject population on V2/F; and body weight on V3/F. Covariates were normalized to the median values for the continuous covariates using the following equation (Eq. 1):

$$\theta_i = \theta_{\text{pop}} \times (\text{COV}_i / \text{COV}_{\text{med}})^{\theta_{\text{cov}}}, \quad (1)$$

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

The following equation was used for the categorical covariates (Eq. 2):

$$\theta_i = \theta_{\text{CAT}_i=0} \times \theta_{\text{CAT}_i=1}^{\text{CAT}_i}, \quad (2)$$

where CAT_i is the individual categorical variable for sex, ethnicity, and subject population with either 0 or 1 (0 for male/non-Japanese/healthy subjects, and 1 for female/Japanese/CLD patients), $\theta_{\text{CAT}_i=0}$ is the typical values of the parameter for the individual categorical variable of 0, and

$\theta_{\text{CAT}_i=1}$ is the covariate effect for the individual categorical variable of 1.

Covariate models were constructed by a combination of screening for inclusion and stepwise backward deletion based on the Chi-square test. The significance level of 0.05 for covariate models versus the base model was used for screening (the difference in the value of the objective function [ΔOBJ] of less than -3.84 for one degree of freedom was significant). The significant covariates at screening were included in the base model to construct a full model. The backward deletion with the significance level of 0.01 between models with and without the covariate was used to construct a final model (the deletion of the covariate with an ΔOBJ of < 6.64 for one degree of freedom was accepted).

2.3 Pharmacokinetic/Pharmacodynamic (PK/PD) Modelling

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 transit and platelet compartments [9]. In the model, lusutrombopag stimulates the zero-order production rate of platelet precursors in a manner dependent of plasma lusutrombopag concentrations. Four- to six-compartment models (three- to five-transit and one-platelet compartment

Table 2 PK/PD parameter estimates of the final models of lusutrombopag

Parameter	Estimate (%RSE)	Bootstrap median (95% CI) ^a
PK parameters		
CL/F [L/h]		
Typical CL/F	0.874 (3.9)	0.876 (0.810–0.935)
Effect of WT	0.750 (fixed)	
Effect of sex	0.874 (3.5)	0.874 (0.816–0.941)
Effect of ethnicity	0.868 (4.1)	0.866 (0.809–0.940)
Effect of subject population	0.870 (4.9)	0.865 (0.788–0.952)
V2/F [L]		
Typical V2/F	12.2 (5.9)	12.3 (5.75–13.9)
Effect of WT	1.00 (fixed)	
Effect of subject population	1.46 (7.1)	1.45 (1.25–2.17)
Q3/F [L/h]	0.872 (8.0)	0.851 (0.672–0.993)
V3/F [L]		
Typical V3/F	9.04 (6.6)	8.95 (7.71–12.1)
Effect of WT	1.00 (fixed)	
Q4/F [L/h]	0.0265 (9.7)	0.0267 (0.0216–0.0341)
V4/F [L]	3.48 (15.2)	3.43 (2.79–5.38)
KA [h]		
Solution in the fed state	0.166 (8.6)	0.165 (0.0925–0.197)
Others (solution in the fasted state, 2 mg tablet in the fed state, 0.25 mg tablet in the fed state, 2.5 mg [2 × 0.25 mg tablets and 1 × 2 mg tablet] in the fed state, 3.0 mg [4 × 0.25 mg tablets and 1 × 2 mg tablet] in the fed state, 1 mg tablet in the fed state, 3 mg tablet in the fed state)	0.218 (6.7)	0.218 (0.117–0.249)
Lag time [h]		
Solution in the fed state	0.568 (6.0)	0.568 (0.504–0.677)
Others (solution in the fasted state, 2 mg tablet in the fed state, 0.25 mg tablet in the fed state, 2.5 mg [2 × 0.25 mg tablets and 1 × 2 mg tablet] in the fed state, 3.0 mg [4 × 0.25 mg tablets and 1 × 2 mg tablet] in the fed state, 1 mg tablet in the fed state, 3 mg tablet in the fed state)	0.193 (3.3)	0.193 (0.183–0.208)
F1 of solution in the fasted state	1.00 (fixed)	
F1 relative to solution in the fasted state		
Solution in the fed state	0.884 (fixed)	
2 mg tablet in the fed state	0.857 (fixed)	
0.25 mg tablet in the fed state	0.725 (fixed)	
2.5 mg (2 × 0.25 mg tablets and 1 × 2 mg tablet) in the fed state	0.831 (fixed)	
3.0 mg (4 × 0.25 mg tablets and 1 × 2 mg tablet) in the fed state	0.813 (fixed)	
1 mg tablet in the fed state	0.973 (5.2)	0.971 (0.860–1.08)
3 mg tablet in the fed state	0.843 (4.2)	0.837 (0.766–0.915)
Interindividual variability		
Variance for CL/F [CV%]	0.0880 [29.7] (9.6)	0.0870 (0.0714–0.104)
Variance for V2/F [CV%]	0.104 [32.2] (23.0)	0.106 (0.0493–0.273)
Variance for KA [CV%]	0.169 [41.1] (22.7)	0.169 (0.00701–0.252)
Intraindividual variability		
Standard deviation for proportional residual error [CV%]	0.180 [18.0] (3.9)	0.181 (0.167–0.195)
PD parameters		
KM [h]	0.0320 (5.3)	0.0318 (0.0288–0.0353)
KL [h]	0.00863 (10.2)	0.00871 (0.00720–0.0108)
SLOP [mL/μg]		
Typical SLOP	9.08 (4.8)	9.09 (8.28–10.0)
Effect of CPS ≥ 9	1.69 (12.7)	1.69 (1.26–2.13)
PLT0 [×10 ⁴ /μL]	3.92 (1.6)	3.92 (3.80–4.05)

Table 2 (continued)

Parameter	Estimate (%RSE)	Bootstrap median (95% CI) ^a
Interindividual variability		
Variance for KM [CV%]	0.109 [33.0] (21.3)	0.107 (0.0642–0.168)
Variance for KL [CV%]	0.423 [65.0] (18.3)	0.419 (0.273–0.591)
Variance for SLOP [CV%]	0.287 [53.6] (15.2)	0.283 (0.199–0.393)
Variance for PLT0 [CV%]	0.0703 [26.5] (11.7)	0.0707 (0.0551–0.0880)
Intraindividual variability		
Standard deviation for proportional residual error [CV%]	0.106 [10.6] (6.2)	0.106 (0.0913–0.118)
Standard deviation for additive residual error [$\times 10^4/\mu\text{L}$]	0.245 (20.0)	0.246 (0.130–0.332)

