Population PK/PD Modeling of Eltrombopag in ITP Patients and Optimization of Response-Guided Dosing

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BACKGROUND

- Eltrombopag is an orally bioavailable, small molecule, non-peptide thrombopoietin receptor (TPO-R) agonist that has been recently approved in the United States for treatment of chronic idiopathic (immune) thrombocytopenic purpura (ITP).
- The population pharmacokinetics (PK) of eltrombopag in ITP patients is described in PAGE 18 (2009) Poster 1502. The model identified weight, East Asian race, concomitant use of corticosteroids and gender as predictors of eltrombopag exposure.

OBJECTIVES

- To characterize the relationship between plasma eltrombopag concentrations and platelet counts (PLTC) in ITP patients.
- To estimate PLTC response for different dosing regimens, subpopulations and dose adjustment schemes guided by PLTC response (target PLTC >50 and <200 Gi/L).

DATA

88 ITP patients on eltrombopag:

- Doses of 30, 50 or 75 mg eltrombopag once-daily (QD) for 6 weeks.
- 627 platelet measurements (weekly PLTC sampling).
- 31% concurrent use of corticosteroids, 75% prior use of ITP medications, 43% splenectomy, 26 to 200 ng/L thrombopoietin concentration.
- Median (range) baseline PLTC 16 (1-40) Gi/L; East Asian patients had on average 8 Gi/L higher baseline PLTC than Caucasians and Others (median 21.5 vs. 13.5 Gi/L).

67 ITP patients on placebo:

- 590 platelet measurements (weekly PLTC sampling).

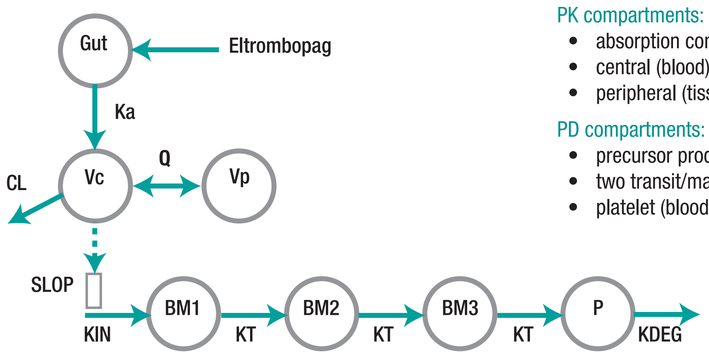
METHODS

- A life-span[1] PK/PD model was implemented in NONMEM.
- PD data were fitted alone using individual posthoc PK parameter estimates from the population PK model (PAGE 18 (2009) Poster 1502) to compute eltrombopag concentrations.
- Mixture model was introduced to account for non-responders.
- Demographics (PAGE 18 (2009) Poster 1502), concurrent use of corticosteroids, prior use of ITP medications, splenectomy and thrombopoietin concentration were explored as potential covariates.
- Simulations were performed using demographics, corticosteroid use and baseline PLTC data from all patients (each patient was replicated 100 times) to understand the impact of age, gender, race, baseline PLTC, corticosteroid use and responder vs. non-responder following 6 weeks of QD dosing of 50 mg eltrombopag.
- Additional simulations were carried out to determine the impact of dose reductions to 25 mg QD/25 mg QOD/12.5 mg QD if PLTC >200 Gi/L or dose increases to 75 mg QD if PLTC <50 Gi/L following at least 2 weeks of dosing.
- Model Evaluation: Visual predictive check (VPC) and comparison of simulated PLTC responses with observed external data from a 6-week study of eltrombopag in ITP patients.

MODEL DESCRIPTION

- 7-compartment PK/PD model with 3 PK and 4 PD compartments (Figure 1).
- Eltrombopag increased PLTC by increasing the zero order production rate of platelet precursors (KIN); KIN increased linearly with eltrombopag concentration (SLOP).

Figure 1 ***Schematic Representation of the Final Eltrombopag PK/PD Model***



PK compartments:
- absorption compartment (Gut)
- central (blood) compartment
- peripheral (tissue) compartment.

PD compartments:
- precursor production compartment (BM1)
- two transit/maturation compartments (BM2, BM3)
- platelet (blood) compartment (P).

