Population pharmacokinetic/ pharmacodynamic modelling of eltrombopag in healthy volunteers and subjects with chronic liver disease

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Eltrombopag is a thrombopoietin receptor agonist that increases platelet counts.
- Thrombocytopenia is observed in chronic liver disease (CLD), necessitating platelet transfusion prior to and/or during invasive procedures.
- The population pharmacokinetics (PK)/pharmacodynamics (PD) of eltrombopag in immune thrombocytopenic purpura and hepatitis C has been previously described.

WHAT THIS STUDY ADDS

- A population PK/PD analysis of eltrombopag in patients with CLD using mixed-effects modelling was conducted.
- The time course of the platelet response in CLD was different from that in immune thrombocytopenic purpura but comparable to that in hepatitis C.

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Keywords

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AIMS

To characterize the pharmacokinetics (PK)/pharmacodynamics (PD) of eltrombopag in chronic liver disease (CLD).

METHODS

The PK/PD model was developed using data from 79 CLD patients using nonlinear mixed-effects modelling.

RESULTS

The PK of eltrombopag were described by a two-compartment model with dual sequential first-order absorption. Gender, race and severity of CLD were predictors of the apparent clearance of eltrombopag. The PD of eltrombopag in CLD were adequately described by a four-compartment lifespan model, in which eltrombopag stimulated platelet precursor production rate. East Asian CLD patients were less sensitive to the stimulatory effect of eltrombopag. Following a daily dose regimen of 50 mg eltrombopag, the time to achieve peak platelet counts was longer for the CLD population compared with patients who had immune thrombocytopenic purpura, but was comparable to patients with hepatitis C. Likewise, it took a longer time for platelet counts to rebound back to baseline once eltrombopag treatment was discontinued.

CONCLUSIONS

The time course of the platelet response in CLD was different from that in immune thrombocytopenic purpura but comparable to that in hepatitis C.

Introduction

Eltrombopag is an orally bioavailable, small-molecule, thrombopoietin receptor agonist that interacts with the transmembrane domain of the human thrombopoietin receptor and initiates signalling cascades to induce proliferation and differentiation of megakaryocytes from bone marrow progenitor cells, resulting in an increased circulating platelet count. Eltrombopag is being developed for medical disorders associated with thrombocytopenia. It is approved for the treatment of chronic idiopathic (immune) thrombocytopenic purpura (ITP), and is being investigated in chronic liver disease (CLD) patients with thrombocytopenia to reduce the need for platelet transfusions for those patients requiring invasive surgical procedures.

Thrombocytopenia is observed in patients with CLD, where it is considered a surrogate marker for the severity of hepatic fibrosis and cirrhosis [1, 2]. The thrombocytopenia in such patients is likely to be due to both reduced hepatocellular mass available for constitutive production of thrombopoietin and to increased portal hypertension, resulting in splenomegaly and splenic sequestration of circulating platelets [3, 4]. When patients whose platelet count is severely reduced require medical or surgical procedures typically associated with risk of bleeding, platelet transfusion is used prior to and/or during the invasive procedure to manage the risk of bleeding complications.

In a phase III study in patients with CLD, the use of eltrombopag was intended to elevate platelet count and to eliminate the need for a platelet transfusion in CLD patients with thrombocytopenia who were undergoing planned invasive procedures. Avoidance of platelet transfusion eliminates the risk of transfusion-related

complications [5–8]. In addition, the use of an oral thrombopoietic agent may potentially reduce the incidence and severity of bleeding during the pre- and postprocedural period in thrombocytopenic patients with CLD.

The population pharmacokinetics (PK) and PK/pharmacodynamics (PK/PD) of eltrombopag have been described previously for patients with immune thrombocytopenic purpura (ITP) [9, 10] and for subjects with hepatitis C (HCV) [11]. The aim of this analysis was to build a population PK/PD model to characterize the relationship between plasma eltrombopag concentrations and platelet count in CLD patients to understand determinants of the response. This model was subsequently used to predict the platelet count response in the CLD population in comparison with healthy subjects as well as other patient populations.

Methods

Study design, dosing regimens and subjects

The population analyses were conducted using data from three studies. The number of subjects, doses, population and PK and PD sampling times for each study are presented in Table 1.

Study 1 was a phase I dose-rising study conducted in healthy male subjects to investigate the safety, tolerability, PK and PD of single and repeat daily oral doses of 5, 10, 20, 30, 50 and 75 mg eltrombopag in healthy adult male subjects [12]. Plasma eltrombopag concentration data following single-dose administration was included in the population PK analysis, and platelet count data were excluded from the population PK/PD analysis. Study 2 was a dose-ranging phase II study in Japanese

Table 1

Clinical trial data included in eltrombopag population pharmacokinetic (PK)/ pharmacodynamic (PD) analysis