CI confidence interval, *CL/F* apparent total clearance, *CPS* Child–Pugh score, *CV%* percentage coefficient of variation, *FI* bioavailability, *KA* first-order rate constant of absorption, *KL* first-order rate constant for elimination of platelet, *KM* first-order rate constant for the maturation of platelet, *Lag time* lag time for absorption, *PD* pharmacodynamic, *PK* pharmacokinetic, *PLT0* baseline platelet count, *Q3/F* and *Q4/F* apparent intercompartmental clearance, *RSE* relative standard error, *SLOP* slope relating plasma lusutrombopag concentrations, *V2/F* apparent volume of distribution in the central compartment, *V3/F* and *V4/F* apparent volumes of distribution in the peripheral compartments, *WT* body weight

CL/F in the final model = $0.874 \times (WT/64.0)^{0.750} \times 0.874^{\text{SEX}} \times 0.868^{\text{Ethnicity}} \times 0.870^{\text{Subject population}}$

$V2/F$ in the final model = $12.2 \times (WT/64.0) \times 1.46^{\text{Subject population}}$

$V3/F$ in the final model = $9.04 \times (WT/64.0)$

(Sex = 0 for male and 1 for female; ethnicity = 0 for non-Japanese and 1 for Japanese; subject population = 0 for healthy subjects and 1 for thrombocytopenic subjects)

$SLOP$ in the final model = $9.08 \times 1.69^{\text{CPS2}}$ (CPS2 = 0 for CPS < 9 and CPS2 = 1 for CPS \geq 9)

^aMedian (95% CI) from 242 and 300 successfully completed runs for PK and PD parameters, respectively

models) were tested and compared based on the objective function values. A five-compartment model (four-transit and one-platelet compartment model) was selected, as shown in Eqs. 3–7.

$$dP1/dt = KPR \cdot (1 + E) - KM \cdot P1, \quad (3)$$

$$dP2/dt = KM \cdot P1 - KM \cdot P2, \quad (4)$$

$$dP3/dt = KM \cdot P2 - KM \cdot P3, \quad (5)$$

$$dP4/dt = KM \cdot P3 - KM \cdot P4, \quad (6)$$

$$dPLT/dt = KM \cdot P4 - KL \cdot PLT, \quad (7)$$

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–P4 are platelet precursor counts, and PLT is the observation variable of platelet counts. KM, KL, and PLT0 were estimated from data in the CLD patients. The KPR was calculated as $PLT0 \times KL$, assuming a steady state of platelet count. The initial conditions at steady state were: $P1(0)–P4(0) = KPR/KM$, $PLT(0) = PLT0$.

The linear model shown in Eq. 8 was tested to explain the drug effect (*E* in Eq. 3).

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

where SLOP is the slope relating to plasma lusutrombopag concentrations, and *C* is the plasma lusutrombopag

concentration. As a saturable manner did not appear in the observation of exposure–response relationship, a sigmoid maximum effect (E_{max}) model was not tested. A first-order rate constant for the production [15] and a feedback function [9, 15] were tested.

IIV for KM, KL, SLOP, and PLT0 was assumed to be log-normally distributed. A proportional residual error model and a combination residual error model were tested.

In the covariate modelling, effects of age, body weight, Child–Pugh class (A, B or C) or numerical score, sex, ethnicity, and observed baseline platelet count on SLOP were tested by screening, followed by the stepwise backward deletion similar to the PK modelling.

2.3.1 Parameter Estimation and Model Evaluation

A sequential PK/PD modelling approach was applied, where PK modelling was first conducted, and then PK/PD modelling was conducted using empirical Bayes-estimated PK parameters. Parameters were estimated from the data with the first-order conditional estimation using the interaction (FOCE-I) method.

The predictive performance of a final model was evaluated by dose-normalized (for PK) or prediction-corrected (for PK/PD) visual predictive check (VPC) [16] with 200 replications, for which 95% prediction intervals of 2.5th, 50th, and 97.5th predictions were calculated and compared with the median and 95% confidence interval (CI) of the

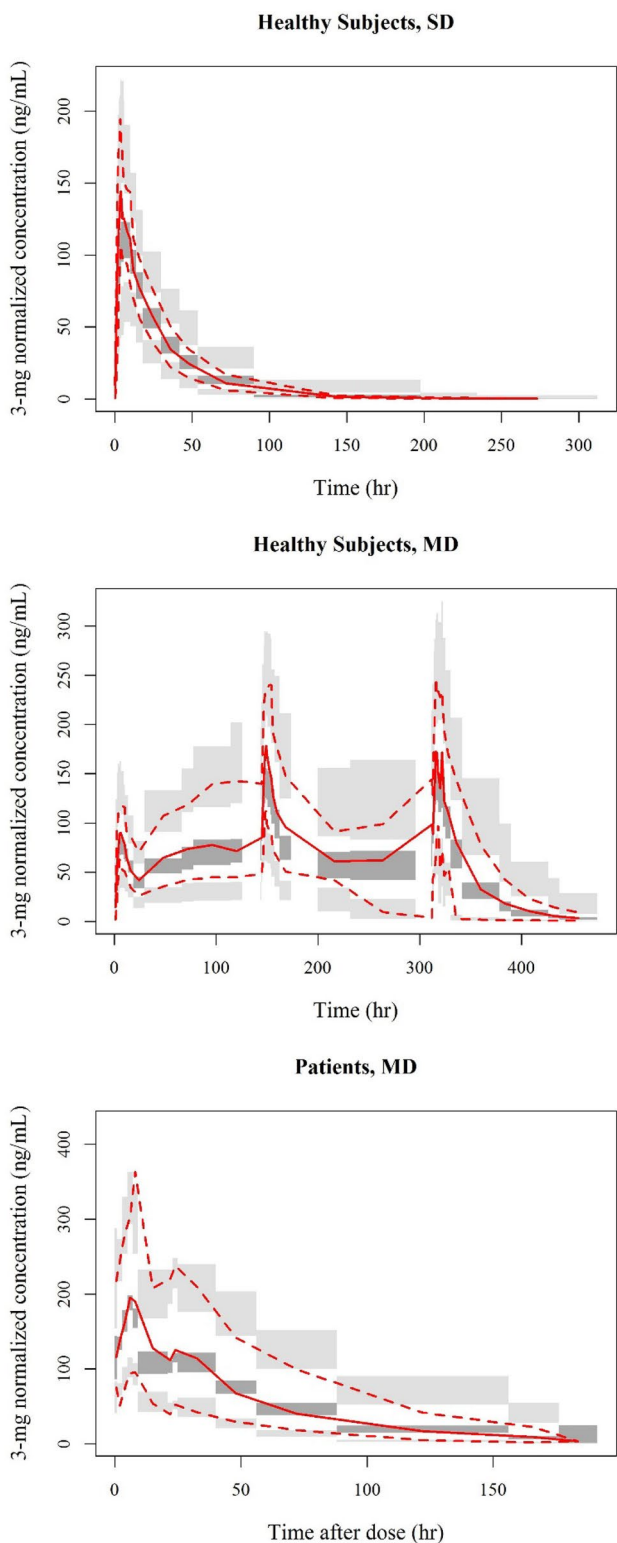


Fig. 2 Dose-normalized visual predictive check for the final PK model by subpopulation normalized for patients receiving 3 mg. Solid line represents the observed median; dashed lines represent the observed 2.5th and 97.5th percentiles; dark-grey-shaded area represents the model-predicted 95% CI of the median; grey-shaded area represents the model-predicted 95% CIs of the 2.5th and 97.5th percentiles. 200 replications. *SD* single dose, *MD* multiple dose, *CI* confidence interval, *PK* pharmacokinetic

