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RESEARCH PAPER

Modeling and Simulation Support Eltrombopag Dosing in Thrombocytopenic Patients with Chronic HCV Infection

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ABSTRACT

Purpose The pharmacokinetics of eltrombopag and its stimulation of platelet production were characterized in patients with chronic hepatitis C virus (HCV) infection to optimize an eltrombopag dosing regimen for treatment of HCV-related thrombocytopenia before and throughout peginterferon (pegIFN)-based antiviral therapy.

Methods Population pharmacokinetic analysis for eltrombopag included 663 individuals (healthy subjects, $n = 28$; patients with HCV, $n = 635$). Population pharmacokinetic/pharmacodynamic analysis for platelet response involved patients with HCV only. Simulations were conducted using various dosing scenarios in the same patient population.

Results Eltrombopag pharmacokinetics were described by a two-compartment model with dual sequential first-order absorption and elimination. Age, race, sex, and severity of hepatic impairment were predictors of eltrombopag clearance. The effect of eltrombopag on platelet counts was adequately described by a model with four transit compartments in which eltrombopag concentrations stimulated the production rate of platelet precursors in an E_{max} manner.

Conclusions Modeling and simulation results support once-daily eltrombopag 25 mg as an appropriate starting dosing regimen followed by biweekly dose escalation (in 25-mg increments) up to once-daily eltrombopag 100 mg to raise platelet counts sufficiently for initiation of pegIFN-based antiviral therapy in patients with HCV. Biweekly dose adjustment allows patients to stay on the lowest possible eltrombopag dose during antiviral therapy.

KEY WORDS Eltrombopag · hepatitis C virus · platelet counts · population pharmacokinetic/pharmacodynamic · thrombocytopenia

ABBREVIATIONS

AST	Aspartate aminotransferase
BASE	Baseline platelet count
CI	Confidence interval
CL/F	Apparent clearance
CLD	Chronic liver disease
CPS	Child-Pugh score
DAA	Direct-acting antiviral agent
HCV	Hepatitis C virus
IFN	Interferon
KIN	Production rate of platelet precursors
KPD	Kinetic-pharmacodynamic
KT	Maturation rate of platelet precursors
PD	Pharmacodynamics
PegIFN	Pegylated interferon
PK	Pharmacokinetics
RBV	Ribavirin
SLPC	Linear effect of pegIFN concentrations on platelet production
Vc/F	Apparent central volume of distribution
VPC	Visual predictive check
Vp/F	Apparent peripheral volume of distribution

INTRODUCTION

Thrombocytopenia is frequently observed in patients with chronic hepatitis C virus (HCV) infection (1) and can be a consequence of both the underlying liver disease and the

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myelosuppressive effects of the interferon (IFN) products used to treat HCV infection. In patients with HCV, thrombocytopenia is mainly attributable to hypersplenism resulting from portal hypertension, whereby progressive, advanced liver fibrosis leads to increased resistance to portal venous inflow within the liver, resulting in hypersplenism and increased sequestration of platelets (2–4). Furthermore, the concentration of endogenous thrombopoietin is lower in cirrhotic subjects than in healthy subjects because the liver is the main organ responsible for thrombopoietin production (5). The current standard of care for genotype 1 HCV infection includes a combination of pegylated IFN (pegIFN) alfa and ribavirin (RBV) with either an NS3/4A protease inhibitor (boceprevir (6), simeprevir (7), or telaprevir (8)) or an NS5B polymerase inhibitor (sofosbuvir; genotype 4 as well) (9). Two pegIFNs are currently available: Pegasys® (pegIFN alfa-2a) (10) and PegIntron® (pegIFN alfa-2b) (11). Data from the pivotal Phase III registration studies for Pegasys® and PegIntron®, which excluded patients with clinically meaningful thrombocytopenia, showed that approximately 20% to 30% of patients had a reduction in platelet count during treatment with pegIFN plus RBV (10,11). Moderate to severe thrombocytopenia (defined as a platelet count <50,000/μL or 50 Gi/L) was experienced by ≤4% of patients. Current clinical management of thrombocytopenic patients with chronic HCV infection who are receiving antiviral therapy relies primarily on modifying the pegIFN dose. Approximately 3% to 6% of patients in the Phase III pivotal registration studies had their pegIFN dose reduced or discontinued due to thrombocytopenia. In addition, the pegIFN alfa product labels recommend a platelet count above 90 Gi/L for use in patients with HCV (10,11).

Eltrombopag is an orally bioavailable, small-molecule thrombopoietin receptor agonist that interacts with the transmembrane domain of the human thrombopoietin receptor and initiates a signaling cascade to induce proliferation and differentiation of megakaryocytes from bone marrow progenitor cells, resulting in increased circulating platelet count. Eltrombopag has been approved for the treatment of medical disorders associated with thrombocytopenia, *e.g.*, chronic idiopathic thrombocytopenic purpura (12,13) and HCV infection (Zhang J, *et al.* Annual Meeting of the Population Approach Group in Europe. 2009. Abstract 1494) (14). It has also been studied for the treatment of thrombocytopenia associated with hematologic malignancies and chemotherapy (Hayes S, *et al.* Annual Meeting of the Population Approach Group in Europe. 2012. Abstract 2392) (15,16).

The use of eltrombopag to increase and maintain platelet count prior to and throughout treatment of HCV infection may afford patients a greater opportunity to initiate pegIFN-based antiviral therapy and to maximize the dose and duration of such therapy, therefore improving the likelihood of achieving a sustained virologic response, defined as undetectable HCV RNA 6 months (*i.e.*, 24 weeks) after the completion of antiviral treatment.

The aim of this analysis was to build a population pharmacokinetics/pharmacodynamics (PK/PD) model to examine the effect of eltrombopag and pegIFNs (alfa-2a and alfa-2b) on platelet counts in thrombocytopenic patients with HCV. This model was subsequently used to predict platelet response for different subpopulations, dosing regimens, and dose-adjustment schemes guided by platelet response.

MATERIALS AND METHODS

Study Design

The population analyses were conducted using data from four studies: one in healthy subjects and three in patients with HCV. These studies were approved by national, regional, or investigational center ethics committees or institutional review boards as applicable, in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice, and the ethical principles that are outlined in the Declaration of Helsinki 2008. The number of subjects, doses, populations, and PK/PD sampling times for each study are presented in Table I. Patients in HCV studies were initially treated with eltrombopag to increase their platelet counts to a level sufficient for starting the subsequent pegIFN (alfa-2a and alfa-2b) + RBV-based antiviral therapy.

Bioanalytical Methods

As previously described, plasma eltrombopag concentrations were determined using a validated analytical method (17). The lower limit of the assay was 10 ng/mL for Study 1 and 100 ng/mL for the other studies, with a within- and between-run precision of ≤9.5% and 8.5%, respectively, and accuracy (% bias) of between −9.3% and 13.6% for all assays. Platelet counts were determined at each study site through a local clinical laboratory.

Population PK and PK/PD Approach

Modeling was performed using a mixed-effects approach with NONMEM® version VII, level 1.2 (ICON Development Solutions, Ellicott City, MD) (18). The first-order conditional estimation with interaction method was used for the parameter estimation. Model selection was based on an evaluation of goodness-of-fit plots, successful convergence, plausibility and precision of parameter estimates, and the minimum objective function value.

