

Pharmacokinetics of Eltrombopag in Patients with Hepatic Impairment

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Background

Eltrombopag is a non-peptide thrombopoietin receptor agonist approved for the treatment of thrombocytopenia in patients with chronic hepatitis C virus (HCV) infection to allow the initiation and maintenance of interferon-based antiviral therapy. It has been reported previously that eltrombopag exposure was influenced by the severity of liver disease [1].

Objectives

The objective of the present analysis was to evaluate the impact of hepatic impairment on eltrombopag pharmacokinetics (PK) in thrombocytopenic patients with hepatic impairment using population PK modelling approach.

Methods

A total of 742 subjects from 6 studies contributed 3817 plasma eltrombopag concentrations, with eltrombopag dose ranging from 12.5 to 100 mg as a single dose or repeat daily doses for up to steady state. Of the 742 subjects, 28 were healthy subjects, 673 were patients with HCV, and 41 were patients with liver disease of other etiology. Of the 714 patients, 642 (90%) had mild hepatic impairment (Child-Pugh Score [CPS] 5-6), 67 (9%) had moderate hepatic impairment (CPS 7-9), and 2 (<1%) had severe hepatic impairment (CPS >9).

Nonlinear mixed effects modelling was conducted using NONMEM VII. A linear two-compartment model with absorption lag time and dual sequential first-order absorption was used as the structural PK model for eltrombopag [2]. Influential covariates were evaluated using a semi-full model approach followed by backward elimination.

The impact of hepatic impairment on eltrombopag CL/F was investigated using the following 3 covariate models:

Linear relationship (Model 1):

$$\theta_{CPS=5} \times [1 + (CPS - 5) \times \theta_{SLOPE}]$$

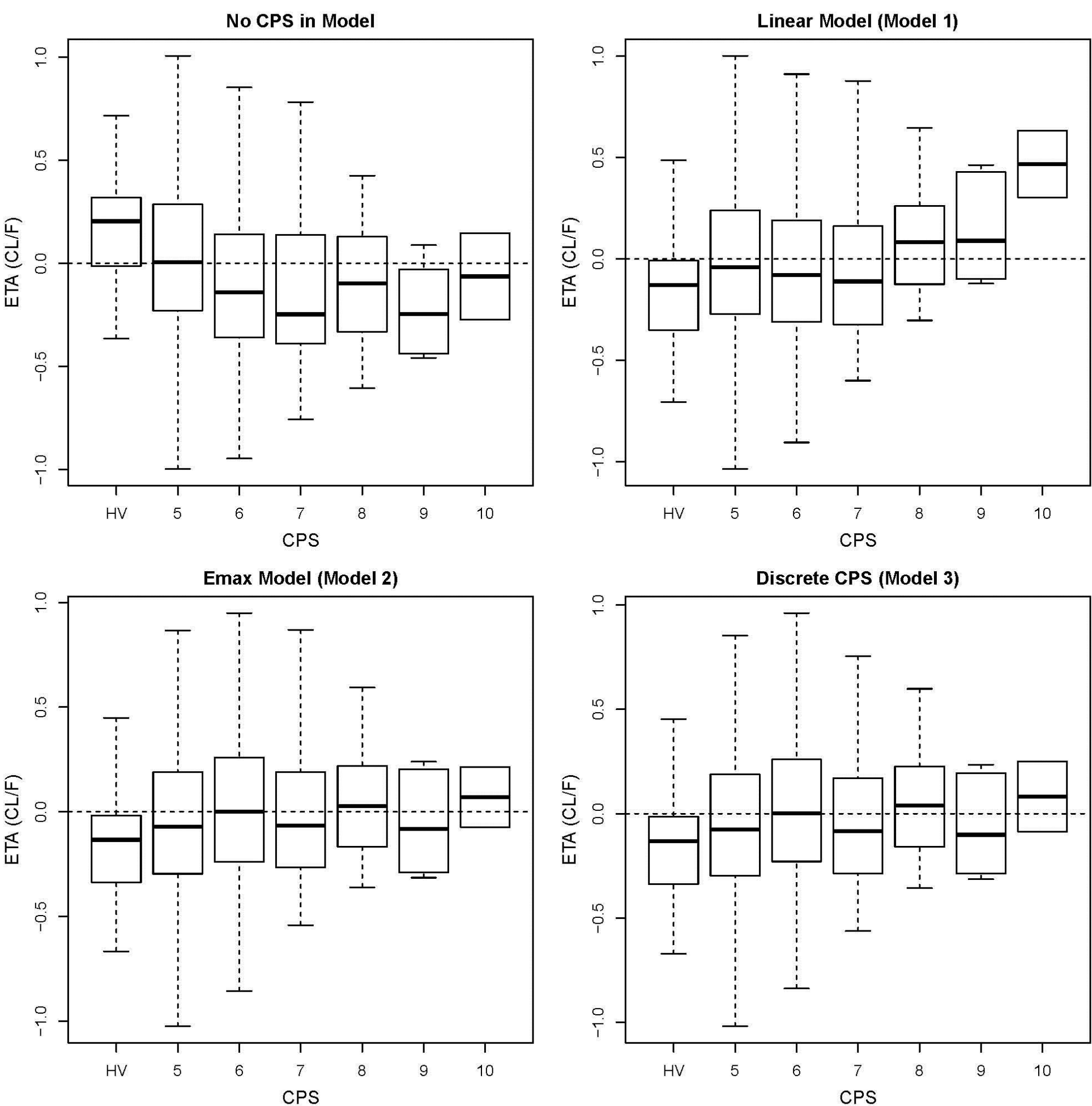
E_{max} relationship (Model 2):

$$\theta_{CPS=5} - (\theta_{CPS=5} - \theta_{E_{max}}) \times (CPS - 5) / [(CPS - 5) + \theta_{EC50}]$$