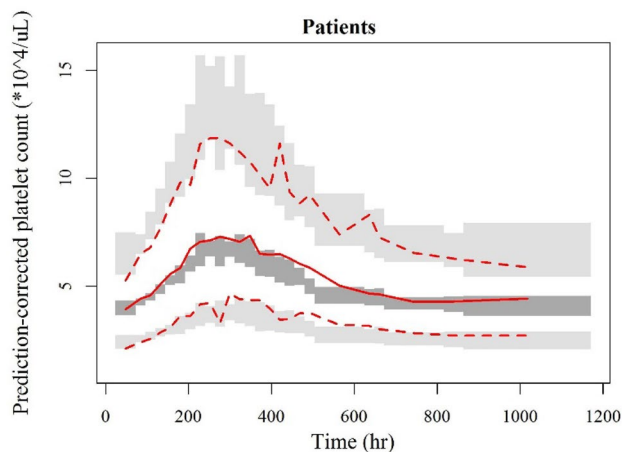


Fig. 3 Prediction-corrected visual predictive check for the final PK/PD model for thrombocytopenic CLD patients. Solid line represents the observed median; dashed line represents the observed 2.5th and 97.5th percentiles; Dark-grey-shaded area represents the model-predicted 95% CI of the median; grey-shaded area represents the model-predicted 95% CIs of 2.5th and 97.5th percentiles. 200 replications. *PK/PD* pharmacokinetic/pharmacodynamic, *CLD* chronic liver disease, *CI* confidence interval

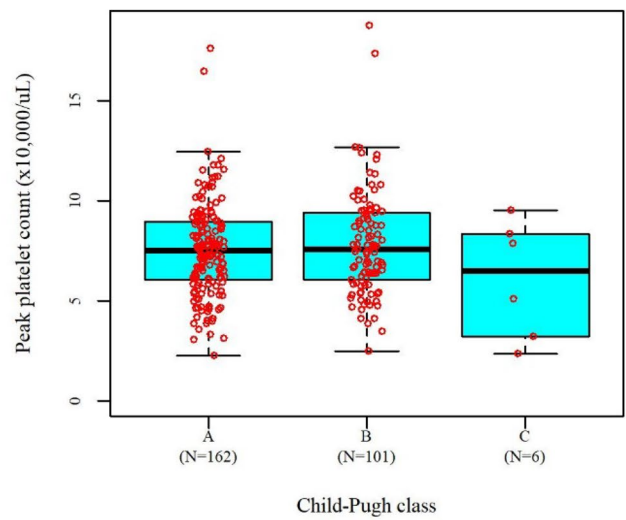
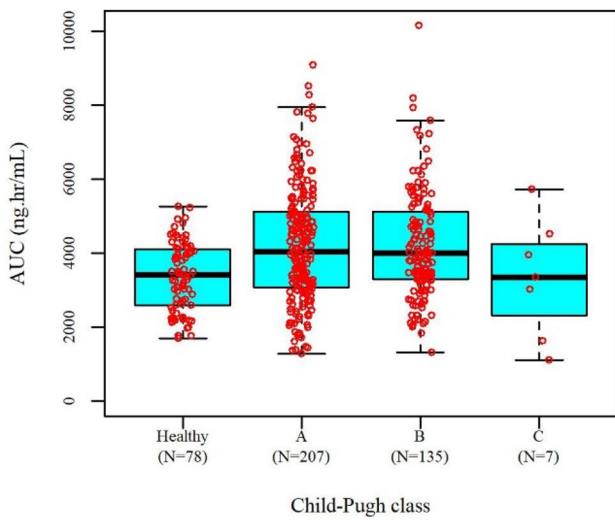
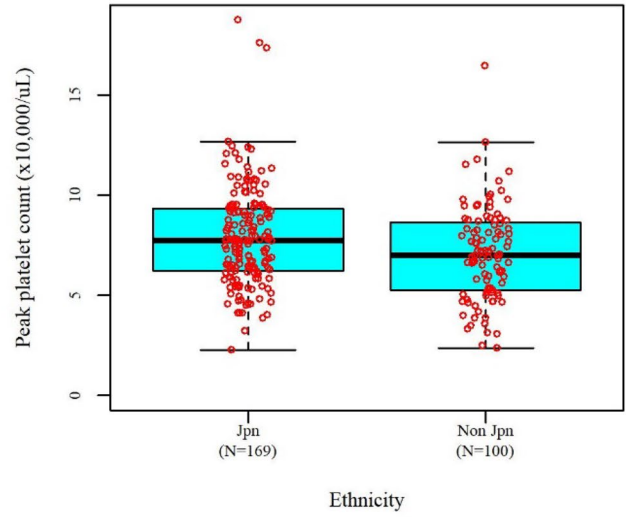
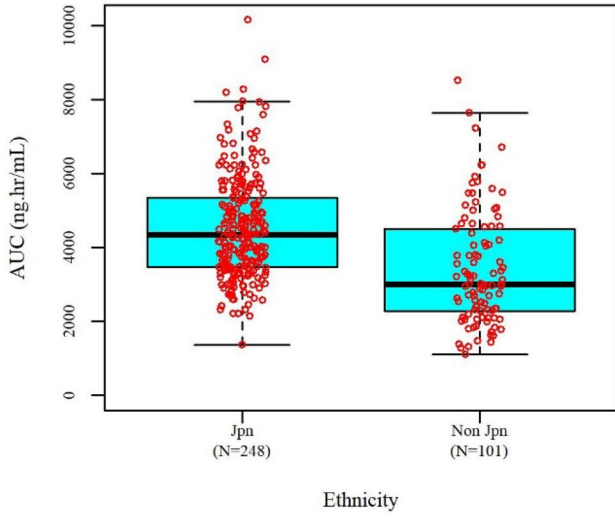
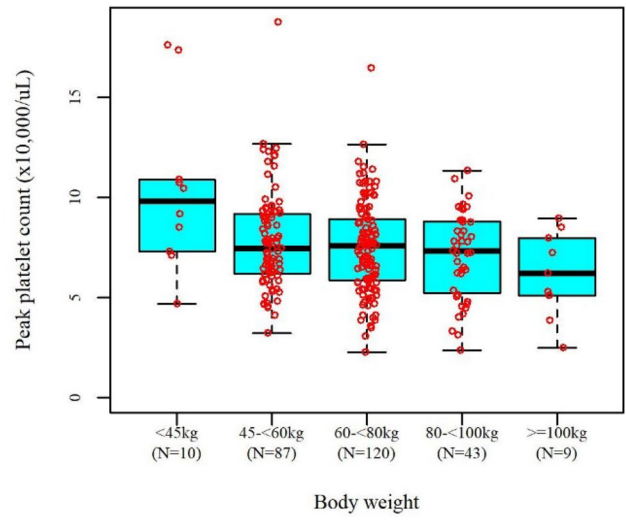
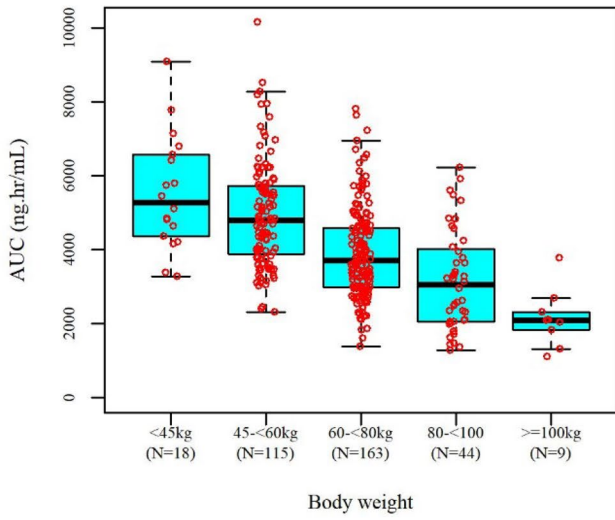
observed data. The dose-normalized VPC was performed based on 3-mg-normalized observed and predicted concentrations. The parameter estimates of the final model were evaluated by bootstrap [17] with 300 replications.