The population PK model of eltrombopag was developed with data from 28 healthy subjects and 635 patients with HCV. A two-compartment linear model with dual sequential

Table I Clinical Trial Data Included in Eltrombopag Population PK/PD Analyses

Study/phase/population	*N*	Dose(s)	Eltrombopag PK	Platelet counts (as measured PD)
Study 1/phase I/healthy volunteers	28 (~9 per dose)	30, 50, and 75 mg SD	SD: pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, and 48 h	NA
Study 2/phase II/HCV patients	45	30, 50, or 75 mg or placebo QD for 16 weeks, starting 4 weeks before initiation of weekly antiviral therapy (Part 1) and for 12 weeks during antiviral therapy (Part 2)	Part 1 (Day 28): pre-dose and 1, 2, 4, 6, 8, and 24 h post-dose Part 2 (Day 43): pre-dose and 1, 2, 4, 6, and 8 h post-dose	Part 1: baseline (Day 1) and Weeks 1, 2, 3, and 4 Part 2: Weeks 5, 6, 8, 12, and 16 and follow-up at Week 20
Study 3/phase III/HCV patients	291	Part 1 (pre-IFN therapy): • Initial dose: 25 mg QD for 14 days • Dose escalation: in 25-mg increments every 2 weeks until achieving platelet counts ≥90 Gi/L Part 2 (IFN therapy): • Initial dose: continue on Part 1 dosing or matching placebo (randomized) • Dose escalation: in 25-mg increments up to 100 mg QD/matching placebo • PegIFN alfa-2a nominal dose: 180 μg/week	Parts 1 and 2: • Serial PK: pre-dose, 1, 2, 4, 6, 8, 10, and 24 h post-dose • Sparse PK: pre-dose and one of the following: 2-4, 5–8, or 9–12 h post-dose	Part 1: • Day 1 (Baseline) • Weeks 1 to 9 Part 2: • Day 0 • Weeks 2, 4, 6, 8, and 12 and then every 4 weeks up to Week 48 Follow-up: • Weeks 4, 12, and 24
Study 4/phase III/HCV patients	299	Part 1 (pre-IFN therapy): • Initial dose: 25 mg QD for 14 days • Dose escalation: in 25-mg increments every 2 weeks until achieving platelet counts ≥100 Gi/L Part 2 (IFN therapy): • Initial dose: continue on Part 1 dosing or matching placebo (randomized) • Dose escalation: in 25-mg increments up to 100 mg QD/matching placebo • PegIFN alfa-2b nominal dose: 1.5 μg/kg/week	Parts 1 and 2: • Serial PK: pre-dose, 1, 2, 4, 6, 8, 10, and 24 h post-dose • Sparse PK: pre-dose and one of the following: 2-4, 5–8, or 9–12 h post-dose	Part 1: • Day 1 (Baseline) • Weeks 1 to 9 Part 2: • Day 0 • Weeks 2, 4, 6, 8, and 12 and then every 4 weeks up to Week 48 Follow-up: • Weeks 4, 12, and 24

HCV hepatitis C virus; *IFN* interferon; *PD* pharmacodynamic; *NA* not applicable; *pegIFN* pegylated interferon; *PK* pharmacokinetic; *QD* once daily; *SD* single dose

first-order absorption and first-order elimination previously developed for healthy volunteers and patients with chronic liver disease (CLD) were used as the starting points for the current population PK analyses (19). Since dose- and time-dependent PK of eltrombopag were not observed previously, it was not further explored in this analysis.

A population PK/PD model was developed to characterize the relationship between plasma eltrombopag concentrations and platelet counts in patients with HCV (N=633). The *post-hoc* PK parameter estimates obtained from the final population PK model were used to predict individual eltrombopag concentration profiles for the population PK/PD analysis. A model with four transit compartments developed previously (13) to characterize the platelet dynamics was used in the present analysis (Fig. 1; see Supplemental Materials for the full set of equations). The effect of eltrombopag and pegIFN on platelet dynamics was constructed in a step-wise fashion. Initially, a PK/PD model was developed using eltrombopag monotherapy data only to describe the stimulatory effect of eltrombopag on platelet counts. This model was then extended to incorporate the inhibitory effects of pegIFN (alfa-2a and alfa-2b) therapy on platelet counts. Due to a lack of pegIFN PK data in the majority of the patients, a kinetic-pharmacodynamic (KPD) modeling approach (20) was used. During KPD analysis, eltrombopag PD parameters were fixed to the final estimates of the eltrombopag monotherapy (pre-antiviral therapy) PK/PD model. The pegIFN PD parameters were estimated separately for pegIFN alfa-2a and pegIFN alfa-2b.

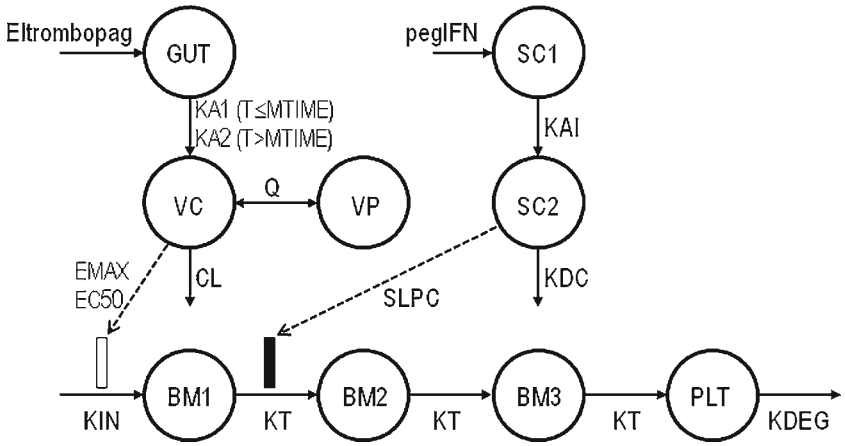

Fig. 1 A schematic representation of the KPD model for eltrombopag and pegIFN in thrombocytopenic subjects with HCV infection.

Investigation of covariate-parameter relationships was based on the range of covariate values in the dataset, scientific interest, mechanistic plausibility, exploratory graphics, and previously reported covariate-parameter relationships in other patient populations such as female sex and East Asian race, which have consistently been reported as significant predictors of eltrombopag PK across a variety of populations (12,19). A full model approach was implemented, where all covariates of interest (as seen in Table II) were entered in the model and parameters were estimated. Insignificant or poorly estimated covariates (less than 10.84-point increase of objective function value for one parameter, and/or confidence intervals [CIs] include the null value, and/or high relative standard error [>50%]) were then excluded from the model during the backward elimination process. Plots of inter-individual random effect *versus* covariate values were reviewed after each major run to ensure all possible covariate-parameter relationships were evaluated. Parameters with excessive (>30%) shrinkage in inter-individual variability were also assessed for covariate effects based on physiological or pharmacological rationale and information from prior analyses. The full model did not simultaneously include highly correlated covariates, such as body weight *versus* body mass index; therefore, several full models (with one of the competing correlated covariates) were investigated. For continuous covariates, either a power or a proportional function was utilized. For categorical covariates, the fractional change in the typical parameter value was determined.

Distributions of inter-individual random effects were assumed to be log-normal. Initial base model building was performed using a diagonal covariance matrix. Correlations between inter-individual random effects were then added if a relationship was evident from the scatter plots of random effects. The residual error of the PK model was described by a combined additive and proportional error model where the variance of the proportional error model was allowed to differ for different populations/time points as dictated by the data. The residual error of the PK/PD model was described by a proportional error model.

Model Evaluation

Visual predictive check (VPC; $N=500$) was performed for final PK and PK/PD models. The number of observed eltrombopag concentrations and platelet counts that fell within the 90% prediction interval was determined. In addition, nonparametric bootstrap analysis was conducted whenever feasible to evaluate model robustness and obtain nonparametric CIs of parameter estimates.

Simulations

Simulations based on the final population PK/PD models were performed to predict the platelet response for different subpopulations (covariates), dosing regimens, and dose-adjustment schemes (guided by platelet response). These simulations were designed to support the dose recommendation for the use of eltrombopag in thrombocytopenic patients with HCV. To avoid unintended alteration of the patient population, all patients who participated in the two Phase III studies (Studies 3 and 4, with or without PK data) were included in these simulations, *i.e.*, each simulated patient maintained his/her own demographic and baseline characteristics. Consequently, the simulated patient population was comprised of a total of 1516 patients. For each simulation scenario, 100 replicates were simulated, from which summaries were calculated.

RESULTS

Subject Demographics and Baseline Characteristics

The majority of subjects were male (61%) and of Caucasian (55%) or East/Southeast Asian (32%) race. The majority of patients with HCV had mild hepatic impairment as defined by a Child-Pugh score (CPS) (21) of 5 to 6 (95%) (Table II).

