Use of Eltrombopag Exposure-Platelet Response Relationship for Dose Optimization in Patients with Chronic HCV-Infection with and without Interferon

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Background

- Eltrombopag is the first oral small-molecule, non-peptide thrombopoietin receptor agonist. It is under development for the treatment of thrombocytopenia in patients with hepatitis C virus (HCV).
- Thrombocytopenia in HCV infected patients can result from both the underlying disease and the myelo-suppressive effects of the antiviral agent Interferon (IFN).

Objectives

- Develop a population PK/PD model to characterize the effect of eltrombopag on platelet counts in HCV patients with and without IFN (peginterferon alfa-2a and alfa-2b) and ribavirin treatment.
- Evaluate the impact of co-administration of IFN on eltrombopag PK in HCV patients.
- Predict platelet response for various doses and dose adjustment schemes to guide the dose selection for Phase III studies in HCV patients.

Studies

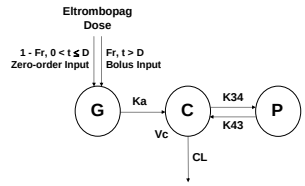
1. Phase I single dose study in healthy adult male subjects (Capsule):
   - Total of 55 subjects;
   - Doses: 5, 10, 20, 30, 50, 75 mg;
   - Series PK sampling with 802 concentration measurements.
2. Phase I single dose study in subjects with hepatic impairment (Tablet):
   - Total of 32 patients;
   - Dose: 50 mg;
   - Series PK sampling with 635 concentration measurements.
3. Phase II repeat dose study in subjects with HCV (Tablet):
   - The study consisted of two-parts:
     - Part 1: Eltrombopag alone for 4 weeks;
     - Part 2: Eltrombopag plus IFN & ribavirin if target platelet counts achieved at Week 4.
   - Total of 43 patients;
   - QD doses of 25, 30, 75 mg for up to 16 weeks;
   - Steady state PK sampling following Weeks 4 & 6 dosing with 402 concentration measurements;
   - Weekly PD sampling with 429 platelet count measurements.

Methods

- Subjects from all 3 studies (N=128) were included in the population PK analysis. The population PK/PD analysis was conducted in subjects with HCV (N = 43).
- Mixed effects modeling was conducted using NONMEM V with FO or FOCE-INTER estimation method.
- Influential covariates were identified using step-wise forward addition and backward elimination technique.
- A sequential PK and PD modeling approach was applied.
- Final model evaluation was performed using visual predictive check (VPC) and nonparametric bootstrapping (Wings for NONMEM) procedures.
- The final PK/PD model was used to predict platelet response to eltrombopag in subjects with HCV using Pharsight Trial Simulator (Version 2.2).
- Parameter uncertainty was incorporated in simulation by random sampling of parameter estimates from bootstrapping.

Results

Population PK Model



Parameter estimates of final population PK model:

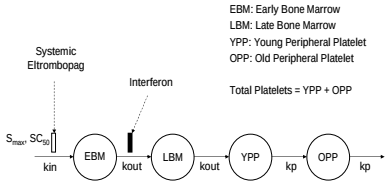
Parameter	Parameter Estimate (%RSE)	Bootstrap Median (90% CI)
$KA[1/hr] = \theta_1 \times \theta_{12}^{CPS-C}$		
θ_{11}	0.97 (6) 0.54 (17)	0.97 (0.89, 1.10) 0.54 (0.27, 0.67)
$CL/F[L/hr] = \theta_2 \times (HVT + \theta_{15} \times HCV + \theta_{16} \times HI) \times EXP(\theta_3 \times (AGE - 40) / 40 + \theta_{13} \times (AST - 62) / 62)$		
θ_2	0.71 (13)	0.73 (0.59, 0.99)
θ_{15}	0.34 (33)	0.34 (0.11, 0.70)
θ_{16}	0.82 (23)	0.83 (0.45, 1.22)
θ_9	-0.90 (27)	-0.83 (-1.27, -0.26)
θ_{13}	-0.039 (179)	-0.025 (-0.22, -0.0)
$V3/F[L] = \theta_4 \times (WT / 80)$		
θ_3	8.72 (6)	8.64 (7.63, 9.65)
$K34[1/hr] = \theta_5$		
θ_4	0.11 (6)	0.11 (0.10, 0.12)
$K43[1/hr] = \theta_6 \times EXP(\theta_{10} \times (AGE - 40) / 40)$		
θ_5	0.065 (5)	0.067 (0.060, 0.075)
θ_{10}	-0.26 (45)	-0.27 (-0.46, -0.09)
$D1[hr] = LAG2[hr] = \theta_7$		
θ_6	0.81 (3)	0.81 (0.74, 0.86)
$FR = \theta_8$		
θ_7	0.77 (6)	0.78 (0.68, 0.85)
Relative Bioavailability of Tablets (FBA):		
$FBA = \theta_{14}$	0.92 (10)	0.90 (0.75, 1.08)
Inter-individual Random-effect Parameters:		
ω^2_{KA}	0.87 (20)	0.86 (0.62, 1.23)
$\omega^2_{CL/F}$	0.12 (19)	0.13 (0.09, 0.21)
Rel. $\omega^2_{CL/F}$ for HCV	1.50 (18)	1.52 (1.05, 2.92)
Rel. $\omega^2_{CL/F}$ for HI	1.92 (17)	1.79 (1.20, 2.49)
$\omega^2_{V3/F}$	0.082 (21)	0.083 (0.059, 0.119)
Rel. $\omega^2_{V3/F}$ for HCV	1.88 (32)	1.90 (0.70, 3.03)
Rel. $\omega^2_{V3/F}$ for HI	1.93 (15)	1.89 (1.43, 2.48)
covariance ($\omega^2_{CL/F}$, $\omega^2_{V3/F}$)	0.053 (25)	0.055 (0.034, 0.082)
ω^2_{K34}	0.044 (70)	0.041 (0.001, 0.112)
ω^2_{K43}	0.087 (27)	0.074 (0.042, 0.121)
$\omega^2_{D1/LAG2}$	0.043 (37)	0.041 (0.019, 0.072)
ω^2_{FR}	6.95 (43)	6.45 (2.87, 14.47)
Intra-individual Residual Variability		
$\sigma^2_{proportional}$	0.016 (15)	0.015 (0.012, 0.020)

HVT: Healthy subjects; HCV: Patients with HCV; HI: Patients with hepatic impairment; AST: aspartate aminotransferase; CPS: Child Pugh score.

Eltrombopag PK is not affected by Interferon:

Comparison	N	Ratio Estimate	%CVw	90% CI	
				Lower	Upper
NAUC(0-τ) Week 6 vs Week 4	26	1.04	19.8	0.95	1.14

Population PD Model



Parameter estimates of final population PD model:

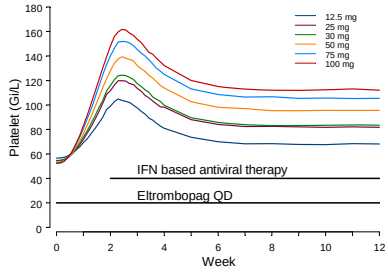
Parameter	Parameter Estimate (%RSE)
$KIN[Gi/L/hr] = \theta_1 \times EXP(\theta_7 \times (BLPT-50)/50)$	
θ_{11}	0.173 (36)
θ_7	0.824 (16)
$KOUT[1/hr] = \theta_2$	
θ_2	0.0218 (40)
$SMAX\ [fold] = \theta_3$	
θ_3	6.40 (20)
$SC50[\mu g/mL] = \theta_4$	
θ_4	17.2 (46)
$KP[1/hr] = \theta_5$	
θ_5	0.00685 (35)
$SLOPE[1/\mu g] = INFP1 \times \theta_8 + INFP2 \times \theta_9$	
θ_8	0.00867 (32)
θ_9	0.00549 (31)
Inter-individual Random-effect Parameters	
ω^2_{SC50}	1.28 (50)
ω^2_{SLOPE}	1.01 (58)
Intra-individual Residual Variability	
$\sigma^2_{proportional}$	0.038 (24)
$\sigma^2_{additive}$	153.0 (62)