2.3.2 Post Hoc Analyses for Predicting Exposure and Peak Platelet Counts

Steady-state daily area under the plasma concentration-time curve (AUC) of lusutrombopag and the peak platelet counts in individual patients following a 3 mg once-daily dose were calculated by empirical Bayes-estimated parameters from the final model. The daily AUC was calculated as the daily dose divided by CL/F (= daily dose/[CL/F]). Peak platelet counts were calculated using the PK/PD model from simulated platelet counts every 24 h from 0 to 696 h, for each of the patients who received a 3-mg dose for up to 7 days. The actual date and time of dosing were used for the simulations of platelet counts. The AUC and peak platelet counts were summarized by body weight, ethnicity, or Child–Pugh class.

2.4 PK/PD Simulation for Platelet Count Profiles

The developed PK/PD model was employed to assess dose response, necessity of platelet monitoring, and effect of body weight on platelet counts. For the dose response, 2, 3 and 4 mg once-daily for 7 days were tested. For the necessity of monitoring platelet counts during treatment, the following treatment completion criterion was employed: if platelet counts were $\geq 50,000/\mu\text{L}$ and an increase from the baseline was $\geq 20,000/$



◀**Fig. 4** Steady-state daily AUC of lusutrombopag and peak platelet counts predicted following a 3 mg once-daily dose using post hoc parameters of thrombocytopenic CLD patients by subpopulation. Left figures: Steady-state daily AUC of lusutrombopag following 3 mg once-daily dosing. Right figures: Peak platelet counts in patients who received the 3 mg dose regimen for up to 7 days. Box plot: thick centre line represents the median; *top and base of the box* represent the first and third quartiles (IQR); whiskers represent the most extreme data within $1.5 \times \text{IQR}$; and circles represent the individual data. *Jpn* Japanese, *non Jpn* non-Japanese, *healthy* healthy subjects, *AUC* area under the plasma concentration-time curve, *CLD* chronic liver disease, *IQR* interquartile range

μL , administration of lusutrombopag was stopped. The Monte-Carlo simulations were performed with or without the treatment completion criterion based on platelet counts prior to the dose on day 6 (1 day) or days 5–7 (3 days). For each simulation scenario, 200-replication simulations were performed by generating 69,400 virtual subjects with resampling of the covariate data from the analysis dataset. For the effect of body weight, 2000 simulations (2000 virtual patients per group), using a 3 mg once-daily dose for 7 days, were performed by body weight group according to the uniform distribution of body weight, Child–Pugh score <9 , and male to female ratio of 1:1 for non-Japanese CLD patients. PLT_0 was simulated according to a log-normal distribution based on the estimate (mean 39,200/ μL and coefficient of variation [CV] 26.5%). The simulated platelet counts using PLT_0 of $>50,000/\mu\text{L}$ were excluded from the summary. Platelet counts of virtual subjects were simulated every 24 h from 0 to 696 h. The following platelet metrics were calculated from the simulated platelet counts for each simulation scenario: (1) 5th, 50th and 95th percentiles of peak platelet count; (2) as an efficacy index, probability to attain 50,000/ μL of platelet count from days 9 to 14, which is the period when invasive procedures are expected to be scheduled; and (3) as a safety index, probability to exceed 200,000/ μL of platelet count on any time points.

2.5 Software

NONMEM version 7.3 (ICON Development Solutions, Ellicott City, MD, USA) was used [18]. Perl-speaks NONMEM version 4.2.0 was used to execute a NONMEM run for parameter estimations and simulations, VPC, and a non-parametric bootstrap method for calculating 95% CIs of parameter estimates [19], and R version 3.0.2 was used for summarization and the graphics [20].

