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

Slobhan Hayes (1), Daniele Ouellet (2), Jiaping Zhang (2), Mary Wire (2), Ekaterina Gibiansky (1)

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

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 (2008) Poster 1502. The model identified weight, East Asian race, concurrent 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 >50x10^9 and <200x10^9/L).

DATA
- 88 ITP patients on eltrombopag:
  - Doses of 30, 50 or 75 mg eltrombopag once-daily (QD) for 4 weeks.
  - 62% platelet measurements (weekly PLTc sampling).
  - 31% concurrent use of corticosteroids, 75% prior use of ITP medications, 43% splenectomy, 26 to 200 mg/d eltrombopag concentration.
  - Median (range) baseline PLTc 16 (1–40) x10^9/L, East Asian patients had on average 8 x10^9/L higher baseline PLTc than Caucasians and Others (median 21.5 vs. 13.5 x10^9/L).
- 67 ITP patients on placebo:
  - 50% platelet measurements (weekly PLTc sampling).

METHODS
- A B-spline 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 (2008) Poster 1502) to compute eltrombopag concentrations.
- Mixed model was introduced to account for non-responder.
- Demographics (PAGE 18 (2008) 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, concentration and baseline PLTc data from all patients (each patient was replicated 100 times) to understand the impact of age, gender, race, baseline PLTc concentration 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/12.5 mg QOD and PLTc >50x10^9/L or dose increases to 75 mg QD and PLTc <50x10^9/L following at least 2 weeks of dosing.
- Model Evaluation: Visual predictive check (VPC) and computation of simulated PLTc responses with observed external data from a 4-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) and KIN increased linearly with eltrombopag concentration (CLP).

RESULTS
- PLTc did not change over time in patients receiving placebo.
- Spares and variable nature of the PLTc data for ITP patients was not sufficient to estimate KIN and K7 uniquely. KIN and K7 population estimates were fixed to the estimates from a PK/PD model developed in healthy volunteers, 1.43 x10^9/L and 0.0253 x10^9/L, respectively.
- 81% of patients responded to eltrombopag (Pt) with a 50% increase in KIN for each 1 µg/L of eltrombopag/plasma concentration; non-responders (3%) had SLP=0.
- Females and older patients were more sensitive to eltrombopag, with higher SLP.
- Diagnostic plots (Figure 2) indicated that the final model adequately described the data.

MODEL SIMULATION
- VPC: 8.6% of the observed PLTc fell outside the 90% prediction interval.
- Comparison of the simulated PLTc to external observed data from a 4-week study demonstrated the model was prospectively predictive (Table 2).

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 ≥55 years, baseline PLTc >15 x10^9/L, female and concurrent corticosteroid use were predictive of higher PLTc rise (in descending order of impact).
- The developed PK/PD model was prospectively predictive of platelet response and 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