Table II Subject and Sample Characteristics

Characteristics	Statistic or category	Healthy subjects	HCV patients	All
Total number		28	635	663
Age (y)	Median (Min-max)	25 (19–38)	53 (24–74)	52 (19–74)
Weight (kg)	Median (Min-max)	77 (57–92)	75 (41–164)	75 (41–164)
Body mass index (kg/m^2)	Median (Min-max)	24 (20–29)	27 (17–53)	27 (17–53)
Aspartate aminotransferase (IU/L)	Median (Min-max)	20 (13–36)	89 (17–478)	86 (13–478)
Alkaline phosphatase (IU/L)	Median (Min-max)	NA	102 (27–361)	102 (27–361)
Albumin (g/L)	Median (Min-max)	50 (45–56)	38 (21–49)	38 (21–56)
Creatinine clearance (mL/min)	Median (Min-max)	110 (86–146)	108 (47–233)	108 (47–150)
Alanine aminotransferase (IU/L)	Median (Min-max)	17 (8–58)	77 (6–450)	75 (6–450)
Total bilirubin (μmol/L)	Median (Min-max)	14 (7–34)	20 (5–77)	20 (5–77)
Baseline platelet count (Gi/L)	Median (Min-max)	NA	60 (16–117)	60 (16–117)
Sex, *n* (%)	Male	28 (100)	375 (59)	403 (61)
	Female	0 (0)	260 (41)	260 (39)
Race, *n* (%)	Caucasian	25 (89)	337 (53)	362 (55)
	Black/African American	1 (4)	11 (2)	12 (2)
	East Asian	0 (0)	145 (23)	145 (22)
	Southeast Asian	0 (0)	69 (11)	69 (10)
	Central/South Asian	2 (7)	72 (11)	74 (11)
	Other	0 (0)	1 (<1)	1 (<1)
Ethnicity, *n* (%)	Hispanic/Latino	0 (0)	68 (11)	68 (10)
	Non-Hispanic/Latino	0 (0)	567 (89)	567 (86)
	Unknown	28 (100)	0 (0)	28 (4)
Child-Pugh class, *n* (%)[a]	A (CPS 5–6)	NA	605 (95)	605 (95)
	B (CPS 7–9)		27 (4.5)	27 (4.5)
	C (CPS 10–15)		0 (0)	0 (0)
	Unknown		3 (0.5)	3 (0.5)
Eltrombopag PK samples, *n* (%)		383 (11)	3031 (89)	3414 (100)
Platelet count data, *n* (%)[a]	Eltrombopag alone	NA	1567 (13)	1567 (13)
	With pegIFN alfa-2a	NA	5668 (45)	5668 (45)
	With pegIFN alfa-2b	NA	5235 (42)	5235 (42)

[a] Out of 635 patients with HCV infection

CPS Child-Pugh score; *HCV* hepatitis C virus; *NA* not applicable; *pegIFN* pegylated interferon; *PK* pharmacokinetic

Population PK Analysis

The PK of eltrombopag following oral administration were adequately described by a two-compartment model with dual sequential first-order absorption and absorption lag-time, and first-order elimination as the final base model, with inter-individual variability in apparent clearance (CL/F) and apparent central volume of distribution (Vc/F), and inter-occasion variability on absorption rate constant and CL/F built into the base model. After completion of the covariate model development and inclusion of covariance between the random effects associated with CL/F and Vc/F, the final PK model showed that CL/F of eltrombopag was influenced by age, race, sex, aspartate aminotransferase (AST), and the severity of hepatic impairment, and that Vc/F was influenced by race and body weight (see Supplement Materials for summary table of covariate model development).

Coadministration of pegIFN+RBV was not a significant covariate to influence eltrombopag PK in the final eltrombopag PK model. Statistical analysis based on individual *post-hoc* estimates of the eltrombopag exposure also demonstrated that concurrent administration of pegIFN alfa-2a+RBV or pegIFN alfa-2+RBV slightly increased steady-state plasma area under the concentration–time curve from time 0 to the end of the dosing interval by 11% and 15% (Table III), respectively, suggesting coadministration of pegIFN+RBV had no clinically meaningful effect on plasma eltrombopag PK.

The parameter estimates of the final PK model are presented in Table IV. The reference population was non-East/Southeast Asian healthy male subjects aged less than 60 years.

Table III Summary of the Effect of PegIFN + Ribavirin on Eltrombopag Exposure

Population	Treatment	AUC_{0-T}[a] (μg.h/mL)
PegIFN alfa-2a (studies 2 and 3)	Eltrombopag alone	0.18 (0.17, 0.20)
	Eltrombopag + pegIFN alfa-2a + ribavirin	0.20 (0.18, 0.23)
PegIFN alfa-2b (studies 2 and 4)	Eltrombopag alone	0.20 (0.19, 0.22)
	Eltrombopag + pegIFN alfa-2b + ribavirin	0.23 (0.21, 0.26)

[a] Dose-normalized to 50 mg. Results are expressed as geometric mean and 95% confidence interval

AUC_{0-T} area under the concentration–time curve from time 0 to the end of the dosing interval; *pegIFN* pegylated interferon

Table IV Parameter Estimates of the Final Eltrombopag Population PK Model in Healthy Volunteers and HCV-Infected Patients

Parameter	Estimate (%RSE)	Bootstrap (95% CI)
CL/F (L/h)	0.938 (23.5)	0.944 (0.816 to 1.09)
Vc/F (L)	12.1 (4.65)	11.9 (10.8 to 13.0)
Vp/F (L)	21.6 (3.81)	21.8 (17.2 to 26.3)
Q/F (L/h)	0.615 (5.04)	0.622 (0.527 to 0.718)
Ka1 (hr^{-1})	0.356 (9.47)	0.363 (0.253 to 0.592)
Ka2 (hr^{-1})	4.10 (12.7)	4.53 (1.64 to 13.4)
ALAG1 (h)	0.442 (1.51)	0.449 (0.412 to 0.477)
MTIME (h)	1.42 (1.31)	1.89 (1.01 to 1.95)
σProp ~ HCV	0.642 (4.70)	0.646 (0.495 to 0.821)
σProp ~ TAD <4 h	1.34 (2.87)	1.36 (1.14 to 1.63)
CL/F ~ females	0.710 (5.20)	0.708 (0.644 to 0.774)
CL/F ~ AST[a]	−0.0476 (20.2)	−0.0487 (−0.0652 to–0.0343)
CL/F ~ Age (>60 y)	0.734 (6.65)	0.737 (0.667 to 0.811)
CL/F ~ CPS 5	0.498 (24.3)	0.503 (0.429 to 0.588)
CL/F ~ East/Southeast Asians	0.645 (5.80)	0.648 (0.589 to 0.708)
CL/F ~ CPS >5[b]	−0.178 (12.1)	−0.186 (−0.241 to–0.140)
Vc/F ~ Central/South Asians	2.27 (9.12)	2.29 (1.75 to 3.02)
Vc/F and Vp/F ~ WT[c]	1 FIX	–
Inter-individual or inter-occasion variability	Estimate (%RSE) [%Shrinkage]	
ω_{CL} (%)	54.3 (9.15) [17.7]	
Corr ω_{CL}, ω_{Vc}	0.608 (8.83)	
ω_{Vc} (%)	72.4 (8.51) [18.7]	
IOV CL/F (%)	43.7 (8.01)	
IOV Ka (%)	119 (11.1)	
Residual variability		
σ_{prop} (%)	14.9 (10.0) [26.3]	
σ_{add} (μg/mL)	0.168 (8.43) [26.3]	

[a] An exponential function was used to evaluate the effect of AST on CL/F: exp(−0.0476*(AST-20)/20)

[b] A coefficient for each unit increase in CPS from CPS of 5, such that the fractional change of CL/F by CPS is expressed as 0.498*[1–0.178*(CPS-5)] in the final PK model

[c] Both Vc/F and Vp/F increased allometrically both with weight as described by $(WT/70)^{1.0}$