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 proportionality constant of drug effect

RESULTS

- PLTC did not change over time in patients receiving placebo.
- Sparse and/or variable nature of the PLTC data for ITP patients was not sufficient to estimate KIN and KT uniquely. KIN and KT population estimates were fixed to the estimates from a PK/PD model developed in healthy volunteers, 1.43 Gi/L.hr and 0.0253 hr^{-1}, respectively.
- 81% of patients responded to eltrombopag (P1) with a 58% increase in KIN for each 1 µg/mL of eltrombopag plasma concentration; non-responders (19%) had SLOP=0.
- Females and older patients were more sensitive to eltrombopag, with higher SLOP.
- Diagnostic plots (Figure 2) indicated that the final model adequately described the data.

Table 1 ***Parameter Estimates of Eltrombopag Population PK/PD ITP Patient Model***

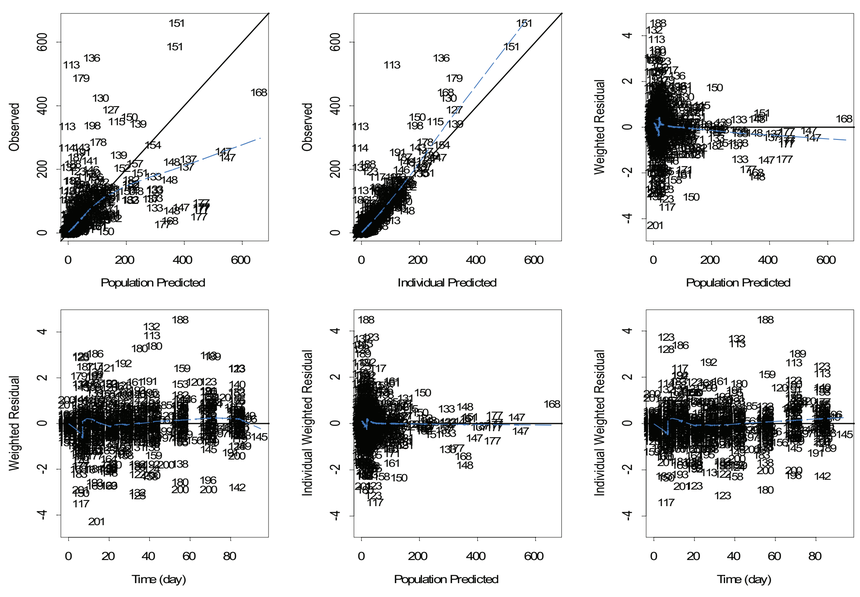
Parameter [Units]	NONMEM Estimates		
	Point Estimate (%RSE)	95% CI	
SLOP [mL/µg]	0.579 (21.1)	0.340-0.818	
KIN [Gi/L.hr]	1.43 FIXED		
KT [hr^{-1}]	0.0253 FIXED		
P(1)	0.811 (6.09)	0.714-0.908	
SLOP ~ SEX	2.42 (26.9)	1.15-3.69	
SLOP~AGE	1.27 (29.9)	0.525-2.01	
Inter-individual variability			**CV%**
ω^2 SLOP	0.804 (29.2)	0.343-1.26	89.7
ω^2 KIN	0 FIXED		
ω^2 KT	0.573 (19.0)	0.359-0.787	75.7
ω^2 BASE	0.0873 (34.9)	0.0275-0.147	29.5
Residual variability			**CV% or SD**
σ prop	0.446 (8.07)	0.375-0.517	44.6
σ add	2.96 (21.4)	1.72-4.20	2.96

Abbreviations: **KIN**: zero order production rate of platelet precursors; **KT**: first order maturation rate of platelet precursors; **SLOP**: linear proportionality constant of drug effect; **P1**: proportion of patients responding to drug; **%RSE:** percent relative standard error of the estimate = SE/parameter estimate * 100; σ^2_{prop} = proportional component of the residual error model; σ^2_{add} = additive component of the residual error model; SD=standard deviation of additive error (=$[\sigma^2_{add}]^{0.5}$)

The reference population for PD parameter **SLOP** is 50 year old male responder. **SLOP~SEX:** $0.579*2.42^{sex}$ [SEX: Male=0, Female=1]. **SLOP~AGE:** $0.579*[AGE/50]^{1.27}$.

