Prediction of Valsartan Pharmacokinetics in Pediatric Population Using Physiologically Based Pharmacokinetic (PBPK) Model
V. Lukacova, M. B. Bolger, W. S. Woltosz
Simulations Plus, Inc.

**Purpose**
A method for transporter-based in vitro-in vivo extrapolation (IVIVE) was previously developed and demonstrated by predicting valsartan PK after i.v. administration. The purpose of this study was to (1) extend the model to describe valsartan PK in human after p.o. administration, and (2) explore the utility of the model to predict valsartan PK in pediatric populations.

**Methods**
An absorption/PBPK model for valsartan PK was developed using GastroPlus™ 8.5 (Simulations Plus, Inc.). The program’s Advanced Compartmental Absorption and Transit (ACAT™) model described the absorption of the drug, while PK was simulated with its PBPKPlus™ module. Physiologies were generated by the program’s internal Population Estimates for Age-Related (PEAR) Physiology™ module. Intestinal absorption and tissue distribution accounted for both passive diffusion and carrier-mediated transport. Total clearance consisted of biliary (major) and renal (minor) secretion. Passive diffusion between the extracellular and intracellular spaces in all tissues was calculated from specific permeability-surface area product (SpecPStc) and tissue cell volumes. SpecPstc along with the carrier-mediated transport kinetics in liver was predicted from previously reported in vitro measurements. Renal secretion was estimated as Fup*GFR. Plasma protein and red blood cell binding was adjusted to account for pediatric plasma protein levels and hematocrit. Effect of intestinal MRP2 on valsartan absorption was included in the model. Model parameters (Vmax for liver and intestinal transporters, and SpecPStc) were also fitted against Cp-time profiles after i.v. and p.o. administration in adults and the refined model was used to predict pediatric PK.

**Results**
The initial model based on PEAR physiologies combined with in vitro estimates of transporter Km and Vmax values for liver transporters and SpecPStc gave reasonable predictions of valsartan exposure in adults and children (Cmax and AUC prediction errors ranged 20%-120%). A model refined against adult in vivo profiles resulted in much improved prediction of pediatric exposure with less than 30% prediction error on both, Cmax and AUC.

**Conclusion**
The transporter-based IVIVE method showed excellent performance for prediction of pediatric PK from adult studies. The method extends the PBPK capabilities to predict pediatric exposure for compounds where PK cannot be described by the simpler, flow-limited, tissue models.