ALAG1 lag-time; *AST* aspartate aminotransferase; *CI* confidence interval; *CL/F* apparent clearance; *CPS* Child-Pugh score; *HCV* hepatitis C virus; *IOV* inter-occasion variability; *Ka1* absorption rate constant prior to MTIME; *Ka2* absorption rate constant after MTIME; *MTIME* time at which absorption rate changes; *Q/F* intercompartmental exchange flow rate; *RSE* relative standard error of the estimate = SE/parameter estimate * 100; *Vc/F* apparent central volume of distribution; *Vp/F* apparent peripheral volume of distribution; *σProp ~ HCV* factor of proportional error for HCV patients; *σProp ~ TAD <4 h* factor of proportional error for TAD <4 h (absorption time); *ω_{CL} and ω_{Vc}* inter-individual variability of CL/F and Vc/F, respectively; *Corr ω_{CL}, ω_{Vc}* correlation between random effect of CL/F and Vc/F; *σprop* proportional component of the residual error model; *σadd* additive component of the residual error model

The estimated typical (95% CI) parameter values for the reference population were CL/F = 0.938 (0.507–1.37) L/h, Vc/F = 12.1 (11.0–13.2) L, apparent peripheral volume of distribution (Vp/F) = 21.6 (20.0–23.2) L, and intercompartmental exchange flow rate = 0.615 (0.554–0.676) L/h. The CL/F of eltrombopag was 29% lower in female subjects compared with males, 27% lower in the elderly (>60 years) compared with younger subjects, and 36% lower in East/Southeast Asian subjects compared with other races who were predominantly Caucasian. Patients with HCV infection exhibited lower eltrombopag CL/F compared with healthy subjects. The CL/F in subjects with a CPS of 5 was estimated to be 50% lower than in healthy subjects. Increased severity of hepatic impairment resulted in a further reduction in CL/F. CL/F was negatively correlated to AST levels. For an average AST level in the HCV population of the current analysis (102 IU/L), the CL/F value was estimated to decrease by 18% compared with HCV-infected patients with normal AST (20 IU/L). Vc/F and Vp/F increased allometrically with body weight. Vc/F in Central/South Asians was 2.3-fold higher compared with all other races.

The model diagnostics indicated that the final model adequately described the data (Fig. 2). All random effects were close to normally distributed and were not correlated apart from a correlation between CL/F and Vc/F accounted for by the model. No strong unexplained covariate-parameter relationships were noticeable. Figure 3 presents the results of the prediction-corrected VPC for the final PK model by healthy subjects and patients with HCV, respectively, supporting the conclusion that the final model adequately described the observed data. The bootstrap results (Table IV) were very similar to the NONMEM estimates from the final PK model, supporting the stability of the population PK model and the good precision of NONMEM parameter estimates.

Population PK/PD Analysis

The PK/PD relationship between eltrombopag concentrations and the platelet response in patients with HCV infection during the eltrombopag monotherapy phase was well described by a model with four transit compartments. The PD model parameters included a zero-order production rate of platelet precursors (KIN), a first-order maturation rate of platelet precursors (KT), and a first-order elimination rate of platelets (k_{deg} = KIN/baseline platelet count [BASE]).

The PK/PD model based on eltrombopag monotherapy data was subsequently extended to incorporate the inhibitory effects of pegIFN therapy on platelet counts using a KPD modeling approach. The same KPD structural model was used for both pegIFN alfa-2a and pegIFN alfa-2b, as shown in Fig. 1. Absorption of pegIFN into a hypothetical compartment was assumed to follow a first-order process following the subcutaneous administration of pegIFN, as described by a first-order rate constant of hypothetical absorption rate constant for IFN. The elimination of pegIFN was described by a hypothetical rate constant. The inhibitory effect of pegIFN on platelet counts was assumed to be linearly related to the concentrations in the hypothetical compartment, with a slope for the linear effect of pegIFN concentrations on platelet production (SLPC). The PD parameters of eltrombopag were fixed to their final estimates of the eltrombopag monotherapy (pre-antiviral treatment phase) PK/PD model during KPD modeling.

The parameter estimates of the final eltrombopag PK/PD model and pegIFN KPD models are presented in Table V and Table VI, respectively. No covariates were found to significantly influence any of the PD model parameters. In patients with HCV infection, the typical estimates for KIN and KT were 10.6 Gi/L/day and 0.667 day^{-1}, respectively. The maximal stimulatory effect of eltrombopag was 15.4-fold with the associated eltrombopag concentration eliciting 50% of maximum effect of 29 μg/mL. For KPD models, the inhibitory effect of antiviral therapy on platelet counts, as described by parameter SLPC, was estimated to be 0.524 μg^{-1} and 0.00727 μg^{-1} for pegIFN alfa-2a and pegIFN alfa-2b, respectively. The estimated inter-individual variability for the slope parameter SLPC was high for both pegIFN alfa-2a and pegIFN alfa-2b. The relatively higher residual errors in the pegIFN KPD model compared to the eltrombopag PK/PD model is consistent with the use of the KPD approach to describe the PK of pegIFN.

The diagnostic plots for the final PK/PD and KPD models are presented in Fig. 4. All three models appeared to have adequately described the platelet count data during eltrombopag monotherapy and during antiviral treatment with pegIFN alfa-2a or pegIFN alfa-2b, with a slight underprediction of platelet counts at the higher observed platelet counts. The conditional weighted residuals did not show any major trend when plotted over sampling time or population prediction. Figure 5 presents the results of the prediction-corrected VPC for the final PK/PD model and KPD models, respectively. Based on model diagnostics and VPCs, the final model was deemed to have acceptable predictive performance for simulation purposes.

Simulations

The final population PK/PD and KPD models were used to perform a number of simulations to assess the impact of alternate eltrombopag dosing regimens prior to the initiation as well as during the course of antiviral therapy. Table VII summarizes various eltrombopag dosing scenarios considered in these simulations. Thrombocytopenic patients with HCV initially underwent eltrombopag monotherapy in order to raise platelet counts sufficient for initiation of antiviral therapy (>90 Gi/L for pegIFN alfa-2a and >100 Gi/L for pegIFN