Study no.	Population	n	Once daily dose (duration)	PK samples	Eltrombopag PD samples
Study 1	Healthy male subjects	28	30, 50 and 75 mg SD	Predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24 and 48 h postdose	NA
Study 2	Japanese thrombocytopenic male and female patients with CLD	38	12.5, 25 and 37.5 mg QD for 14 days	In Part A (12.5 mg): predose and 1, 2, 4, 6, 8, 10 and 24 h postdose on day 14. In Part B (25 and 37.5 mg): either Schedule 1 [predose (0 h) and 0.5–3 and 22–29 h postdose] or Schedule 2 (4–6, 8–12 and 22–29 h postdose).	Screening, days 1, 8 and 15. Additional PD samples were collected depending on day 15 platelet counts: day 18, 22 and 29 if day 15 platelet counts were $\geq 80 \text{ Gi l}^{-1}$; days 22, 25, 29 and 36 if day 15 platelet counts were $< 80 \text{ Gi l}^{-1}$
Study 3	Thrombocytopenic male and female patients with CLD	41	75 mg QD for 14 days	Serial ($n = 18$, active) on day 14: predose and 1, 1.5, 2, 4, 6, 8, 10 and 24 h postdose. Sparse ($n = 23$, active) on day 14: predose and two additional samples from the following time intervals: 2–4, 5–8 and 9–12 h postdose	Screening, day 1 predose, day 8; if procedure was done on day 15: day 15 preprocedure, else if procedure was done between days 16 and 19: day 15, days 16–19 preprocedure, weeks 1, 2, 3 and 4 postprocedure

Abbreviations are as follows: CLD, chronic liver disease; NA, not applicable; QD, once daily; SD, single dose.

thrombocytopenic subjects with CLD (baseline platelet counts $<50 \text{ Gi l}^{-1}$) [13]. In Part A, study subjects were administered 12.5 mg eltrombopag once daily (QD) for 14 days. After completion of Part A, Part B commenced with subjects assigned to either 25 or 37.5 mg eltrombopag QD for 14 days. Subjects who participated in Part A could not participate in Part B. For subjects with platelet counts $<80 \text{ Gi l}^{-1}$ on day 15 in Part B, dosing could continue for one additional week if the investigator considered it appropriate and the subject consented. Study 3 was a phase III study to evaluate the safety and efficacy of eltrombopag to reduce the need for platelet transfusion in thrombocytopenic subjects with CLD undergoing elective invasive procedures [14]. In this study, thrombocytopenic (baseline platelet count $<50 \text{ Gi l}^{-1}$) CLD patients requiring an elective invasive procedure were randomized to receive either 75 mg eltrombopag or matching placebo QD dosing for 14 days. Upon completion of the dosing period, subjects underwent their invasive procedure within 1–5 days following the final dose (i.e. on day 15–19).

All protocols and consent forms were reviewed and approved by the institutional review boards for each of the study sites, and all subjects provided signed informed consent. All studies were conducted in accordance with the ethical standards of the Declaration of Helsinki.

Plasma eltrombopag concentrations were determined using a validated analytical method based on protein precipitation followed by high-performance liquid chromatography with tandem mass spectrometry analysis [15]. The lower limit of quantification of the assays was 10 ng ml^{-1} for Study 1 and 100 ng ml^{-1} for Studies 2 and 3. Platelet counts were determined at each study site through a local clinical laboratory.

Population pharmacokinetic/ pharmacodynamic approach

The population PK model was developed with data from 28 healthy male subjects from Study 1 and 79 patients with CLD, including all 38 CLD patients from Study 2 and the 41 CLD patients from Study 3 who participated in the PK substudy of that trial. The population PK/PD model was developed from patients with CLD ($n = 79$) for whom the PD data were modelled using the *post hoc* PK parameter estimates for each patient from the final population PK model (accounting for significant covariates) to predict the eltrombopag concentrations. The previously published eltrombopag PK and PK/PD models for healthy volunteers, ITP patients and patients with HCV were the starting points for the present analyses [9–11].

Modelling was performed using a mixed-effects approach with NONMEM® versions VI or VII level 1.0 (ICON) [16]. The first-order conditional estimation method with interaction was used for estimation of parameters. Model selection was driven by the data and was based on evaluation of goodness-of-fit plots (observed vs. predicted concentration, conditional weighted residuals vs. predicted

concentration or time, histograms of individual random effects, etc.), successful convergence (with at least three significant digits in parameter estimates), plausibility and precision of parameter estimates, and the minimal objective function value.

Investigation of covariate–parameter relationships was based on the range of covariate values in the data set, scientific interest, mechanistic plausibility, exploratory graphics and previously reported covariate–parameter relationships for eltrombopag PK and PK/PD in other patient populations, such as female sex and East Asian race, which have been reported as significant predictors of eltrombopag PK in healthy subjects and patients with ITP [9]. A full model approach was implemented, where all covariate–parameter relationships of interest were entered in the model, and parameters were estimated. Insignificant or poorly estimated covariates [less than 6.63-point increase of objective function value for one parameter and/or confidence intervals include null value and/or high relative standard error ($>50\%$)] were then excluded from the model during the backward elimination process. Plots of interindividual random effect vs. covariate were reviewed after each major run to ensure that all possible covariate–parameter relationships were evaluated.

Of the available covariates, the Child-Pugh Class C was represented by only 3% of the population; this classification was combined with Child-Pugh Class B for the purposes of covariate analysis.

The full model did not simultaneously include highly correlated covariates, such as body weight and body mass index or gender and body weight/body mass index; therefore, several full models (with one of the competing correlated covariates) were investigated.

For the covariates to be explored in the analysis, the covariate should have had a sufficient range of values and/or it should be represented by at least 10% of the population. In addition, only one of highly correlated covariates could enter the model at a time. For continuous covariates, a power function was used. For categorical covariates, the fractional change in the typical parameter value was determined.

A visual predictive check was performed for both the final PK (prediction-corrected) and PK/PD models. From each model, 100 data sets were simulated using the final model parameters, covariates, sampling times, individual PK parameters and dosing histories. The number of observed eltrombopag concentrations and platelet counts that fell within the 90% prediction interval was determined.

