Title: Semi-Physiological Population PK/PD Modeling of Eltrombopag in Healthy Volunteers and Patients with Idiopathic Thrombocytopenic Purpura

Authors: Siobhan Hayes (1), Daniele Ouellet* (2), Jianping Zhang (2), Mary Wire (2), Ekaterina Gibiansky (1)

Institutions: (1) ICON Development Solutions, Ellicott City, MD, USA; (2) GlaxoSmithKline, Research Triangle Park, NC, USA

Background: Eltrombopag is an orally bioavailable small molecule agonist of thrombopoietin receptor (TPO-R) that has been recently approved in the USA for treatment of chronic idiopathic (immune) thrombocytopenic purpura (ITP). The population pharmacokinetics of eltrombopag in healthy volunteers and patients with ITP has been previously described [1]. The model identified health status (healthy volunteer vs. ITP patient), weight, Asian race, concomitant use of corticosteroids, gender and dose ($\leq$ 20 mg) as predictors of eltrombopag exposure.

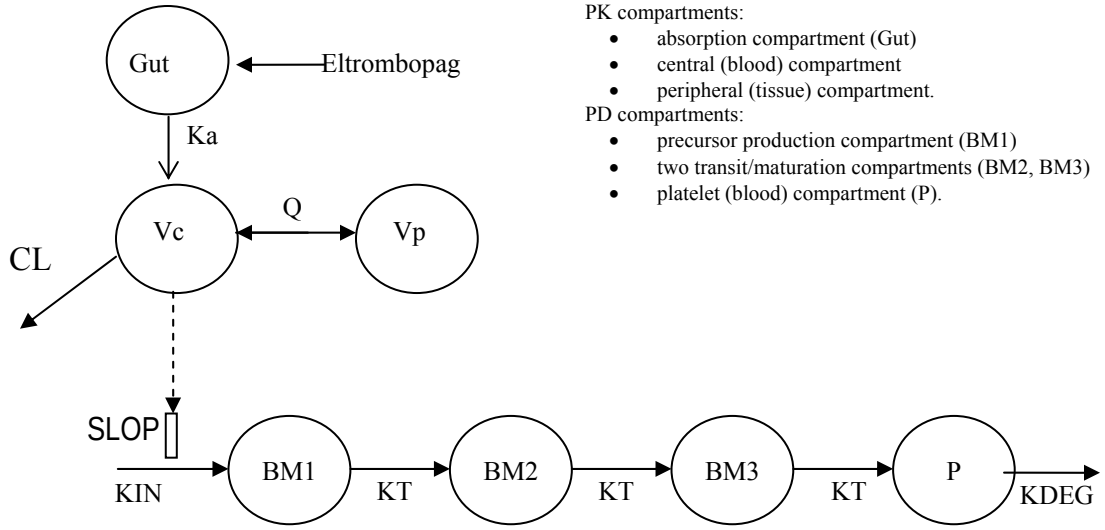
Objectives: The aim of this analysis was to develop a population pharmacokinetic/pharmacodynamic (PK/PD) model to characterize the relationship between plasma eltrombopag concentrations and platelet counts (PLTC) in healthy volunteers and patients with ITP.

Methods: Data were available from 3 Phase 1 studies in healthy volunteers (n=111 subjects with 1728 PLTC) and a Phase 2/3 study in patients with ITP (n=88 patients on eltrombopag and 67 patients on placebo with 627 and 590 PLTC, respectively). Dosing ranged from 5 to 200 mg as a single dose, or as daily doses administered for up to 10 days in healthy volunteers and from 30 to 75 mg daily for 6 weeks in ITP patients. The analysis was performed using a mixed-effects modeling approach with the first-order conditional method (FOCEI) of NONMEM. PLTC did not change over time in patients receiving placebo and were excluded from the modeling. Baseline platelet values were different between healthy volunteers and ITP patients (with median values of 217 Gi/L for healthy volunteers and 16 Gi/L for ITP patients). Due to the pathophysiology of ITP disease, the natural life-span of platelets was expected to differ between patients with ITP and healthy volunteers. The platelet response to eltrombopag could also be different between the two populations. Therefore, population PK/PD analysis were performed sequentially, first for healthy volunteers and then for patients. A semi-physiologic model that described the life-span of platelets was developed. The life-span [2] PK/PD model included 1 precursor production compartment, 2 maturation compartments, and 1 blood platelet compartment. Individual plasma eltrombopag concentrations, computed from the population PK model, increased the production rate of platelet precursors. Race, gender, age, weight and baseline platelet count were explored as potential covariates in healthy volunteers. The base model from the healthy volunteer analysis was used as the initial model in the PK/PD analysis of patients with ITP. A mixture model was introduced to account for non-responders. Demographics, use of corticosteroids, prior use of ITP medications, splenectomy, and thrombopoietin concentration were explored as potential covariates in patients. Posterior predictive checks were used to evaluate the PK/PD model in healthy volunteers and patients with ITP; nonparametric bootstrap analysis stratified by gender was performed for healthy volunteers.