3 Results

3.1 Population PK and PK/PD Modelling

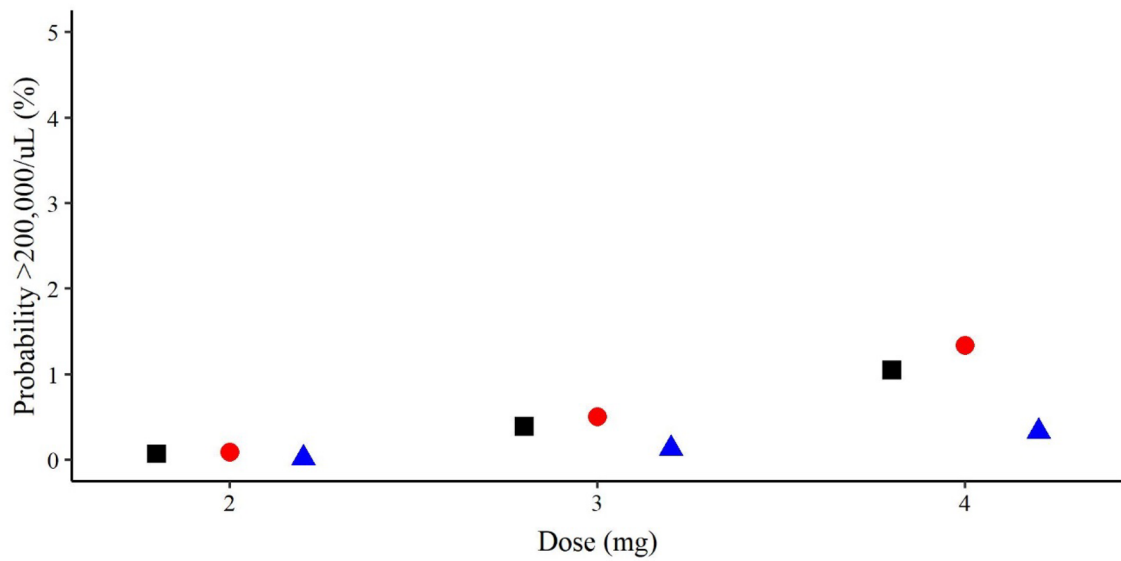
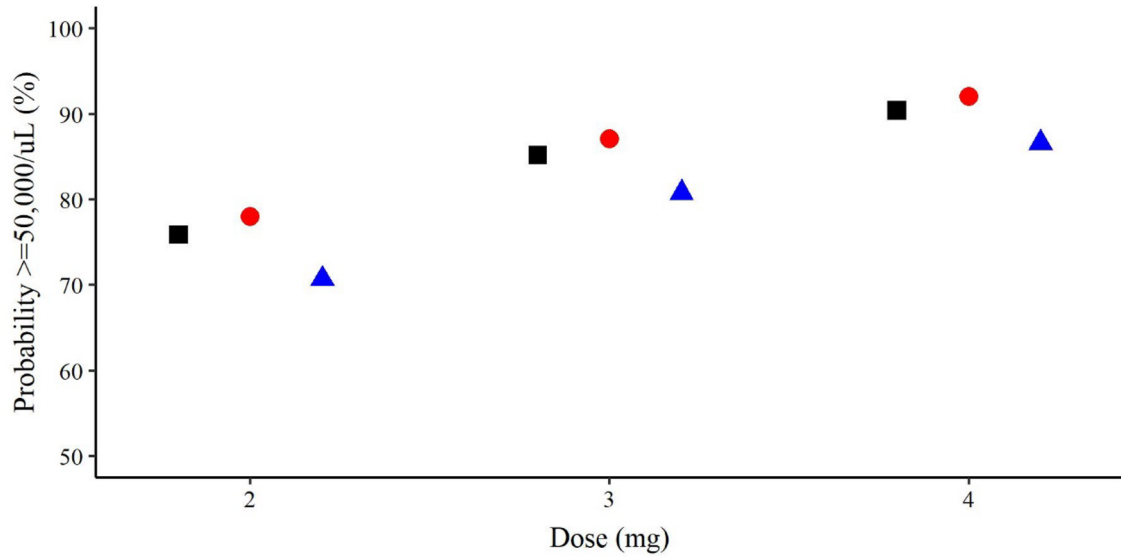
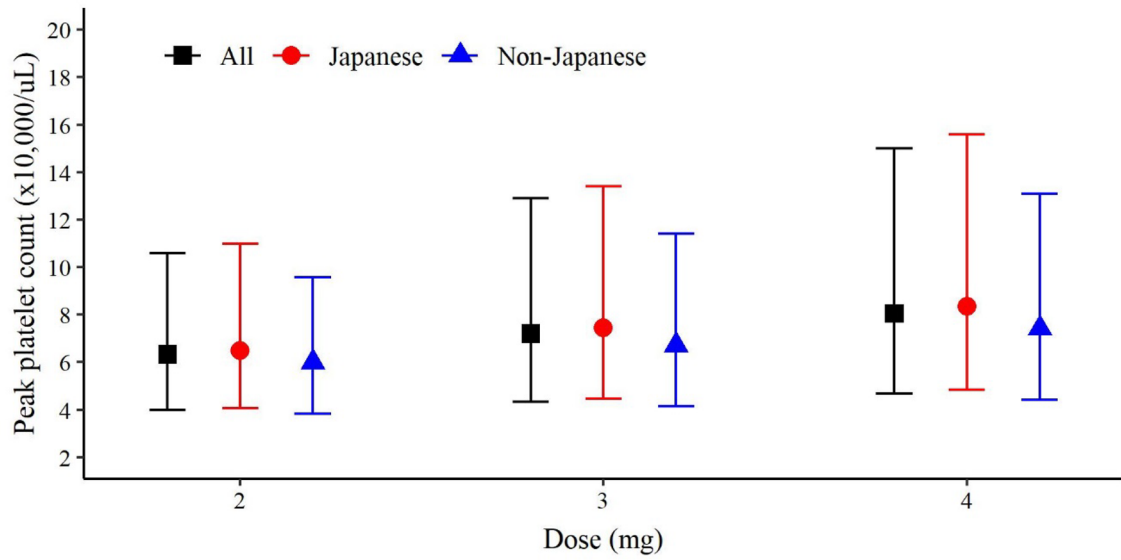
Demographic data are presented in Table 1. Figure 1 shows the scheme of the final PK/PD model, and Table 2

shows the population PK/PD parameters of the final model. The relative standard error for parameter estimates was $\leq 23.0\%$. The 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.

For the PK data, the three-compartment model with the first-order absorption and lag time, and the proportional residual error model, were selected. The IIV for Q3/F, Q4/F and V4/F was excluded because it was close to zero. The dose-normalized VPC indicated the predictions of the final PK model described the observed PK profiles in healthy subjects and thrombocytopenic CLD patients (Fig. 2). The following covariates were retained in the final model: body weight on CL/F, V2/F and V3/F; sex and ethnicity (Japanese/non-Japanese) on CL/F; and subject population (healthy subjects/thrombocytopenic CLD patients) on CL/F and V2/F. The CI from the bootstrap for the effect of sex and ethnicity on CL/F was within 0.80–1.25 (electronic supplementary Fig. S2). The CL/F ratio was 0.870 (95% CI 0.788–0.952) in CLD patients relative to healthy subjects. As the lower limit of the 95% CI was close to 0.80, the difference in CL/F between the subject populations was not considered clinically significant. The V2/F in CLD patients was 1.46-fold (95% CI 1.25–2.17) higher than that in healthy subjects.