In addition to the visual predictive check, the final PK model was also subjected to nonparametric bootstrap analysis, generating a sufficient number of data sets through random sampling with replacement from the original data using the individual as the sampling unit. Population parameters of the final PK model for each data

set were estimated using NONMEM. This resulted in a distribution of estimates for each population model parameter. Empirical 95% confidence intervals were constructed by obtaining the 2.5th and 97.5th quantiles of the resulting parameter distributions. Estimates from all NONMEM runs (with successful and unsuccessful minimization) were reported.

The final PK/PD model was used to simulate the platelet response in all 144 eltrombopag-treated CLD patients in Study 3, including those without any PK observations. A comparison of the PK/PD model predictions with the observed platelet response for this wider data set served as an additional validation of the PK/PD model to determine the predictability of the model in the broader CLD patient population and to support its use for simulations.

The time to achieve peak platelet count following 14 days of eltrombopag dosing and the time to both 50 and 80% reduction of platelet counts from peak platelet response were calculated for the CLD population and for the healthy volunteer, ITP and HCV populations included in previous analyses. Simulated median platelet count vs. time profiles were generated for each population.

Results

Data, demographics and baseline characteristics

The basic distribution of covariates and number of concentration/platelet count samples by study is described in Table 2. Of the 107 subjects included in the population PK analysis, 28 were healthy subjects and 79

were thrombocytopenic patients with CLD. The median (range) age across the 107 subjects was 50 (19–81) years, and 78 subjects (73%) were male. The median (range) body weight was 67.9 (40.6–120) kg. Of the 107 individuals, 37 subjects (35%) were White, two (2%) were Black or African-American, 45 (42%) were East Asian, 21 (20%) were South/Central Asian and two (2%) were classified as 'other'.

The median (range) values for creatinine clearance (CRCL), alanine aminotransferase, aspartate aminotransferase, albumin (ALB), and total bilirubin were 104 (30.0–196) ml min⁻¹, 29.0 (7–230) IU l⁻¹, 40.0 (13–318) IU l⁻¹, 36.0 (24–56) µmol l⁻¹ and 20.7 (6.0–87.0) µmol l⁻¹, respectively. There were eight patients with moderate renal impairment (CRCL <50 ml min⁻¹), and no patients with severe renal impairment (CRCL < 10 ml min⁻¹).

All samples from Studies 2 and 3 were quantifiable for patients receiving eltrombopag treatment. For Study 1, there were only nine postdose samples reported as below limit of quantification. These samples were excluded from the analysis. A total of 786 plasma concentrations were included in the final PK data set. Almost half of the plasma concentrations came from healthy subjects (383, 49%), while the remaining 51% (403) of concentrations came from the 79 thrombocytopenic patients with CLD.

Of the 79 CLD patients included in the population PK/PD analysis, 37 were classified as Child-Pugh Class A (Child-Pugh score of 5–6), 40 as Child-Pugh Class B (Child-Pugh score of 7–9) and two as Child-Pugh Class C (Child-Pugh score of 10–15). Study 2 was stratified to ensure an equal distribution of subjects in Child-Pugh Classes A and B. Within Child-Pugh Class A, 41% of patients were female, 70% were East Asian and 14% each were White and South/

Table 2

Subject and sample characteristics included in eltrombopag population PK/PD analysis

Study	Statistic or category	Study 1	Study 2	Study 3 (PK substudy)	All
Total number		28	38	41	107
Age (years)	Median [min–max]	24.5 [19–38]	63 [44–81]	50 [25–74]	50 [19–81]
Weight (kg)	Median [min–max]	76.7 [57.4–92.2]	62.0 [40.6–102.0]	68.0 [50.0–97.0]	67.9 [40.6–102.0]
Body mass index (kg m ⁻²)	Median [min–max]	23.5 [20.2–28.6]	23.4 [18.3–37.7]	23.9 [20.1–34.8]	23.6 [18.3–37.7]
Baseline platelet count (Gi l ⁻¹)	Median [min–max]		41.5 [19.0–49.0]	41.0 [20.0–54.5]	41.0 [19.0–54.5]
Sex [n (%)]	Female	0 (0)	12 (32)	17 (41)	29 (27)
	Male	28 (100)	26 (68)	24 (59)	78 (73)
Race [n (%)]	White	25 (89)	0 (0)	12 (29)	37 (35)
	Black/African-American	1 (4)	0 (0)	1 (2)	2 (2)
	East Asian	0 (0)	38 (100)	7 (17)	45 (42)
	South/Central Asian	0 (0)	0 (0)	21 (51)	21 (20)
	Other	2 (7)	0 (0)	0 (0)	2 (2)
Health status [n (%)]	Healthy	28 (100)	0 (0)	0 (0)	28 (26)
	Chronic Liver Disease	0 (0)	38 (100)	41 (100)	79 (74)
Child-pugh Class [n (%)]	A	0 (0)	23 (61)	14 (34)	37 (47)
	B	0 (0)	15 (39)	25 (61)	40 (51)
	C	0 (0)	0 (0)	2 (5)	2 (3)
Total no. of PK samples [n (%)]		383 (49)	174 (22)	229 (29)	786 (100)
Total no. of PD samples [n (%)]		0 (0)	197 (44)	254 (56)	451 (100)

Central Asian. Within Child-Pugh Classes B and C, 33% of patients were female, 45% were East Asian, 17% were White and 38% were South/Central Asian.