Results: The same structural 7-compartment PK/PD model (3 PK, 1 precursor, 2 maturation, and 1 circulation compartment) described both healthy volunteer and ITP patient data.

Differences in platelet degradation rate (KDEG) between the 2 populations were introduced indirectly through PLTC at baseline (KDEG=KIN/BASE). Consistent with the pathophysiology of the disease where auto-antibodies increase platelet destruction and possibly impair platelet production and maturation [3], thrombopoesis parameters (KIN, KT) were initially assumed to be different in healthy volunteers and patients. However, the data in patients were too sparse and variable to adequately estimate all model parameters. Consequently, thrombopoesis was assumed to be the same in healthy volunteers and patients.

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



Healthy Volunteer Results: The zero-order production rate (KIN) and the first-order maturation rate of platelet precursors (KT) were estimated to be 1.43 Gi/L/hr (CV_{KIN}=87.3%) and KT=0.0253 hr^{-1} (CV_{KT}=40.1%), respectively. Given the median baseline PLTC (BASE) of 217 Gi/L, the first-order platelet degradation rate (KDEG=KIN/BASE) was calculated to be 0.00659 hr^{-1}, which equates to a blood platelet half-life of 105 hr in healthy volunteers. KIN increased linearly with eltrombopag plasma concentration (32.3% increase in KIN with each 1 μg/mL increase in eltrombopag plasma concentration, CV=55.9%). Female healthy volunteers were less sensitive to eltrombopag, with lower SLOP estimates compared to male healthy volunteers (36% lower, 95%CI=16%-55%). Administration of eltrombopag 50 mg for 10 days resulted in peak response on Day 15 with a predicted 1.5- and 1.8-fold increase from baseline value in non-Asian and Asian patients, respectively.

ITP Patient Results: The typical values of the production rate (KIN) and maturation rate of platelet precursors (KT) in patients were fixed to those estimated in healthy volunteers (while CV_{KIN} and CV_{KT} were estimated as 0% and 75.7%). The percent of responders was estimated as 81%, with KIN increasing linearly with eltrombopag concentration (57.9% increase in KIN with each 1 μg/mL increase in eltrombopag plasma concentration, CV=89.7%) while non-responders had a slope of 0. KDEG was calculated to be 0.0894 hr^{-1}, which equates to a blood platelet half-life of 8 hr in ITP patients. SLOP increased with age with a power coefficient of 1.27 for AGE/50 (95%CI=0.525-2.01). In addition, female patients were more sensitive to eltrombopag with an estimated SLOP of 2.42-fold (95%CI=1.15-3.69) higher than males. With continuous daily dosing of eltrombopag 50 mg, 70%, 90%, and 98% of maximal response was predicted to be achieved at Week 1, 2, and 3, respectively. The median platelet count at baseline was 15 Gi/L. Following 6 weeks of dosing, the median predicted platelet count was 26, 33, 48 and 63 Gi/L for doses of 12.5, 25, 50 and 75 mg once daily, a 73%, 120%, 220% and 320% increase from baseline, respectively. Covariates predictive of greater response were (presented in order of magnitude) Asian race, age ≥65 years, baseline platelet count >15 Gi/L, female, and concurrent corticosteroid use, either because of greater PD response or greater exposure to eltrombopag.

Conclusions: The developed semi-physiological population PK/PD model adequately described the relationships between plasma eltrombopag concentrations and PLTC in healthy volunteers and patients with ITP, identified patient characteristics predictive of the effects of eltrombopag on platelet response, and enabled exploration of different titration regimens in ITP patients.

References:

[1] E. Gibiansky, J. Zhang, D. Williams, Z. Wang, D. Ouellet. Population Pharmacokinetics of Eltrombopag in Healthy Subjects and Patients with Chronic Idiopathic Thrombocytopenic Purpura. PAGE 18 (2009) Abstr 1502 [www.page-meeting.org/?abstract=1502].

[2] Friberg L. *et al*. Semiphysiological Model for the Time Course of Leukocytes after Varying Schedules of 5-Fluorouracil in Rats, JPET, 2000.

[3] Stasi R. *et al*. Idiopathic thrombocytopenic purpura: Current concepts in pathophysiology and management, Thromb Haemost, 2008.