For the PD data, the five-compartment model (four-transit compartment and one-platelet compartment models) with the zero-order rate for production was selected as a base model. The drug effect was well-described with the linear model. The KL in the PD model with feedback function was estimated to be 0.00444/h, which was lower than in healthy subjects (0.00648/h) [9]. As the feedback is a regulation function on production in case of excessive platelets, the feedback function was not applied. The prediction-corrected VPC indicated the predictions of the final PK/PD model described the platelet counts in thrombocytopenic CLD patients (Fig. 3). In the covariate modelling, SLOP increased for Child–Pugh score of ≥ 9 , while no clear relationships were observed between SLOP and age, body weight, ethnicity, sex, or observed baseline platelet counts (electronic supplementary Fig. S3).

The steady-state daily AUC and peak platelet counts were predicted based on empirical Bayes-estimated parameters following a 3 mg once-daily dose for 7 days in thrombocytopenic CLD patients (Fig. 4). The AUC of lusutrombopag decreased with increasing body weight. Furthermore, the AUC was 1.3-fold higher in Japanese patients than in non-Japanese patients. The median peak platelet counts were higher in the lowest body weight group (35 to <45 kg) than in the other groups (45–130 kg), while the individual peak platelet counts overlapped among the body weight groups. Peak platelet counts in Japanese patients were similar to those in non-Japanese patients. Median AUC and peak platelet counts in patients with Child–Pugh class C were lower than those in patients with



◀**Fig. 5** Simulated platelet metrics for a dose response of 2, 3 and 4 mg once daily for 7 days by CLD patients. Simulations were performed with 200 replications. Probability $\geq 50,000/\mu\text{L}$ represents the probability of attaining $50,000/\mu\text{L}$ platelet count on days 9–14, and probability $> 200,000/\mu\text{L}$ represents the probability of exceeding $200,000/\mu\text{L}$ platelet count. The treatment completion criterion was applied on days 5–7

Child–Pugh class A or B, but the AUC was comparable with that in healthy subjects. The individual AUC and peak platelet counts overlapped among Child–Pugh classes.

3.2 PK/PD Simulations for Platelet Counts

Figure 5 shows simulated platelet metrics for 2, 3 and 4 mg once-daily doses for 7 days. The peak platelet counts were slightly different among the dose regimens. The probabilities to attain $50,000/\mu\text{L}$ on days 9–14 were 75.9%, 78.0% and 70.7% at the 2 mg dose; 85.2%, 87.1% and 80.8% at the 3 mg dose; and 90.4%, 92.0%, and 86.6% at the 4 mg dose, in all patients, Japanese and non-Japanese patients, respectively. The probabilities to exceed $200,000/\mu\text{L}$ were 0.07%, 0.09% and 0.02% at the 2 mg dose; 0.39%, 0.50% and 0.13% at the 3 mg dose; and 1.05%, 1.34% and 0.33% at the 4 mg dose, in all patients, Japanese patients and non-Japanese patients, respectively.

Figure 6 shows the simulated platelet metrics at 3 mg once daily for 7 days with or without the treatment completion criterion. Median peak platelet counts were similar between groups with or without the treatment completion criterion in any patient population. The probabilities of exceeding $200,000/\mu\text{L}$ in all patients, Japanese patients and non-Japanese patients, respectively, were 1.20%, 1.52% and 0.43% without the treatment completion criterion; 0.59%, 0.74% and 0.20% with the treatment completion criterion on day 6; and 0.39%, 0.50% and 0.13% with the treatment completion criterion on days 5–7. The probabilities of attaining $50,000/\mu\text{L}$ were similar between groups with and without the treatment completion criterion in any patient population. The probability for $\geq 50,000/\mu\text{L}$ was independent of days for treatment completion criterion since dose was stopped for patients who achieved $50,000/\mu\text{L}$.

Figure 7 shows the simulated platelet metrics at a 3 mg once-daily dose for 7 days, by body weight group. Differences in median peak platelet counts were $3900\text{--}12,000/\mu\text{L}$ in each body weight group relative to the reference group (60 to < 80 kg). The probabilities of attaining $50,000/\mu\text{L}$ and exceeding $200,000/\mu\text{L}$ were 90.8% and 2.05% in the lowest body weight groups (35 to < 45 kg), respectively, and 69.5% and 0.12% in the highest body weight group (100–130 kg), respectively. The simulated platelet metrics between 3 and 4 mg in heavier patients (≥ 80 kg of body weight) indicated the differences were $\leq 6300/\mu\text{L}$ in median peak platelet counts

and $\leq 8\%$ in probability for $\geq 50,000/\mu\text{L}$ (electronic supplementary Fig. S4). It is suggested the 4 mg dose would provide the limited platelet increase in the heavier patients.

4 Discussion

In the PK/PD simulations in this study, the 3 mg dose provided high probabilities of attaining $50,000/\mu\text{L}$ and low probabilities of exceeding $200,000/\mu\text{L}$ in Japanese and non-Japanese thrombocytopenic CLD patients, suggesting that the 3 mg once-daily dose would be effective and well-tolerated in these patients. The simulations and the results of pivotal studies [11, 12] support the lusutrombopag 3 mg once-daily dose for 7 days.

In the simulations, the median peak platelet counts were similar among the tested conditions of extensive, limited, or no interim platelet monitoring. With the 7-day fixed dose of 3 mg with no monitoring, the probabilities of exceeding $200,000/\mu\text{L}$ were low in Japanese and non-Japanese patients and were not considered clinically relevant. In an open-label study (1338M0633), a decreased frequency of monitoring (no or 1-day monitoring) for treatment completion was explored, with 47 patients in each group. In the open-label study, no patient had a platelet count $> 200,000/\mu\text{L}$ (maximum platelet count of $173,000/\mu\text{L}$) and there was a low incidence of thrombotic events (3.2%, 3/94 patients), with no association between thrombotic events and high platelet counts (maximum platelet counts of $48,000\text{--}86,000/\mu\text{L}$ prior to the onset of event). Based on the PK/PD simulations and the results of the open-label study, no platelet monitoring during a 7-day dose was considered necessary. Not monitoring platelets during treatment greatly reduces the physical burden for patients.