A total of 451 platelet count measurements were included in the final PK/PD data set. The median baseline platelet count from eltrombopag-treated CLD patients was 41 Gi l^{-1} .

Population pharmacokinetic analysis

The PK of eltrombopag in CLD patients following repeated QD dosing were adequately described by a two-compartment model with dual sequential first-order absorption and absorption lag time. The parameter estimates of the final PK model are presented in Table 3.

The reference population was the White male healthy volunteers. The estimated typical [(95% confidence interval (CI)) parameter values for the reference population were $CL/F = 0.953 (0.671, 1.24) \text{ l h}^{-1}$, $V_d/F = 9.75 (8.00, 11.5) \text{ l}$, $V_p/F = 9.41 (7.60, 11.2) \text{ l}$ and $Q/F = 0.633 (0.522, 0.744) \text{ l h}^{-1}$. Oral CL/F of eltrombopag was, on average, 38% lower in female subjects than in males and, on average, 52% lower in East Asian subjects than in White subjects. Chronic liver disease patients with Child-Pugh Class A had 46–59%

lower CL/F than the reference healthy volunteers, while CLD patients with Child-Pugh Class B had 59–71% lower CL/F than the reference healthy volunteer population. The V_d/F was estimated to be 3-fold higher in South/Central Asians compared with all other races/ethnicities. The interindividual variability for CL/F and V_d/F was 40.1 and 48%, respectively, while the corresponding value for absorption rate constant (K_a) was much higher, at 127%.

All of the fixed-effect parameters were estimated with good precision, with relative standard error <22%. The interindividual random effects were also estimated with reasonable precision, with relative standard error <34%.

The diagnostic plots for the final model (Figure 1) indicated that the model described the data adequately. The distributions of the random effects were close to normal and they were not correlated, apart from a correlation between CL/F and V_d/F accounted for by the model. No strong unexplained covariate–parameter relationships were noticeable.

Figure 2 presents the results of the prediction-corrected visual predictive check for the final PK model. Approximately 2% of the observed concentrations for the healthy volunteers and 5% of the observed concentrations

Table 3

Parameter estimates of the final eltrombopag population PK model in healthy volunteer and CLD patients

Parameter (units)	NONMEM estimates			Bootstrap estimates*		
	Point estimate	%RSE	95% CI	Median	95% CI	
<i>CL/F</i> (l h ⁻¹)	0.953	15.1	0.671–1.24	0.947	0.817–1.100	
<i>V_d/F</i> (l)	9.75	9.14	8.00–11.5	9.70	8.51–11.0	
<i>V_p/F</i> (l)	9.41	9.82	7.60–11.2	9.45	7.92–12.4	
<i>Q/F</i> (l h ⁻¹)	0.633	8.94	0.522–0.744	0.637	0.561–0.736	
<i>K_{a1}</i> (h ⁻¹)	0.333	20.2	0.201–0.465	0.357	0.205–0.582	
<i>K_{a2}</i> (h ⁻¹)	5.26	21.9	3.01–7.51	5.88	2.54–33.8	
ALAG1 (h)	0.447	1.42	0.435–0.459	0.449	0.170–0.480	
MTIME (h)	1.46	1.28	1.42–1.50	1.47	1.030–2.50	
σProp ~HV	0.453	5.39	0.405–0.501	0.456	0.324–0.625	
σProp ~TAD < 4 h	1.72	6.40	1.50–1.94	1.77	1.40–2.43	
<i>CL/F</i> ~Females	0.622	10.4	0.495–0.749	0.614	0.508–0.750	
<i>CL/F</i> ~CP Score 5	0.536	16.5	0.363–0.709	0.540	0.405–0.734	
<i>CL/F</i> ~East Asians	0.476	8.63	0.395–0.557	0.478	0.385–0.595	
<i>CL/F</i> ~ CP Score > 5†	−0.113	16.2	−0.149 to −0.0771	−0.115	−0.151 to −0.074	
<i>V_d/F</i> ~South/Central Asians	2.98	13.2	2.21–3.75	2.98	1.88–5.08	
Interindividual or interoccasion variability				CV% or R‡		
ω ² _{CL}	0.161	15.2	0.113–0.209	CV = 40.1%	0.153	0.107–0.211
Covar ω _{CL} , ω _{V_c}	0.106	33.7	0.0360–0.176	R = 0.547	0.106	0.059–0.155
ω ² _{V_c}	0.233	28.5	0.103–0.363	CV = 48.3%	0.221	0.104–0.365
ω ² _{K_a}	1.61	27.7	0.736–2.48	CV = 127%	1.45	0.889–2.18
Residual variability				CV% or SD	Median	95% CI
σ ² _{prop}	0.0237	12.2	0.0180–0.0294	CV = 15.4%	0.022	0.015–0.033
σ ² _{add} (ng ml ⁻¹)	1110	69.8	−409 to 2630	SD = 33.3	1030	0.051–2860

