Utility of Physiologically-Based Pharmacokinetic Model (PBPK) for Prediction of Effects of Renal Impairment: A Learn-Confirm Paradigm

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Objectives: Renal impairment (RI) not only affects drug elimination in the kidney, but may also the non-renal routes clearance. The objective of this PBPK modeling was to predict the effects of RI on the exposure in subjects with RI relative to healthy volunteers (HV).

Methods: A PBPK model of an investigational agent for treatment cancer patients was developed and verified in SimCYP integrating in vitro, in silico, and in vivo PK data in healthy subjects. The virtual population with moderate and severe RI incorporated changes in CYP abundance, protein binding, renal function, tissue composition and blood flows in subjects with varying degrees of RI from the literatures. PK profiles of a single dose were simulated using a virtual population (10 trials of 8 individuals each) with normal, moderate and severe RI and used to optimize clinical trial design of a Phase 1 special population study in RI subjects. The results of the Phase 1 study and later a population PK modeling using pooled Phase 1 to 3 data allowed to verify the PBPK modeling and simulation results.

Results: Simulated concentration-time profiles of in HV were consistent with observed data in the Phase 1 study. However, PBPK model over-predicted exposures (≥ 2 fold) in subjects with moderate and severe RI. After modifying CYP abundance in default virtual population with RI, concentration time profiles of subjects with normal renal function, moderate and severe RI were reasonable captured. PBPK model successfully predicted the RI effects (1.4 fold predicted vs 1.3 fold observed in moderate RI, 1.8 fold predicted vs 1.6 fold observed in severe RI). PBPK model predicted the effect was also confirmed using a population PK modeling. The PBPK model was utilized to further investigate of the RI effects at different dose and dose regimens (repeated doses vs single dose).

Conclusions: PBPK model predicted of effects of RI on PK exposure and was utilized to clinical development and supported potential dose modification for renal impairment population.