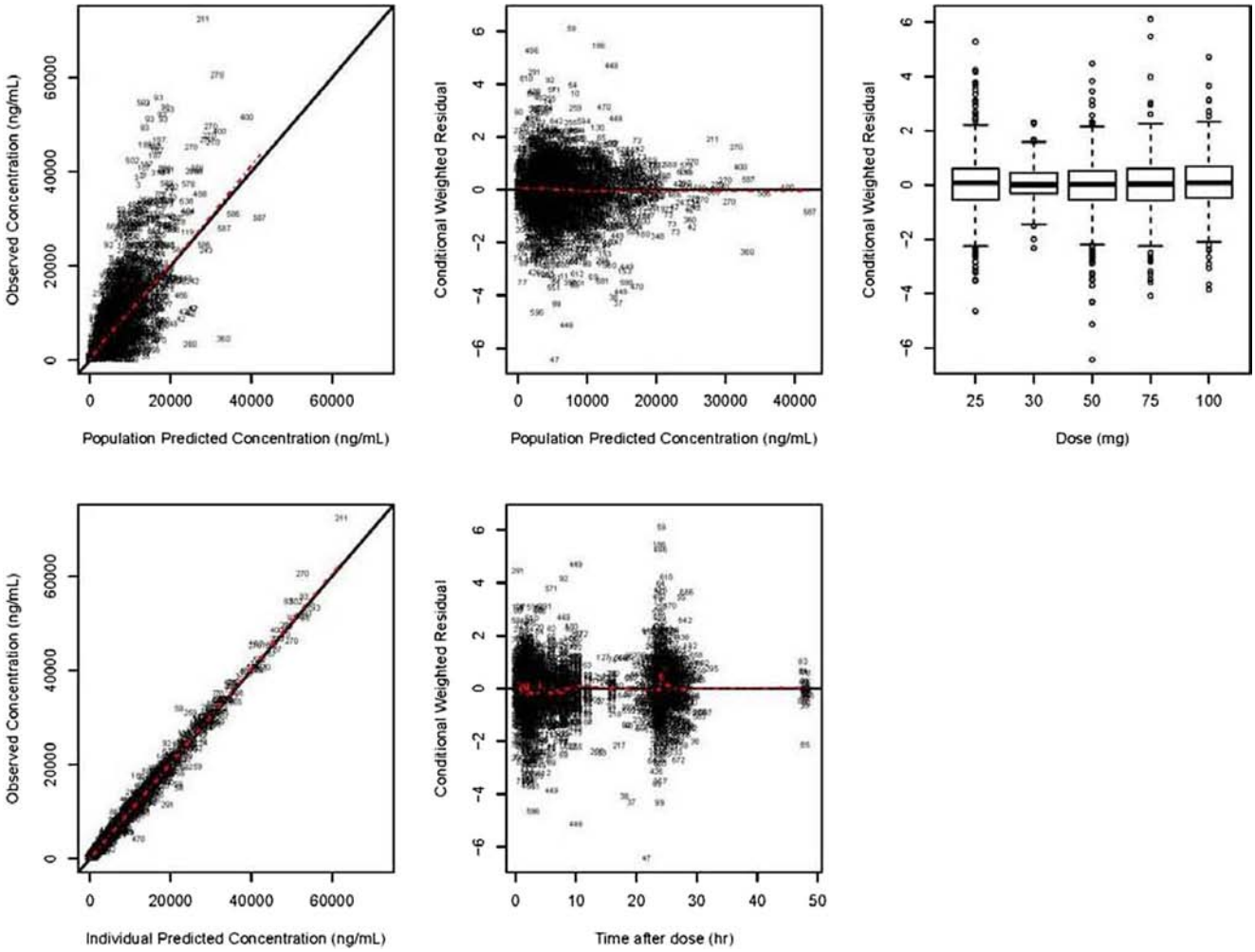

Fig. 2 Goodness-of-fit and diagnostic plots for final eltrombopag population PK model. *Solid line*: line of unity, *dashed line*: loess line.

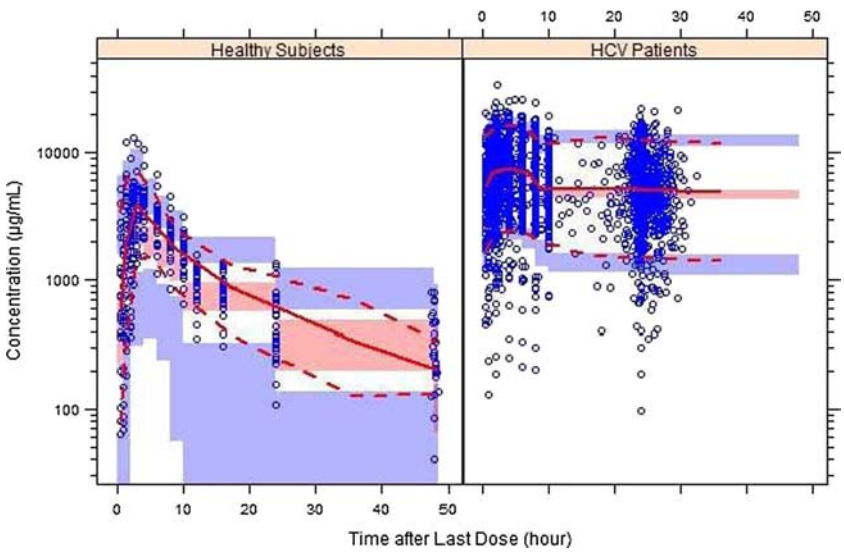

Fig. 3 Prediction-corrected visual predictive check for the final eltrombopag population PK model. *Open circles*: observed data, *red lines*: observed median (solid), 5th and 95th percentiles (dashed), *shaded areas*: 90% confidence intervals for median (red), 5th and 95th percentiles (blue) of simulated data.

Table V Parameter Estimates of the Final Eltrombopag Monotherapy Population PK/PD Model for Patients with HCV Infection

Parameter	Estimate (%RSE)
KIN (Gi/L/day)	10.6 (17.8)
KT (day^{-1})	0.667 (9.67)
E_{max} (fold)	15.4 (12.9)
EC_{50} (μg/mL)	29.0 (17.5)
Inter-individual variability	Estimate (%RSE) [%Shrinkage]
ω_{KIN} (%)	43.0 (41.4) [67.7]
ω_{EC50} (%)	80.9 (6.07) [14.5]
Residual variability	
σ_{prop} (%)	13.7 (7.07) [18.9]
σ_{add} (Gi/L)	7.82 (8.22) [18.9]

EC_{50} eltrombopag concentration eliciting 50% of maximum effect; *E_{max}* maximum effect of eltrombopag concentration on platelet production; *HCV* hepatitis C virus; *KIN* production rate of platelet precursors; *KT* maturation rate of platelet precursors; *PD* pharmacodynamic; *PK* pharmacokinetic; *RSE* relative standard error of the estimate = SE/parameter estimate * 100; *ω_{EC50} and ω_{KT}* inter-individual variability of EC_{50} and KT, respectively; *σ_{prop}* proportional component of the residual error model; *σadd* additive component of the residual error model

alfa-2b). During antiviral therapy, eltrombopag dose adjustment was considered to maintain platelet counts >50 Gi/L and <200 Gi/L, which would allow patients to avoid dose reduction of pegIFN at the lowest possible eltrombopag dose.

Table VI Parameter Estimates of Population KPD Model for Patients with HCV Infection

Parameter	Estimate (%RSE)	
	PegIFN alfa-2a	PegIFN alfa-2b
KAI (day^{-1})	0.0789 (8.66)	0.922 (fixed)[a]
KDC (day^{-1})	9.64 (68.7)	0.133 (2.57)
SLPC (μg^{-1})	0.524 (69.5)	0.00727 (9.04)
Inter-individual variability	Estimate (%RSE) [%Shrinkage]	
ω_{KAI}	110 (13.5) [28.3]	–
ω_{SLPC}	134 (8.50) [9.5]	124 (10.7) [12.0]
Residual variability		
σ_{prop} (%)	20.7 (1.56) [7.0]	23.0 (1.73) [5.8]
σ_{add} (Gi/L)	13.3 (1.42) [7.0]	12.5 (2.97) [5.8]

[a] The absorption rate constant KAI for pegIFN alfa-2b was fixed to the estimate from population pegIFN alfa-2b PK modeling in a subset of patients (data not shown)

HCV hepatitis C virus; *KAI* hypothetical absorption rate constant for IFN; *KDC* hypothetical elimination rate constant for IFN; *KPD* kinetic-pharmacodynamic; *pegIFN* pegylated interferon; *RSE* relative standard error of the estimate = SE/parameter estimate * 100; *SLPC* slope for the linear effect of pegIFN concentrations on platelet production; *ω_{SLPC} and ω_{KAI}* inter-individual variability of SLPC and KAI, respectively; *σ_{prop}* proportional component of the residual error model; *σ_{add}* additive component of the residual error model

Key simulation results are summarized in Table VIII. Simulated platelet response following eltrombopag regimens of 12.5, 25, 50, 75, and 100 mg once daily supports eltrombopag 25 mg once daily as an appropriate starting dose. Approximately 40% of patients receiving eltrombopag 25 mg once daily for 2 weeks would achieve target platelet counts to enable initiation of antiviral therapy. Following biweekly dose escalation up to 100 mg once daily, approximately 97% of patients would qualify for antiviral therapy. Simulations support this eltrombopag dose-escalation schedule for patients of all demographics, including subpopulations with the lowest plasma eltrombopag exposure (non-East/Southeast Asian males <60 years old) and with the highest exposure (East/Southeast Asian females ≥60 years old).

Simulations involving antiviral therapy with pegIFN indicated that rapid platelet count reduction occurred during the first 2 to 3 weeks after initiation of pegIFN therapy, which was then followed by a gradual reduction toward equilibrium in 5 to 6 weeks. The reduction of platelet counts was most prominent in patients who initiated antiviral therapy at eltrombopag 100 mg once daily (Fig. 6), which is consistent with the lower platelet response to eltrombopag treatment in these patients.