KIN and **KT** fixed based on estimates from Healthy Volunteer model

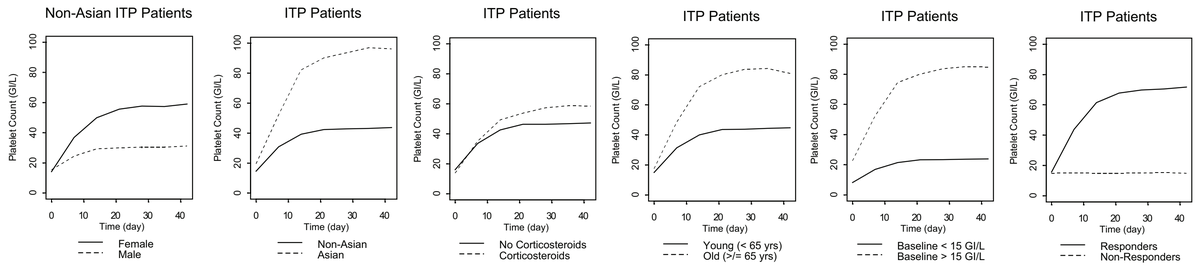
Figure 2 ***Diagnostic Plots***



SIMULATION RESULTS

- PLTC were higher in East Asian race > (Age ≥65 years) > (baseline PLTC >15 Gi/L) > Females > Corticosteroid use (Figure 3).

Figure 3 ***Simulated Median Platelet Count versus Time by Gender, Race, Corticosteroid use, Age, Baseline Platelet Count and Responder Status for Eltrombopag 50 mg QD x 6 weeks in ITP Patients***



- Steady state was achieved after 3 weeks of dosing; the median PLTC at steady state was 26, 33, 48 and 63 Gi/L for doses 12.5, 25, 50 and 75 mg QD, a 73%, 120%, 220% and 320% increase from baseline (15 Gi/L), respectively.
- 50 mg QD was supported as an appropriate starting regimen in non-Asian patients and a reduced dose of 25 mg QD for East Asian patients.
- 90% of steady-state platelet response was achieved by week 2, supporting biweekly individual dose adjustment.
- Dose titration is effective in limiting % of patients with PLTC >200 Gi/L or <50 Gi/L:
  - 60% of patients who had a dose decrease (to 25 mg QD) would have PLTC <200 Gi/L 2 weeks after dose adjustment.
  - 29% of patients who had a dose increase (to 75 mg QD) would have PLTC >50 Gi/L 2 weeks after dose adjustment.

MODEL EVALUATION

- VPC: 4.8% of the observed PLTC fell outside the 90% prediction intervals.
- Comparison of the simulated PLTC to external observed data from a 6-week study demonstrated the model was prospectively predictive (Table 2).

Table 2 ***Predicted vs. Observed Percent of Patients Achieving Specified Platelet Counts following Initial Eltrombopag Dose or Eltrombopag Dose Change***

Dosing Scenario	PLTC (Gi/L)	Predicted (Week 6)	External Observed Data (Week 6)[2] N=73**
Initial Eltrombopag Dose			
All ITP patients 50mg QD	>50	49%	59%
	50 to 200	31%	34%
	>200	18%	25%
Eltrombopag Dose Change[3]	**Platelet Count (Gi/L)**	**Predicted***	**Observed[2]* N=73**
Patients with PLTC ≤50Gi/L who increased dose from 50mg to 75mg QD	>50	29%	29% (10 of 34)
Patients with PLTC >200Gi/L who decrease dose from 50mg to 25mg QD	>200	60%	NA

* Predictions at 2 weeks after dose change; observed within 3 weeks after dose change.

** 5 of the 73 patients were included in PK/PD analysis

NA: Patients in the 6-week Phase III study discontinued study drug if platelet counts went above 200Gi/L.

CONCLUSIONS

- The developed population PK/PD model and subsequent simulations identified and quantified patient characteristics predictive of PLTC response to eltrombopag; East Asian race, age ≥65 years, baseline PLTC >15 Gi/L, female and concurrent corticosteroid use were predictive of higher PLTC (in descending order of impact).
- The developed PK/PD model was prospectively predictive of platelet response and of the impact of dose adjustment on PLTC.
- Simulations based on the model support dose adjustment regimens that minimized the risk of high PLTC and maximized the patient's chance to respond to treatment.

REFERENCES

1. Friberg L. *et al.* Semiphysiological Model for the Time Course of Leukocytes after Varying Schedules of 5-Fluorouracil in Rats, JPET, 2000.
2. Bussel J *et al.* Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial. Lancet. 2009.
3. Bussel J. *et al.* Eltrombopag for the Treatment of Chronic Idiopathic Thrombocytopenic Purpura. N Engl J Med 2007.