BLPT: Baseline platelet counts; INFP1: Dose of peginterferon alfa-2a; INFP2: Dose of peginterferon alfa-2b

Simulations

1. HCV patients were initially dosed for 2 weeks with eltrombopag alone (Monotherapy). Those who achieved target platelet counts at Week 2 were to initiate antiviral therapy with IFN.
   - Eltrombopag doses: 12.5, 25, 30, 50, 75, and 100 mg QD;
   - Baseline platelet counts: 20-70 Gi/L
   - Target platelet counts for antiviral therapy:
     - Alfa-2a (180 µg weekly): ≥70 Gi/L
     - Alfa-2b (1.5 µg/kg weekly): ≥100 Gi/L

Simulated Median Platelet Response:



Percent of HCV Patients Achieving Target Platelet Counts:

Dose (mg)	Platelet Counts ≥50 Gi/L (%)			Platelet Counts ≥75 Gi/L (%)		
	Observed Monotherapy Results	Monotherapy Prediction (90% CI)	Combination Prediction (90% CI)	Observed Monotherapy Results	Monotherapy Prediction (90% CI)	Combination Prediction (90% CI)
12.5	–	90 (80, 97)	63 (33, 86)	–	40 (27, 57)	43 (14, 70)
25	–	93 (87, 100)	73 (50, 91)	–	63 (47, 73)	53 (33, 75)
30	100	97 (90, 100)	73 (54, 88)	70	67 (53, 77)	55 (36, 75)
50	92	97 (90, 100)	79 (60, 90)	77	80 (67, 90)	63 (44, 78)
75	100	100 (93, 100)	83 (65, 95)	88	87 (77, 97)	68 (48, 83)
100	–	100 (97, 100)	83 (68, 96)	–	93 (80, 100)	68 (54, 85)

Dose (mg)	Platelet Counts ≥0 Gi/L (%)			Platelet Counts ≥200 Gi/L (%)		
	Observed Monotherapy Results	Monotherapy Prediction (90% CI)	Combination Prediction (90% CI)	Observed Monotherapy Results	Monotherapy Prediction (90% CI)	Combination Prediction (90% CI)
12.5	–	23 (13, 33)	33 (7, 60)	–	0 (0, 3)	0 (0, 17)
25	–	43 (30, 57)	43 (23, 67)	–	3 (0, 7)	7 (0, 23)
30	50	50 (33, 60)	43 (25, 65)	0	3 (0, 10)	6 (0, 20)
50	62	63 (50, 77)	53 (35, 71)	8	10 (3, 17)	10 (0, 21)
75	88	77 (63, 87)	60 (39, 75)	25	13 (3, 23)	13 (4, 25)
100	–	83 (70, 93)	60 (44, 78)	–	20 (10, 30)	16 (4, 29)

Monotherapy: Eltrombopag alone, measured at Week 2; Combination: Eltrombopag plus IFN based antiviral therapy, measured at steady state; Observed data obtained from Phase II study. Simulation results were summarized as median (5th, 95th percentiles) from 200 simulated studies.

2. Following initial 50 mg QD regimen, a 25 mg dose increase was permitted when:
   - Target platelet counts not achieved following 2 week monotherapy with eltrombopag;
   - Platelet counts became <50 Gi/L during combination therapy with antiviral treatment.

Dose increase strategy enables more HCV patients to initiate and complete the full course of antiviral therapy:

Simulation Scenario	Eltrombopag Dose Increase not Permitted	Eltrombopag Dose Increase Permitted	% Patients Continued Treatment Following Dose Increase
% patients achieving target platelet counts during eltrombopag alone monotherapy	69%	88%	68%
% patients maintaining platelet counts ≥50 Gi/L during antiviral therapy	76%	81%	24%

Predictions were summarized as mean from 200 simulated studies.

Conclusions

- The relationship between eltrombopag exposure and platelet response in HCV patients with and without IFN was well characterized by the population PK/PD model .
- Optimization of Phase III dosing strategies through simulations should enable more HCV patients to achieve adequate platelet counts in order to initiate and maintain antiviral therapy.