Mechanistic Modeling to Predict Transporter-Mediated Disposition of Telmisartan in Human Using PET Derived Tissue-Plasma Patrician Coefficients and New IVIVE Scaling Factors

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**Purpose**
Hepatoselective uptake of telmisartan is driven by organic anion transport polypeptide (OATP) 1B3 with diverse datasets available providing an ideal test compound for transporter driven physiologically based pharmacokinetic (PBPK) model development. To extend a previously published whole-body PBPK model, we have developed a novel method to estimate partition coefficients (Kps) between tissues and plasma based on positron emission tomography (PET) data and additionally developed a new global approach to derive scaling factors between in vitro and in vivo hepatic clearance for forward prediction.

**Methods**
In vitro hepatic active uptake rate, passive diffusion rate and biliary clearance were determined in a sandwich-cultured human hepatocyte (SCHH) assay with both telmisartan and telmisartan glucuronide monitoring. The in vitro glucuronidation rate was determined in human liver microsomes (HLM). The PBPK model was implemented in NONMEM and MATLAB with a grid-based search method. Scaling factors were determined using in vitro and in vivo uptake rates of 7 other OATP substrates from the literature. The Kps were estimated from published PET data. Forward prediction of clinical telmisartan plasma concentration-time curves was calculated with these parameters.

**Results**
In vitro active uptake rate, passive diffusion rate, biliary clearance and glucuronidation rate were determined from the SCHH data and HLM data. The grid-based approach successfully found a consistent set of scaling factors to fit in vivo PK for all 7 literature compounds. The complexity of the system necessitated the use of a grid-based approach to prevent trapping within local minima. Parameterized appropriately, the PBPK model was shown to be able to predict the intravenous plasma concentration of telmisartan. In addition, PET-derived Kps allowed the PBPK model to more accurately describe drug distribution into non-liver tissues.

**Conclusion**
A PBPK model of telmisartan based on in vitro SCHH clearance, PET based Kps, and scaling factors, was developed. This approach can be used to improve the prediction of liver concentration and plasma pharmacokinetics of OATP substrates.