Fractional changes of CL/F at CPS of 5, 6, 7 and CPS ≥ 8 (grouped due to limited sample size) compared to healthy subjects (Model 3):

$$\theta_{CPS=5} (CPS = 5) + \theta_{CPS=6} (CPS = 6) + \theta_{CPS=7} (CPS = 7) + \theta_{CPS \geq 8} (CPS \geq 8)$$

Figure 1. Influence of CPS on CL/F



Results

- Race (East+South East Asian vs. Others), gender, and severity of hepatic impairment were the primary predictors of eltrombopag CL/F, whereas Race (Central+South Asian vs. Others) and body weight were the predictors of eltrombopag V_c/F.
- CL/F of eltrombopag in elderly (≥65 years) subjects was 29% lower compared to younger subjects, resulting in approximately 41% higher in plasma eltrombopag AUC(0-τ).
- Covariate Model 3 best characterized impact of hepatic impairment on CL/F.
- Plasma eltrombopag exposure increases with worsening of hepatic impairment. Patients with Child-Pugh Class A are predicted to have 111% higher eltrombopag AUC(0-τ) compared to healthy subjects, and patients with Child-Pugh Class B are predicted to have 183% higher eltrombopag AUC(0-τ) compared to healthy subjects.

Table 1. Parameter Estimates of the Final Population PK Model

Parameter [Units]	NONMEM Estimates			
	Point Estimate	%RSE	95% CI	
CL/F [L/hr]	0.915	21.4	0.531 – 1.3	
Vc/F [L]	11.8	4.38	10.8 – 12.8	
Vp/F [L]	20.6	3.94	19.0 – 22.2	
Q/F [L/hr]	0.619	4.62	0.563 – 0.675	
Ka1 [hr ⁻¹]	0.35	8.63	0.291 – 0.409	
Ka2 [hr ⁻¹]	3.65	11.7	2.81 – 4.49	
ALAG1 [hr]	0.443	1.41	0.431 – 0.455	
MTIME [hr]	1.42	1.27	1.38 – 1.46	
σProp ~HCV	0.606	4.49	0.553 – 0.659	
σProp ~TAD<4hr	1.29	2.67	1.22 – 1.36	
CL/F ~ Females	0.7	4.86	0.633 – 0.767	
CL/F ~ AST	-0.0407	22.0	-0.0582 – -0.0232	
CL/F ~ East/ South-East Asians	0.631	5.34	0.565 – 0.697	
CL/F ~ Age (≥65 years)	0.707	8.56	0.588 – 0.826	
CL/F ~ CPS 5 (fraction of HV)	0.508	22.2	0.287 – 0.729	
CL/F ~ CPS 6 (fraction of HV)	0.363	22.8	0.201 – 0.525	
CL/F ~ CPS 7 (fraction of HV)	0.344	24.8	0.177 – 0.511	
CL/F ~ CPS≥8 (fraction of HV)	0.312	29.2	0.133 – 0.491	
Vc/F ~ Central/South Asians	2.45	8.2	2.06 – 2.84	
Vc/F and Vp/F ~ WT ^a	1 FIX	–	–	
Inter-individual or inter-occasion variability			CV% or R	
ω ² _{CL}	0.271	8.75	0.225 – 0.317	52.1%
Covar ω _{CL} , ω _{Vc}	0.223	8.39	0.186 – 0.260	0.613
ω ² _{Vc}	0.489	7.89	0.413 – 0.565	69.9%
IOV CL/F	0.184	7.66	0.156 – 0.212	42.9%
IOV Ka	1.41	11.4	1.09 – 1.73	118.7%
Residual variability			CV% or SD	
σ ² _{prop}	0.0242	9.5	0.0197 – 0.0287	15.6%
σ ² _{add}	2.62x10 ⁴	7.9	2.2x10 ⁴ – 3.0x10 ⁴	162

a. Both V_c/F and V_p/F increased allometrically with both weight as described by (WT/70)^{1.0}.

Table 2. Estimated Impact of Hepatic Impairment on Plasma Eltrombopag Exposure relative to Subjects with Normal Hepatic Function

Child-Pugh Classification	Child-Pugh Score	Increase in AUC(0-τ) ^a	
A	5	97% (37%, 248%)	111% (45%, 283%)
	6	175% (90%, 398%)	
B	7	191% (96%, 465%)	183% (90%, 459%)
	8	221% (104%, 652%) ^b	

AUC(0-τ) was calculated by Dose/CL/F.

a. Expressed as geometric mean and 95% confidence intervals.

b. Estimate for CPS ≥ 8.

Conclusions

Population PK modelling of eltrombopag from multiple studies enabled robust quantification of the influence of hepatic impairment on eltrombopag pharmacokinetics, which further supported the eltrombopag dosing strategy in patients with greater degree of hepatic impairment.

References

- Bauman JW et al. J Clin Pharmacol (2011) 51:739-50.
- Farrel C et al. Hepatology (2010) 52(S1):920A.