Population Pharmacokinetics of Eltrombopag in Patients with Cancer and Healthy Subjects
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BACKGROUND
• Eltrombopag is an oral once-daily nonpeptide thrombopoietin receptor (TPO-R) agonist;
• Approved in US for patients with chronic idiopathic thrombocytopenia purpura (ITP);
• In development for chemotherapy induced thrombocytopenia (CTT).
• The population pharmacokinetics (PK) of eltrombopag in patients with ITP and healthy subjects (HV) have been described previously [1].

OBJECTIVES
• To develop a population PK model of eltrombopag in patients with cancer;
• To identify demographic/covariate factors influencing eltrombopag exposure and quantify relative impact of these covariates in patients with cancer.

DATA
753 eltrombopag concentrations from 125 patients with advanced solid cancers receiving pacritinib/carboplatin (mix of sparse and serial PK sampling);
33-81 years; 30-111 kg; 51% females; 8% East Asian, 100% administered tablets;
50, 75 or 100 mg eltrombopag once-daily (QD) on days 2-11 of each 21-day cycle.

METHODS
• Mixed-effects modeling approach; first-order conditional method (FOCE) of NONMEM VI;
• The population PK model [1] developed for healthy volunteers and ITP patients was used; covariate relationships were investigated in the new population.

RESULTS
• Structural and absorption model [1] was adequate for the new population;
• Model parameter estimates are presented in Table 1;
• All model parameters were independent of weight;
• Apparent clearance (CL-F):
  ➢ Decreased with AGe: for patients >50 years old (43% lower at 81 years relative to <50 year-old patients);
  ➢ 47% lower in Asians compared to all other races;
  ➢ 15% lower in females compared to males;
• Apparent Volume (Vc/F):
  ➢ 34% lower in Asians compared to all other races;
  ➢ 26% lower in HV relative to patients with cancer;
• At low (<20 mg) CL/F was 67% higher, Vc/F was 61% higher, Vc/F was 69% lower;
• No influence of moderate renal impairment (based on 11 patients);
• No influence of smoking (based on 55 smokers, despite being a CYFRA212 substrate);
• Graphical diagnostics did not show any deficiencies;
• No bias; approximately 90% of observations were within 90% prediction intervals for each of doses and studies.

CONCLUSIONS
• The model adequately described eltrombopag PK in patients with cancer and healthy subjects.
• CL-F in patients with cancer and HV was higher (17%) than in that estimated earlier for ITP patients [1];
• CL-F decreased in older patients with cancer (<50 years), and did not depend on weight. Female and Asian patients with cancer had lower CL-F, consistent with findings in ITP patients and HVs.

REFERENCES