Simulations were further conducted to allow eltrombopag dosage modification during antiviral therapy in order to determine the optimal dose-modification strategy. During simulation, platelet counts were monitored weekly. An eltrombopag dosage increase in 25-mg increments (up to 100 mg once daily) was implemented when platelet counts were <60 Gi/L, and conversely, an eltrombopag dosage decrease when platelet counts were >200 Gi/L (25 mg once daily was the lowest simulated dose). Dose-adjustment frequency of once every 1, 2, and 3 weeks was simulated to determine the appropriate waiting period before the subsequent dose adjustment. The dose of pegIFN remained unchanged during the course of simulation.

Simulation results suggested that patients were more likely to stay on a lower eltrombopag dose to complete antiviral therapy with a biweekly eltrombopag dose-modification schedule compared to weekly dose modification. Patients who initiated antiviral therapy at eltrombopag 25 mg once daily were more likely to maintain the same eltrombopag dose throughout antiviral therapy, whereas patients who initiated antiviral therapy at a higher eltrombopag dose (75 mg) were more likely to require an eltrombopag dose increase to 100 mg. Overall, approximately 50% of patients would need at least one eltrombopag dose modification during antiviral therapy.

Following the final eltrombopag dose modification during antiviral therapy, approximately 36% of patients would stay or be dose-adjusted to an eltrombopag 25-mg once-daily dose and 33% of patients would require a 100-mg dose. Overall, ≥99% of patients receiving eltrombopag doses of 25, 50, or

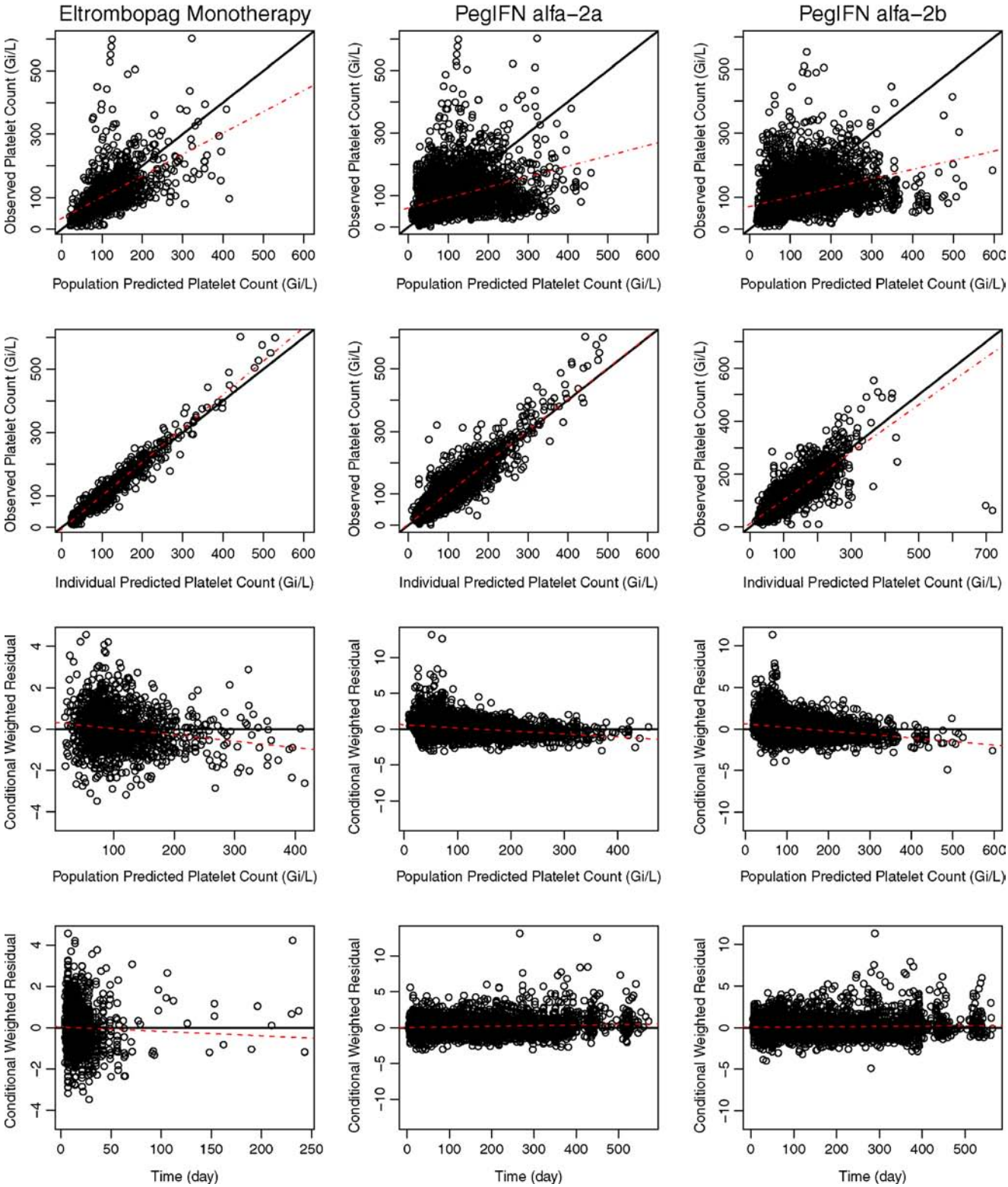

Fig. 4 Diagnostic plots for final eltrombopag and pegIFN population PK/PD models. *Open circles*: observed data, *solid black line*: unity line, *solid red line*: linear regression line.

75 mg once daily would maintain platelet counts >50 Gi/L, whereas approximately 58% of patients receiving eltrombopag 100 mg once daily would have platelet counts >50 Gi/L 6 weeks after the last eltrombopag dose modification. Following final eltrombopag dose modification during antiviral therapy, ≥99% of patients receiving eltrombopag doses of

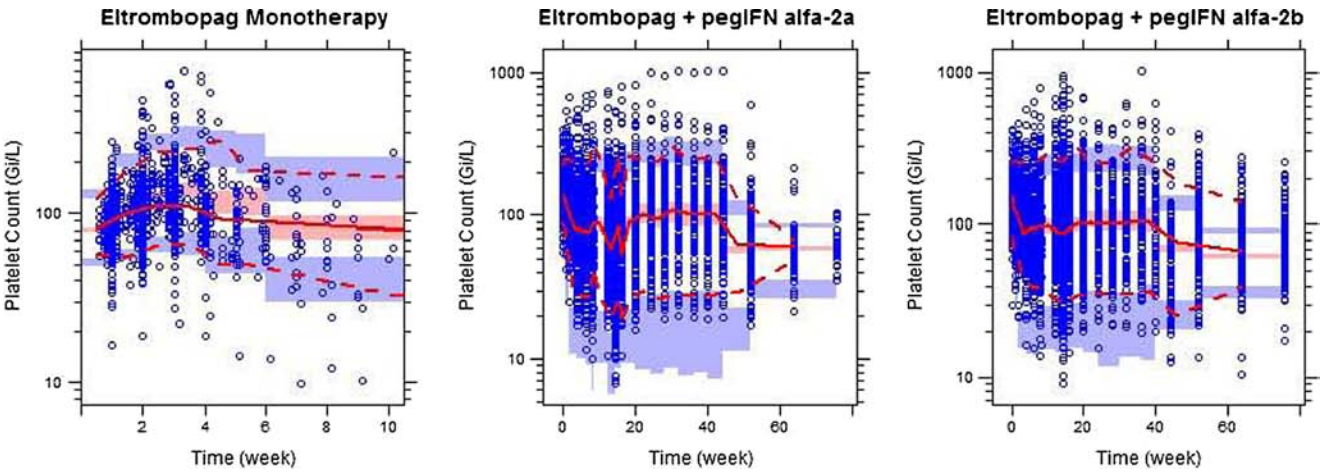

Fig. 5 Prediction-corrected visual predictive check of final population PK/PD model for eltrombopag and pegIFN. *Open circles*: observed data, *red lines*: observed median (solid) 5th and 95th percentiles (dashed), *shaded areas*: 90% confidence intervals for median (red) 5th and 95th percentiles (blue) of simulated data.