Abbreviations and symbols are as follows: %RSE, percentage relative standard error of the estimate = $SE/\text{parameter estimate} \times 100$; σ^2_{add} , additive component of the residual error model; ω^2_{CL} and $\omega^2_{V_d}$, covariance of random effect of CL/F and V_d/F , respectively; $\omega^2_{K_a}$, covariance of random effect of IOV on K_{a1} ; σ^2_{prop} , proportional component of the residual error model; $\sigma_{\text{Prop}} - \text{ITP}$, factor of proportional error for ITP subjects; $\sigma_{\text{Prop}} - \text{TAD} < 4 \text{ h}$, factor of proportional error for TAD $< 4 \text{ h}$ (absorption time); 95% CI, 95% confidence interval on the parameter; ALAG1, lag time; CL/F , apparent clearance; Covar ω_{CL} , ω_{V_d} , correlation between covariance of random effect of CL/F and V_d/F ; CV, coefficient of variation of proportional error (= [σ^2_{add}] [0.5] $\times 100$); K_{a1} , absorption rate constant prior to MTIME; K_{a2} , absorption rate constant after MTIME; MTIME, time at which absorption rate changes; Q/F , intercompartmental exchange flow rate; R, correlation coefficient; SD, standard deviation of additive error (= [σ^2_{add}] [0.5]); V_d/F , volume of central compartment; V_p/F , volume of peripheral compartment. *From 803 completed bootstrap runs; †A coefficient for each unit increase in Child-Pugh (CP) score from CP score of 5, such that the fractional change of CL/F by CP score is expressed as $0.536 \times [1 - 0.113 \times (\text{CP score} - 5)]$ in the final PK model. ‡Correlation coefficient.

Figure 1

Goodness-of-fit and diagnostic plots for final pharmacokinetics (PK) model for eltrombopag-treated patients with chronic liver disease. ○, chronic liver disease; ●, healthy volunteers

for the CLD patients fell outside the 90% prediction intervals, respectively, supporting the conclusion that the final model adequately describes the observed single-dose healthy volunteer data and the steady-state CLD patient data, although the model may have slightly overestimated the variability.

Of the 803 bootstrap runs completed, only 94 (12%) failed to minimize successfully; however, the parameter estimates from these runs were similar to those obtained from successfully minimized bootstrap runs and were included in the calculation of the median and 95% CI for the bootstrap estimates. The bootstrap results were very similar to the NONMEM estimates from the final PK model (Table 3), supporting the stability of the population PK model and the good precision of NONMEM parameter estimates.

Individual *post hoc* estimates of steady-state CL/F , C_{max} , $AUC_{(0-t)}$ and half-life ($t_{1/2}$) were also derived following repeat dosing of 50 mg eltrombopag QD and are summarized by subpopulation in Table 4. Plasma eltrombopag exposure is higher in patients with CLD than in healthy volunteers. For the repeat daily dose of 50 mg eltrombopag, the median steady-state $AUC_{(0-t)}$ and C_{max} in all CLD patients were 4.2- and 2.8-fold higher, respectively, than in healthy volunteers. The elimination half-life of eltrombopag was also significantly longer in CLD patients due to their reduced CL/F . Within CLD patients, exposure is higher in both

females and East Asians due to lower CL/F . The severity of CLD, as assessed by Child-Pugh Class (A vs. B), had a relatively small impact on the predicted eltrombopag exposure, but the potential impact was confounded by a higher proportion of females (41 vs. 33%) and East Asians (70 vs. 45%) with Child-Pugh Class A vs. B. To describe the impact of the severity of CLD on the plasma eltrombopag exposure when accounting for the other covariates within the PK model, a summary of the individual posterior PK parameter estimates by Child-Pugh Class and other subpopulations is presented in Table 5. Within each of the subpopulations of the CLD patients, eltrombopag exposure in those patients with Child-Pugh Class B was consistently higher than in those with Child-Pugh Class A.

Population pharmacokinetic/ pharmacodynamic analysis

The PK/PD relationship between eltrombopag concentrations and the platelet response in patients with CLD following repeated QD dosing was well described by a four-compartment lifespan model, representing different stages of differentiation/maturation of platelet cell development originating from bone marrow progenitor cells. As illustrated in Figure 3, the stimulation of platelets was linearly related to the eltrombopag concentrations. Of all covariates evaluated, race (East Asian) was the only

Figure 2
Prediction-corrected visual predictive check for the final PK model

Table 4
Summary of individual posterior PK parameter estimates by population

Population	n	CL/F (l h ⁻¹)	t _{1/2} (h)	AUC _(0-t) (µg h ml ⁻¹)	C _{max} (µg ml ⁻¹)
Healthy volunteers	28	0.944	21.1	53.0	5.37
		0.817–1.09	19.9–22.4	45.9–61.2	4.71–6.13
CLD (All)	79	0.227	76.4	221	15.2
		0.199–0.258	69.5–84.0	194–251	13.5–17.2
CLD (Males)	50	0.263	68.5	190	13.3
		0.223–0.310	61.4–76.4	161–224	11.4–15.5
CLD (Females)	29	0.175	92.3	285	19.2
		0.147–0.210	78.9–108	238–341	16.3–22.5
CLD (East Asians)	45	0.174	81.2	287	19.7
		0.151–0.201	72.7–90.6	249–330	17.4–22.3
CLD (non-East Asians)	34	0.320	70.5	156	10.8
		0.267–0.384	59.9–83.0	130–187	9.09–12.8
CLD (CP A)	37	0.239	66.4	209	15.0
		0.200–0.285	57.6–76.7	175–250	12.8–17.6
CLD (CP B)	40	0.214	86.3	234	15.5
		0.175–0.261	76.7–97.2	192–285	12.8–18.8

AUC_(0-t) and C_{max} were dose-normalized to 50 mg. Results are presented as geometric means and 95% confidence intervals. CL/F, apparent clearance; t_{1/2}, half-life; AUC_(0-t), area under the concentration-time curve between dose interval; C_{max}, maximum plasma concentration.

covariate that was shown to influence the PD of eltrombopag in patients with CLD.

