Pharmacokinetic and Pharmacokinetic / Pharmacodynamic Modeling to Inform Optimal Dose of Vorapaxar

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Objectives: Vorapaxar is a protease-activated receptor-1 (PAR-1) antagonist indicated for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD). During the clinical development of vorapaxar, two of the key program questions were
- What is the optimal dose of vorapaxar?
- Can the same dose be given to all patients?

Population PK and PK/PD models were developed to address these questions.

Methods: A population PK model was developed using data from 12 healthy volunteer (HV) and 4 patient studies. TRAP-induced platelet aggregation (TIPA), a target engagement biomarker, was the PD endpoint in the PK/PD model. TIPA data were available in a subset of studies.

Results: The final population PK model was a 2-compartment model with first-order absorption. Body weight, race, gender, and creatinine clearance had mild to modest effects on vorapaxar exposure. These effects were not clinically relevant.
The PK/PD model was a sigmoid Emax model with an effect compartment. No significant covariate effects were found, except a slight age effect (not clinically relevant) and a substantial study effect on EC50. EC50 was ~5-fold higher for two HV studies compared to that for the patient studies and the other HV studies. This difference could not be explained by demographic or study design/execution factors and was considered indicative of uncertainty in the PK/PD relationship.
The clinical pharmacodynamic target for the prevention of thrombotic events is >=80% inhibition in TIPA response. Simulations based on PK and PK/PD models demonstrated that ≥ 2.5 mg QD dose is required to provide ≥ 80% TIPA inhibition in most patients (Figure).

Conclusions: Modeling results suggest that no dose adjustment based on intrinsic factors is needed and all patients who are eligible to take vorapaxar should be given a daily dose of 2.5 mg.

Figure: Simulation results for proportion of patients achieving ≥ 80% TIPA inhibition