50, 75, or 100 mg once daily would maintain platelet counts <200 Gi/L, whereas approximately 69% of patients receiving eltrombopag 25 mg once daily were predicted to have platelet counts <200 Gi/L.

DISCUSSION

The PK of eltrombopag and the relationship between eltrombopag concentration and platelet response in patients with HCV following repeated once-daily dosing were adequately described by a two-compartment model with dual sequential first-order absorption and absorption lag-time as well as a transit compartment model in which the production rate of the bone marrow progenitor cells is stimulated by eltrombopag. These models have been used previously to characterize the PK of eltrombopag and its PD relationship with platelet counts in healthy subjects and other patient populations. The population PK and PK/PD models in patients with HCV presented here were developed based on a valid assumption that the structural PK and PD models are preserved across different populations, which was also supported by the goodness-of-fit results as described in the current analysis.

The final population PK model showed that CL/F is influenced by age, race, sex, AST, and the severity of hepatic impairment, while Vc/F is influenced by race and body weight. There were only limited numbers of subjects with a CPS of 7 or higher (~5%). Thus, the impact of more severe hepatic impairment on eltrombopag clearance needs to be interpreted with caution. In a Phase I single-dose study in patients with hepatic impairment, patients with moderate and severe hepatic impairment had comparable geometric mean plasma eltrombopag area under the plasma concentration–time curve from time 0 to infinity following a single dose of eltrombopag 50 mg (22). Therefore, it is possible that a further increase in eltrombopag exposure may not occur in patients with more severe hepatic impairment.

The relationship between eltrombopag concentrations and platelet counts during the eltrombopag dose-escalation phase (Part 1, pre-antiviral treatment phase) of the studies was well described by a model with four transit compartments, in which the stimulation of platelets was related to

Table VII Summary of Simulation Scenarios

Simulation	Description
Eltrombopag fixed dose	Dose: 12.5/25/50/75/100 mg once daily; duration: 2/3 weeks
Eltrombopag dose escalation	Starting dose: 25 mg once daily; dose escalation every 2 weeks at 25-mg increments up to 100 mg until target platelet count was achieved
Antiviral treatment following eltrombopag dose escalation	Eltrombopag dose: dose at the end of eltrombopag dose escalation pegIFN dose: 180 μg/week for alfa-2a; 1.5 μg/kg/week for alfa-2b
Antiviral treatment allowing eltrombopag dose modification	pegIFN dose: 180 μg/week for alfa-2a; 1.5 μg/kg/week for alfa-2b Eltrombopag dose: up/down adjustment in 25-mg increments to maintain platelet count >50 Gi/L and <200 Gi/L; modification frequency: every 1/2/3 weeks

PegIFN pegylated interferon

Table VIII Predicted Proportion of Patients Requiring Eltrombopag Doses of 25 to 100 mg Once Daily, Able to Initiate Antiviral Therapy, and Maintain Platelet Counts >50 Gi/L and <200 Gi/L During Antiviral Therapy

Population (*N*)	Eltrombopag dose (once daily)	Predicted proportion of patients				
		Receiving dose prior to AVT (%)	Initiating AVT (%)	Receiving dose at end of dose modification during AVT (%)	Maintaining platelet count during AVT[a]	
					>50 Gi/L (%)	<200 Gi/L (%)
Overall (*N* = 1516)	25 mg	40	100	36	100	69
	50 mg	40	100	18	100	99
	75 mg	12	100	13	99	99
	100 mg	8	63	33	58	100
	Overall	—	97	—	86	88
East/Southeast Asian female ≥60 y (*N* = 60)	25 mg	55	100	58	100	52
	50 mg	37	100	15	100	100
	75 mg	7	100	8	100	100
	100 mg	2	100	17	58	100
	Overall	—	100	—	93	72
Non-East/Southeast Asian male <60 y (*N* = 733)	25 mg	33	100	29	100	75
	50 mg	41	100	18	100	99
	75 mg	14	100	14	99	100
	100 mg	12	58	39	57	100
	Overall	—	95	—	83	92

[a] Prediction at 6 weeks following last dose adjustment (on stable dose)

AVT pegylated interferon-based antiviral therapy

the eltrombopag concentrations by a model of the maximum effect of eltrombopag concentration on platelet production. The estimated typical (95% CI) parameter value for platelet precursor production (KIN) was 10.6 (6.90–14.3) Gi/L/day, corresponding to 0.442 Gi/L/h, which is higher than those previously reported in a CLD population (0.211 Gi/L/h) involving patients with more severe liver impairment (22).

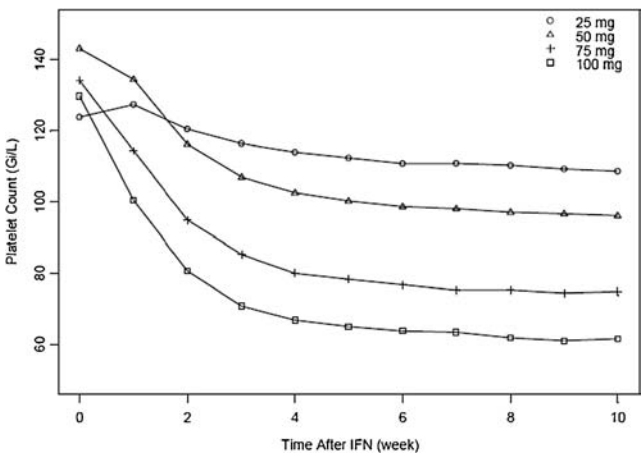

Fig. 6 Median platelet count *versus* time profiles in thrombocytopenic HCV patients during the first 10 weeks of pegIFN therapy (eltrombopag dose unchanged throughout simulation).

However, this value is still lower than that estimated from healthy subjects (1.43 Gi/L/h) (13), consistent with impaired liver function in patients with HCV infection. The estimated typical (95% CI) parameter value for the rate of platelet maturation (KT) was 0.667 (0.541–0.793) day^{-1}, which corresponds to 0.028 h^{-1} and is very similar to those previously reported for patients with CLD (0.0214 h^{-1}). The median BASE in HCV-infected patients was 60 Gi/L. Therefore, parameter k_{deg} (KIN/BASE) was estimated to be 0.18 day^{-1}, corresponding to a blood platelet half-life ($\ln 2/k_{deg}$) of 94 h, which is somewhat lower than literature-reported values (105 to 107 h) for healthy subjects (13,23).

Simulations support the same once-daily eltrombopag 25-mg starting dose and biweekly (in 25-mg increments) dose-titration schedule for all HCV-infected patients, despite differences in plasma eltrombopag exposure. Almost all patients (97%) were predicted to achieve target platelet counts to allow initiation of antiviral therapy, with the majority at once-daily eltrombopag doses ≤50 mg. This is in agreement with the clinical data from the two Phase III studies (14).

Following initiation of antiviral therapy, the simulations predicted an initial rapid decline in platelet counts during the first 2 to 3 weeks, followed by a slower decline towards equilibrium in 5 to 6 weeks (Fig. 3). These simulations appear to be consistent with the observations from the clinical studies, in that

the first adjustment of either the pegIFN or eltrombopag dose occurred within the first 3 weeks after initiation of antiviral therapy for almost 40% of HCV-infected patients, due to initial rapid decline in platelet counts (14). Close monitoring of platelet counts during the first 2 to 3 weeks after initiation of antiviral therapy is essential to reduce the risk of a rapid drop in platelet counts and consequent pegIFN dose reductions.