The parameter estimates of the final PK/PD model are presented in Table 6. The typical (95% CI) estimated values for KIN and KT were 0.211 (0.187, 0.236) Gi l⁻¹ h⁻¹ and

0.0214 (0.0202, 0.0226) h⁻¹, respectively. Administration of eltrombopag increased the rate of platelet production in a linear manner, with a 64.8% increase in the production rate for each 1 µg ml⁻¹ increase in plasma eltrombopag concentrations. The model demonstrated that the linear effect

Table 5

Summary of individual posterior PK parameter estimates for CLD patients by Child-Pugh class and subpopulation

Subpopulation	Child-Pugh category	n	AUC _(0-∞) * (μg h ml ⁻¹)	C _{max} * (μg ml ⁻¹)
Males	A	22	174	12.8
			141–215	10.5–15.5
	B	27	204	13.8
Females	A	15	159–263	10.8–17.6
			274	19.1
	B	13	211–355	15.3–23.8
Non-East Asians	A	11	310	19.9
			239–403	15.5–25.7
	B	21	168	11.0
East Asians	A	26	130–218	8.62–14.3
			255	17.9
	B	19	212–306	15.2–21.1
			336	22.5
			274–413	18.8–26.9

Results are presented as geometric means and 95% confidence intervals. *Dose-normalized to 50 mg.

Figure 3

A schematic representation of the eltrombopag PK/pharmacodynamic (PD) model. CL = Clearance, Ka: first order absorption rate constant, Vc = volume of central compartment, Q = inter-compartmental clearance, Vp = volume of peripheral compartment, KIN = zero-order production rate of platelet precursors, KT = first-order maturation rate of platelet precursors, KDEG: first-order platelet degradation rate, SLOP = linear coefficient of drug effect.

of eltrombopag concentration on platelet production (SLOP) was influenced by race, with East Asian CLD patients having an estimated value of, on average, 34% (95% CI, 21–47%) lower than CLD patients of other races (non-East Asian).

The structural parameters for the model were estimated with excellent precision, with relative standard error <11%.

The individual derived platelet half-life values (derived from $\ln(2)/KP$, where $KP = KIN/\text{baseline platelet count}$) ranged from 60 to 213 h across the eltrombopag-treated

Table 6

Parameter estimates of the final eltrombopag population PK/PD model for patients with chronic liver disease

Parameter (units)	Point estimate	NONMEM estimates	
		%RSE	95% CI
SLOP (ml μg ⁻¹)	0.648	6.47	0.566–0.730
KIN (Gi l ⁻¹ h ⁻¹)	0.211	5.92	0.187–0.236
KT (h ⁻¹)	0.0214	2.96	0.0202–0.0226
SLOP–East Asians	0.660	10.2	0.529–0.791
Interindividual variability			
ω ² _{SLOP}	0.287	36.9	0.0792–0.495
ω ² _{KT}	0.313	31.8	0.118–0.508
Residual variability			
σ _{prop}	0.197	8.73	0.163–0.231

Abbreviations are as follows: %RSE, percentage relative standard error of the estimate = $SE/\text{parameter estimate} \times 100$; ω²_{prop}, proportional component of the residual error model; ω²_{SLOP} and ω²_{KT}, covariance of random effect of SLOP and KT, respectively; KIN, production rate of platelet precursors; KT, maturation rate of platelet precursors; SLOP, slope for the linear effect of eltrombopag concentrations on platelet production.

CLD patients, with an average of 121 h, indicating an average platelet half-life of approximately 5 days. The derived rate of platelet elimination (KP) was similar in both Studies 2 and 3 and similar across ethnic groups.

The diagnostic plots for the final PK/PD model (Figure 4) indicated that the model described the platelet count data adequately for those CLD patients treated with eltrombopag. The distributions of the random effects were close to normal and they were not correlated. No strong unexplained covariate–parameter relationships were observed.

Figure 5 presents the results of the visual predictive check for the final PK/PD model. Approximately 9% of the observed concentrations fell outside the 90% prediction intervals, supporting the conclusion that the final PK/PD model describes the observed data adequately. The predictability of the final PK/PD model was further investigated by comparing the model predicted proportion of CLD patients achieving target platelet counts of >80, <150 and <200 Gi l⁻¹ with those observed in the PK substudy, as well as the entire eltrombopag-treated patient population in Study 3 (Table 7). The PK/PD model slightly overpredicted the observed platelet response of the entire eltrombopag-treated patient population in Study 3, with the observed proportion of patients achieving <150 Gi l⁻¹ platelet counts close to the predicted upper limit of 95% CI, whereas the observed proportion of patients achieving <200 Gi l⁻¹ platelet counts fell outside the predicted 95% CI. This is consistent with the observations that the response rate in the PK substudy was higher than that in all the eltrombopag-treated patients in Study 3. In keeping with the higher eltrombopag exposure in subjects classified as Child-Pugh Class B, the PK/PD model

Figure 4

Goodness-of-fit and diagnostic plots for final PK/PD model for eltrombopag-treated patients with chronic liver disease

Figure 5

Visual predictive check for final PK/PD model for eltrombopag-treated patients with chronic liver disease

Table 7

Comparison of observed and model-predicted proportion of CLD patients achieving threshold platelet count following 75 mg QD eltrombopag treatment for 14 days