Body weight affected lusutrombopag exposure. Although the probability of attaining $50,000/\mu\text{L}$ on days 9–14 was approximately 10% less in the highest body weight group (≥ 100 kg) compared with in the reference group (60–80 kg), the difference in median peak platelet counts were slight (less than $10,000/\mu\text{L}$) between the two body weight groups. In addition, individual peak platelet counts calculated by the Bayes-estimated parameters overlapped among the body weight groups, although the sample size was limited for patients with the lower (< 45 kg) and higher (≥ 100 kg) body weight. Body weight did not clinically significantly influence the platelet counts, suggesting that no dose adjustment based on body weight is necessary.

In the post hoc analysis, the predicted exposure to lusutrombopag was slightly higher in Japanese patients than in non-Japanese patients. This difference would mainly be due to the difference in body weight between both groups, as shown in the demographics. Predicted peak platelet counts

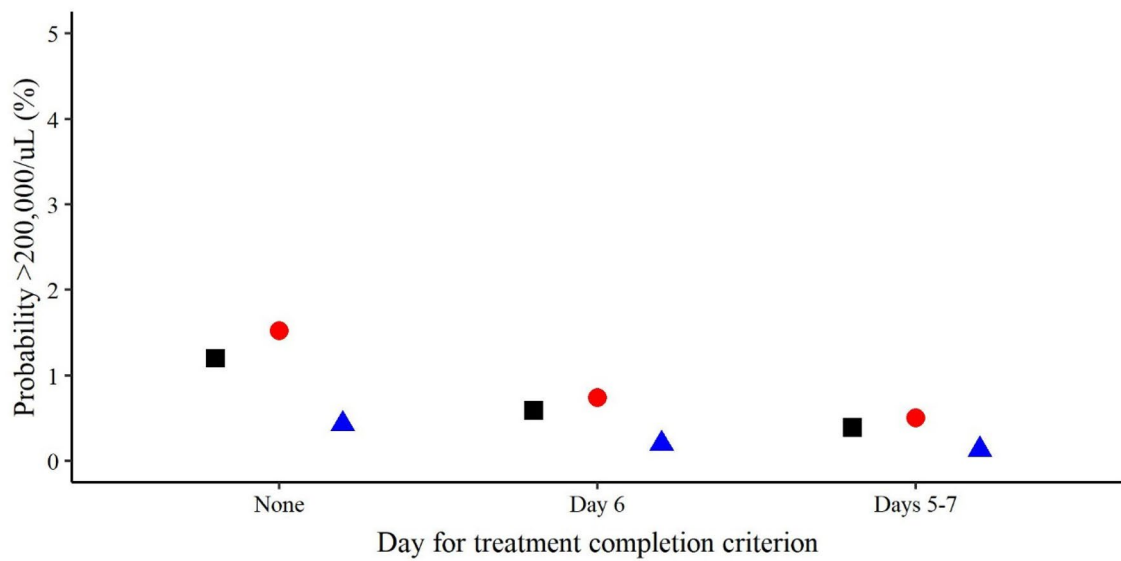
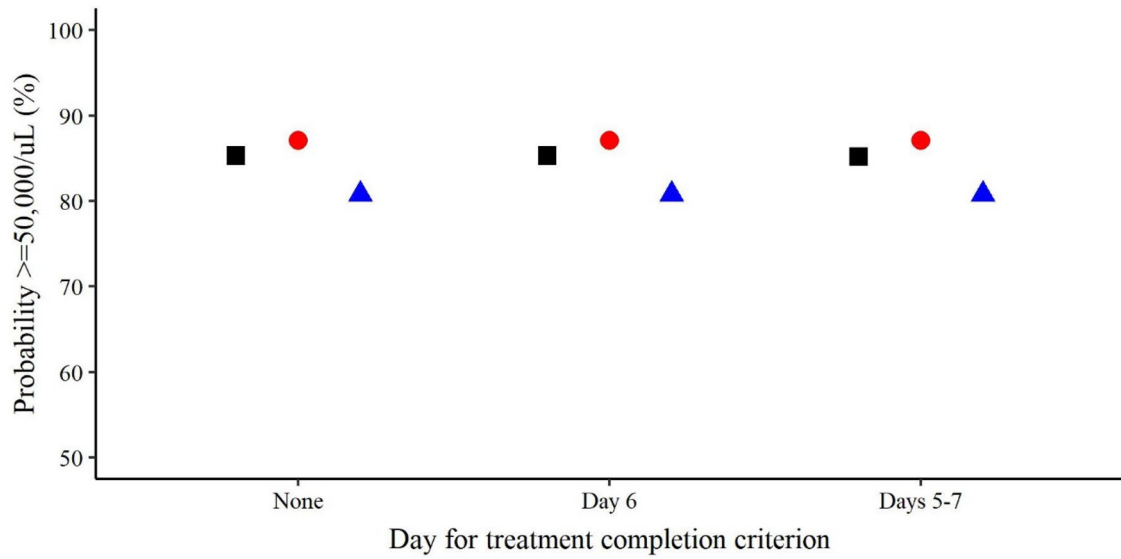
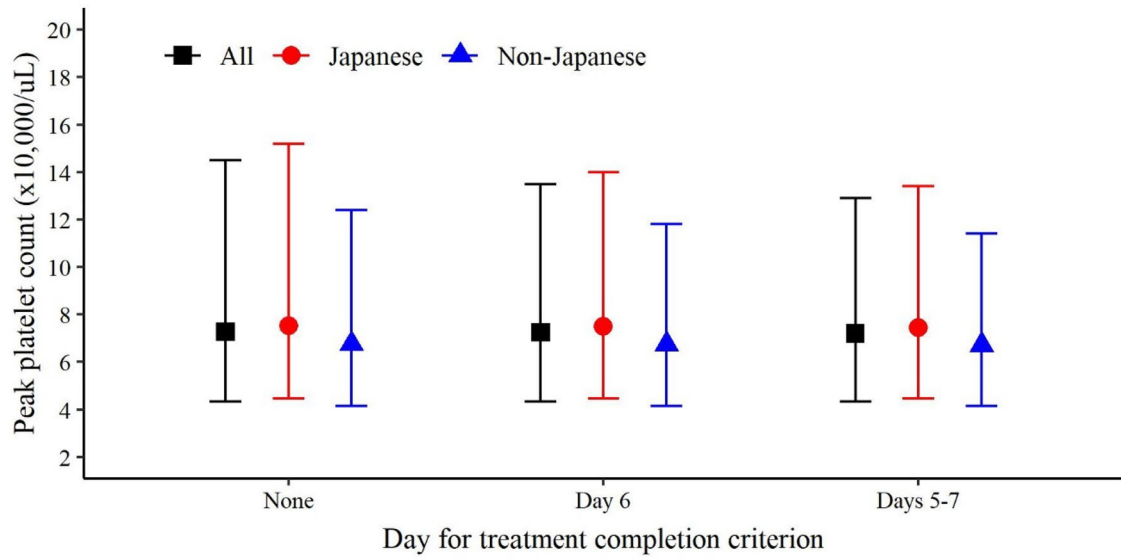


Fig. 6 Summary of simulated platelet metrics at 3 mg once daily with or without treatment completion criterion based on platelet counts. Simulations were performed with 200 replications. 7-day fixed dosing represents no platelet monitoring. Probability $\geq 50,000/\mu\text{L}$ represents the probability of attaining a platelet count of $50,000/\mu\text{L}$ on days 9–14, and probability $> 200,000/\mu\text{L}$ represents the probability of exceeding a platelet count of $200,000/\mu\text{L}$

in Japanese patients were similar to those in non-Japanese patients, suggesting there is no clinically significant difference in the PK/PD profile of lusutrombopag between Japanese and non-Japanese patients.