The simulations also predicted that, although the eltrombopag 100-mg dose is only required in a small proportion of HCV-infected patients (5%) to qualify for antiviral therapy, approximately 30% to 40% of patients would require further dose adjustment up to 100 mg at some point during antiviral therapy in order to maintain a sufficient platelet count. However, for patients who initiated antiviral therapy at the lowest eltrombopag dose of 25 mg, a smaller decline in platelet counts was predicted in response to the antiviral therapy. The clinical data support the simulation results that patients who qualified for antiviral therapy at the lowest eltrombopag dose of 25 mg were most likely to maintain their platelet counts during antiviral therapy on either the same dose or with just one dose adjustment (14). Those patients who required dose escalation in order to qualify for antiviral therapy were most likely to require a further dose increase up to the maximal eltrombopag dose of 100 mg during antiviral therapy in order to maintain a sufficient platelet count.

The simulation predicted that approximately 30% of patients who were on or eventually dose-adjusted to eltrombopag 25 mg during antiviral therapy would have platelet counts >200 Gi/L. Although the observed data in two Phase III studies also indicated that approximately 30% of patients on eltrombopag 25 mg had at least one incidence of a platelet count >200 Gi/L during antiviral therapy, most of these incidences occurred during the first few weeks of antiviral therapy. Platelet counts in most subjects (90%) were reduced to <200 Gi/L after 5 to 6 weeks of treatment with pegIFN. The difference between the simulation results and the observed data suggests that the inhibitory effect of pegIFN may have been underestimated by the model.

Eltrombopag is indicated for the treatment of thrombocytopenia in patients with HCV to allow the initiation and maintenance of IFN-based antiviral therapy (24). Since its approval, direct-acting antiviral agents (DAAs) have emerged, including the NS3/4A protease inhibitors, boceprevir (6), simeprevir (7), and telaprevir (8), and the NS5B polymerase inhibitor, sofosbuvir (9). Triple therapy (DAA+pegIFN/RBV) has become the new standard of care for patients with HCV genotype 1 (and genotype 4 for sofosbuvir). No clinically significant drug interaction was observed between eltrombopag and boceprevir or telaprevir (25). The interaction between eltrombopag and simeprevir and sofosbuvir has not been studied, although no clinically significant interaction is expected. The safety and efficacy of eltrombopag have not been established in combination with DAAs used without IFN for treatment of chronic HCV infection.

CONCLUSIONS

In summary, simulations from the final PK/PD model support once-daily eltrombopag 25 mg as an appropriate starting dosing regimen followed by biweekly dose escalation (in 25-mg increments) up to eltrombopag 100 mg once daily, in order for thrombocytopenic patients with HCV infection to raise platelet counts sufficient for initiation of antiviral therapy with pegIFN. The same eltrombopag starting dose is appropriate for all thrombocytopenic HCV-infected patients because similar platelet results were predicted across patient subpopulations despite differences in plasma eltrombopag exposure. During antiviral therapy, biweekly dose adjustment allows patients to maintain a sufficient platelet count to continue antiviral treatment while staying on the lowest possible eltrombopag dose.

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REFERENCES

1. Streiff MB, Mehta S, Thomas DL. Peripheral blood count abnormalities among patients with hepatitis C in the United States. Hepatology. 2002;35(4):947–52.
2. Medina J, García-Buey L, Moreno-Otero R. Hepatitis C virus-related extra-hepatic disease–aetiopathogenesis and management. Aliment Pharmacol Ther. 2004;20(2):129–41.
3. Peck-Radosavljevic M, Zacherl J, Meng YG, *et al.* Is inadequate thrombopoietin production a major cause of thrombocytopenia in cirrhosis of the liver? J Hepatol. 1997;27(1):127–31.
4. Dieterich D, Spivak JL. Hematologic disorders associated with hepatitis C virus infection and their management. Clin Infect Dis. 2003;37(4):533–41.
5. Kaushansky K. Thrombopoietin. N Engl J Med. 1998;39(11):746–54.
6. Victrelis® (boceprevir) prescribing information. Whitehouse Station, NJ: Merck & Co, Inc; 2013. Available from: http://www.merck.com/product/usa/pi_circulars/v/victrelis/victrelis_pi.pdf.
7. Olysio™ (simeprevir) prescribing information. Titusville, NJ: Janssen Therapeutics; 2013. Available from: http://www.olysio.com/shared/product/olysio/prescribing-information.pdf.

8. Incivek® (telaprevir) prescribing information. Cambridge, MA: Vertex Pharmaceuticals Inc; 2013. Available from: http://pi.vrtx.com/files/uspi_telaprevir.pdf .
9. Sovaldi® (sofosbuvir) prescribing information. Foster City, CA: Gilead Sciences, Inc; 2013. Available from: http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi.pdf.
10. Pegasys® (peginterferon alfa-2a) prescribing information. South San Francisco, CA: Genentech USA, Inc; 2013. Available from: http://www.gene.com/gene/products/information/pegasys/pdf/pi.pdf.
11. PegIntron® (peginterferon alfa-2b) prescribing information. Whitehouse Station, NJ: Merck & Co, Inc; 2013. Available from: http://www.merck.com/product/usa/pi_circulars/p/pegintron/pegintron_pi.pdf.
12. Gibiansky E, Zhang J, Williams D, Wang Z, Ouellet D. Population pharmacokinetics of eltrombopag in healthy subjects and patients with chronic idiopathic thrombocytopenic purpura. J Clin Pharmacol. 2011;51(6):842–56.
13. Hayes S, Ouellet D, Zhang J, Wire MB, Gibiansky E. Population PK/PD modeling of eltrombopag in healthy volunteers and patients with immune thrombocytopenic purpura and optimization of response-guided dosing. J Clin Pharmacol. 2011;51(10):1403–17.
14. Afdhal NH, Dusheiko GM, Giannini EG, *et al.* Eltrombopag increases platelet numbers in thrombocytopenic patients with HCV infection and cirrhosis, allowing for effective antiviral therapy. Gastroenterology. 2014;146(2):442–52.
15. Olnes MJ, Scheinberg P, Calvo KR, *et al.* Eltrombopag and improved hematopoiesis in refractory aplastic anemia. N Engl J Med. 2013;367(1):11–9.
16. Chawla SP, Staddon A, Hendifar A, Messam CA, Patwardhan R, Kamel YM. Results of a phase I dose escalation study of eltrombopag in patients with advanced soft tissue sarcoma receiving doxorubicin and ifosfamide. BMC Cancer. 2013;13:121–9.
17. Williams DD, Peng B, Bailey CK, *et al.* Effects of food and antacids on the pharmacokinetics of eltrombopag in healthy adult subjects: two single-dose, open-label, randomized-sequence, crossover studies. Clin Ther. 2009;31(4):764–76.
18. Beal SL, Sheiner LB, Boeckmann AJ, Bauer RJ. NONMEM user's guides (1989–2009). Ellicott City: ICON Development Solutions; 2009.
19. Farrell C, Hayes S, Giannini EG, *et al.* Gender, race, and severity of liver disease influence eltrombopag exposure in thrombocytopenic patients with chronic liver disease [abstract 1236]. Hepatology. 2010;52(4 Suppl 1):920A.
20. Jacqmin P, Snoeck E, van Schaick EA, *et al.* Modelling response time profiles in the absence of drug concentrations: definition and performance evaluation of the K-PD model. J Pharmacokinet Pharmacodyn. 2007;34(1):57–85.
21. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60(8):646–9.
22. Bauman JW, Vincent CT, Peng B, Wire MB, Williams DD, Park JW. Effect of hepatic or renal impairment on eltrombopag pharmacokinetics. J Clin Pharmacol. 2011;51(5):739–50.
23. Fritz E, Ludwig H, Scheithauer W, Sinzinger H. Shortened platelet half-life in multiple myeloma. Blood. 2008;68(2):514–20.
24. Promacta® (eltrombopag) prescribing information. Research Triangle Park, NC: GlaxoSmithKline; 2014. Available from: https://www.gsksource.com/gskprm/htdocs/documents/PROMACTA.PDF.
25. Wire MB, Fang L, Hussaini A, Kieha JF, Theodore D. Lack of clinically significant pharmacokinetic interaction between the thrombopoietin receptor agonist eltrombopag and hepatitis C virus protease inhibitors boceprevir and telaprevir. Antimicrob Agents Chemother. 2014;58(11):6704–9.