Population	Threshold (Gi l ⁻¹)	Observed n/N (%)	Eltrombopag dose (75 mg) once daily for 14 days		
			PK substudy Predicted* Median [% (95% CI)]	All eltrombopag-treated patients Observed n/N (%)	Predicted† Median [% (95% CI)]
All	<200	23/41 (56)	50 (37, 66)	100/144 (69)	56 (48, 63)
	<150	12/41 (29)	32 (22, 44)	68/144 (47)	39 (31, 46)
	>80	38/41 (93)	95 (87, 100)	106/144 (74)	91 (87, 94)
CP A	<200	10/14 (71)	64 (32, 86)	54/72 (75)	65 (53, 74)
	<150	6/14 (43)	43 (21, 64)	38/72 (53)	47 (37, 57)
	>80	12/14 (86)	93 (75, 100)	48/72 (67)	89 (80, 94)
CP B	<200	13/27 (48)	44 (30, 63)	38/72 (53)	47 (38, 58)
	<150	6/27 (22)	26 (11, 44)	24/72 (33)	31 (23, 40)
	>80	26/27 (96)	96 (87, 100)	51/72 (71)	94 (88, 97)

*Predicted results include simulations for PK substudy patients in Study 3. †Predicted results include simulations for all eltrombopag-treated patients in Study 3.

Table 8

Cross-population comparison to peak platelet count and time to 50 and 80% reduction in platelet count after the last dose following 50 mg eltrombopag QD for 14 days [median (95% CI)]

Population	Time (days) to peak platelet count	Time (days) to 50% reduction in platelet count	Time (days) to 80% reduction in platelet count
CLD	8 (7, 8)	12 (11, 13)	21 (20, 22)
HV	4 (4, 5)	11 (10, 12)	17 (16, 19)
HCV	9 (7, 10)	16 (15, 18)	29 (27, 31)
ITP	2 (1, 4)	4 (3, 5)	7 (6, 8)

Abbreviations are as follows: CLD, chronic liver disease; HCV, hepatitis C; HV, healthy volunteers; ITP, immune thrombocytopenic purpura.

predicted higher platelet response in this subpopulation (Table 7).

The comparison of simulated platelet response following administration of eltrombopag 50 mg QD for 14 days in the different populations predicted a longer time to achieve peak platelet counts and a longer time for platelet counts to return to baseline levels in HCV and CLD patients, compared with either healthy volunteers or patients with ITP (Table 8), which is consistent with the longer plasma eltrombopag half-life in the HCV and CLD populations. The peak change from baseline platelet count was slightly higher for the CLD population compared with the HCV population, with the magnitude of the response for both being considerably higher than that for the ITP population, but lower than that for healthy volunteers (Figure 6).

Discussion

The PK of eltrombopag in CLD patients following repeated QD dosing were adequately described by a two-

Figure 6

Comparison of predicted platelet response for eltrombopag dosed 50 mg once daily for 14 days in healthy volunteers, and patients with chronic liver disease, hepatitis C and immune thrombocytopenic purpura. —, chronic liver disease; ----, healthy volunteers; ---, immune thrombocytopenic purpura; ·····, hepatitis C

compartment model with dual sequential first-order absorption and absorption lag time. The absorption model was slightly different from that used in the previous modelling in HCV subjects, where a sequential zero- and first-order absorption model was selected [10]. This absorption model was also assessed for the present CLD analysis but did not improve the fit compared with the sequential dual first-order absorption. The estimated typical (95% CI) PK parameter values for the reference White male healthy volunteer population were comparable to previously reported values [9].

The final covariate model included the influence of disease (CLD vs. healthy), the severity of CLD (characterized by Child-Pugh score), gender and race on *CL/F*.

Chronic liver disease patients with Child-Pugh Class A had 46–59% lower CL/F than the reference healthy volunteers, while CLD patients with Child-Pugh Class B had 59–71% lower CL/F than the reference healthy volunteer population. In the present analysis, there were only two patients with Child-Pugh score of 10, which was not sufficient to demonstrate further decrease of eltrombopag CL/F in patients with Child-Pugh Class C. Therefore, extrapolation of eltrombopag CL/F to patients with more severe CLD should be made with caution. It has been shown in the phase I single-dose study in patients with hepatic impairment (TRA103452) that patients with moderate and severe hepatic impairment had comparable geometric mean plasma eltrombopag $AUC_{(0-\infty)}$ (area under the concentration-time curve from time 0 to infinity) following a single dose of 50 mg eltrombopag [17]. Although the phase I study was probably too small to show a difference between patients with moderate and severe hepatic impairment, it is nevertheless possible that further reduction in eltrombopag CL/F may not occur in patients with more severe CLD.

Female sex and East Asian race have consistently been associated with lower plasma eltrombopag CL/F across the healthy volunteer, ITP, chemotherapy induced thrombocytopenia (CIT; unpublished observations) and CLD populations. In the previous ITP population PK analysis, eltrombopag CL/F was, on average, 33% lower in East Asian subjects than in non-East Asian subjects who were predominantly Caucasian; and in the previous CIT population PK analysis, eltrombopag CL/F was, on average, 47% lower in Asian subjects (mixture of East Asian and South/Central Asian) than in non-Asian subjects who were predominantly Caucasian. Results from the present analysis revealed an average of 52% lower CL/F in East Asian subjects compared with White subjects. The CL/F in patients with CLD was estimated to be, on average, 38% lower in females than in males, whereas the estimate was only 19 and 15% in the previous analyses in patients with ITP and CIT, respectively. The impact of both gender and race on CL/F of eltrombopag appeared to be more profound in patients with CLD. The underlying mechanism of this greater gender and racial difference seen in patients with CLD is unknown. Eltrombopag is predominantly metabolized in the liver through oxidation (CYP1A2 and CYP2C8) and glucuronidation (UGT1A1 and UGT1A3). It is known that females have lower activity relative to males for the cytochrome P450 (CYP) isoenzyme CYP1A2 and for some isoforms of glucuronyltransferases [18]. It is also well documented that the racial difference in hepatic drug metabolism can be associated with the different catalytic activity of CYP enzymes [19]. Hepatic impairment due to CLD may have resulted in a reduced drug metabolism that impacted more on patients with lower enzyme activity, and therefore further signified the gender and racial difference of eltrombopag on CL/F in patients with CLD.