The V2/F in CLD patients was approximately 50% higher than in healthy subjects. Lusutrombopag is highly bound to proteins, such as albumin, α_1 -acid glycoprotein and γ -globulin. The decrease in protein binding of drugs was reported in CLD patients and may result in an increase in unbound drugs, which can distribute into tissues [21]. Potential mechanisms include reduced protein synthesis, accumulation of endogenous compounds such as bilirubin that inhibit plasma protein binding of drugs, and qualitative changes in proteins. In the in vitro study, the binding ratios of lusutrombopag to albumin were independent of albumin concentrations (data on file). Therefore, the reduced protein synthesis may not contribute to higher V2/F in the patients. No data are available to discuss the other potential mechanisms.

The SLOP increased for the group with the higher Child–Pugh score (≥ 9), although the difference is mechanistically unknown. In addition, because the sample size of patients with a Child–Pugh score ≥ 9 was limited ($n = 20$), modelling the relationship of SLOP to Child–Pugh score was challenging. The median AUC in patients with Child–Pugh class C was lower than that in patients with Child–Pugh class A or B. Patients with hepatic impairment may have intestinal structural alterations that decrease the extent of drug absorption [22]. The individual peak platelet counts overlapped among the Child–Pugh classes, although the sample size was limited for patients with Child–Pugh class C ($n = 6$). Although no firm conclusion could be provided, these results suggest there is no clinically significant difference in platelet response based on the severity of hepatic impairment.

The feedback and sigmoid E_{max} models were used as a PD model for healthy subjects [9], while both models were not applied for CLD patients. The KL in CLD patients was 1.34-fold compared with healthy subjects (0.00871 vs. 0.00648/h), while the KPR in CLD patients was 0.26-fold compared with healthy subjects. The enhanced platelet destruction and decreased platelet production are consistent with the previously reported clinical features of thrombocytopenia in CLD patients [1]. Mean transit time (4/KM) was similar to the time required for megakaryocytes to fully mature cells and then shed platelets (3.5–5 days) [23].

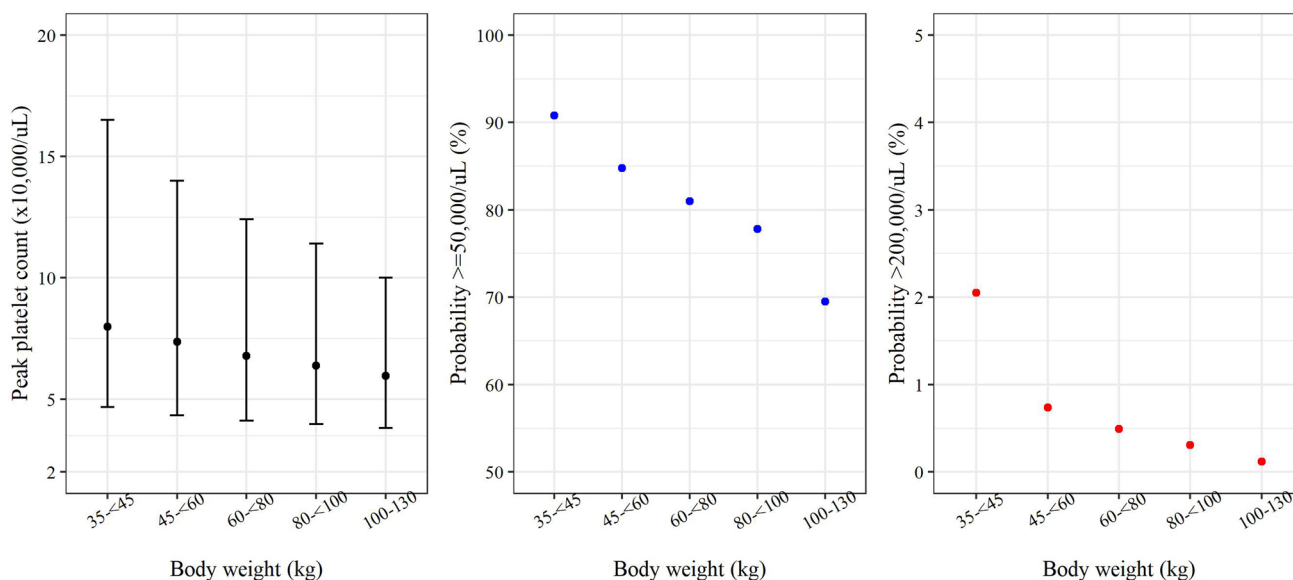


Fig. 7 Summary of simulated platelet metrics by body weight in patients treated with a 3 mg once-daily dose for 7 days. For this analysis, 2000 simulations were performed. Body weight was simulated according to uniform distribution. Child–Pugh score was set to < 9 . The simulations were performed based on a male to female ratio of

1:1 for non-Japanese CLD patients. Probability $\geq 50,000/\mu\text{L}$ represents the probability of attaining a platelet count of $50,000/\mu\text{L}$ on days 9–14, and probability $> 200,000/\mu\text{L}$ represents the probability of exceeding a platelet count of $200,000/\mu\text{L}$. A treatment completion criterion was not applied in this simulation. CLD chronic liver disease

5 Conclusion

The developed PK/PD model well-described the PK profiles and platelet counts following the administration of lusutrombopag in CLD patients. Body weight was an influential covariate on the PK profile of lusutrombopag; however, no effects of the tested covariates on platelet counts were clinically significant. The PK/PD simulations support the efficacy and safety of lusutrombopag 3 mg once daily for 7 days without interim monitoring of platelet counts.

Compliance with Ethical Standards

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Conflicts of interest Takayuki Katsube, Ryosuke Shimizu, Takahiro Fukuhara, Takeshi Kano and Toshihiro Wajima are all employees of Shionogi & Co., Ltd.

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