The final covariate model also identified race (South/Central Asian) as a predictor of V_d/F . The typical V_d/F (95% CI) was 3-fold (2.2- to 3.8-fold) higher in South/Central Asian patients compared with all other races. The underlying mechanism for the higher V_d/F of eltrombopag in South/Central Asian CLD patients is unknown, but a number of factors may contribute to the estimated higher V_d/F in this patient population. Patients with CLD are known to have a low ALB level due to cirrhosis. In the present analysis, the average ALB concentration in South/Central Asian CLD patients was lower than in CLD patients of other races (median ALB of 29 vs. 35 $\mu\text{mol l}^{-1}$). Given that eltrombopag is highly bound to plasma proteins, lower ALB concentrations may have contributed to the larger volume of distribution observed in South/Central Asian CLD patients. In Study 3, the majority of patients who contributed serial PK samples were South/Central Asians. The difference in PK sampling (serial vs. sparse) could also be a partial contributor to the estimated higher V_d/F in South/Central Asian CLD patients.

The PK/PD relationship between eltrombopag concentrations and the platelet response in patients with CLD following repeated QD dosing was well described by a four-compartment lifespan model, in which the stimulation of platelets was linearly related to the eltrombopag concentrations. The estimated typical value of parameter KIN (0.211) for the CLD population was much lower than that previously estimated for either healthy volunteer or ITP populations (1.43). This result is consistent with the aetiology of thrombocytopenia in patients with CLD, reflecting the reduced hepatocellular mass available for thrombopoietin production due to hepatic fibrosis and cirrhosis. The estimate of parameter SLOP (0.648) for the CLD population was similar to that estimated for the ITP population (0.579), but higher than that for healthy volunteer population (0.323), suggesting a comparable stimulating effect of eltrombopag on the bone marrow progenitor cells across ITP and CLD patient populations.

In the previous PK/PD model developed for HCV patients, the stimulation of platelets by eltrombopag concentrations was described by an E_{max} model [11]. The concentration of eltrombopag that gives half the maximal stimulation of platelets was estimated to be 17.2 $\mu\text{g ml}^{-1}$. This estimate falls within the upper end of the range of plasma concentration values in the CLD PK data set, in which only 48 of the 786 concentration observations were $>17.2 \mu\text{g ml}^{-1}$. Therefore, the lower range of eltrombopag concentrations in the CLD population relative to that obtained in the HCV population may explain why the platelet stimulatory effect of eltrombopag in CLD patients was adequately described by a linear model rather than an E_{max} model.

The combined PK and PK/PD results indicated that, although eltrombopag CL/F is lower in East Asian CLD patients, resulting in higher plasma eltrombopag

exposure for a given dose, East Asian CLD patients were less sensitive to the platelet stimulatory effect of eltrombopag, with an estimated parameter SLOP to be 34% lower in East Asian CLD patients than other CLD patients. These findings suggest that the lower sensitivity to eltrombopag could offset the higher exposure of eltrombopag in East Asian CLD patients. This model prediction is consistent with the pharmacodynamic observations from the two CLD studies, where the platelet response rates were lower in Study 2 (East Asian patients only) than in Study 3 at similar eltrombopag exposures. However, it is in contrast to the pharmacodynamic observations in both healthy subjects and patients with ITP, in which an interethnic difference in sensitivity to eltrombopag was not observed between White and East Asian subjects [10]. In the present analysis, 62% of non-East Asian CLD patients were South/Central Asians. The lower plasma ALB concentrations in these patients (median ALB of 29 $\mu\text{mol l}^{-1}$, vs. 35 $\mu\text{mol l}^{-1}$ in patients of other races) may have resulted in an elevated free fraction of eltrombopag concentration, which may have contributed to the overall greater platelet response in non-East Asian CLD patients compared with the East Asian CLD patients. Given that the majority of East Asian patients for the present population PK and PK/PD analyses were from Study 2, it is also possible that the racial effect on the platelet response of eltrombopag was confounded by the difference or variability between studies and, as a result, the real racial effect may be less than what was estimated by the model.

Patients with CLD and HCV required ~3 weeks to achieve peak platelet counts compared with ~2 weeks for ITP patients, following daily dosing for 14 days. Likewise, the time for platelet counts to return back to baseline following eltrombopag discontinuation was considerably longer for patients with CLD and HCV than for ITP patients. The delayed time to peak platelet response and the sustained platelet response following treatment discontinuation seen in patients with liver disease may have some clinical implications on the administration of eltrombopag in such patient populations. The population PK/PD model for CLD will be used to support dose selection for potential future studies in this patient population.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: the clinical trials described in this article were funded by GlaxoSmithKline; CF and SCH were consultants for GlaxoSmithKline; JZ and MW were GlaxoSmithKline employees.

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