Application of Physiologically Based Pharmacokinetic Modeling to Predict Raltegravir Pharmacokinetics in Children

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Objectives: Raltegravir is a potent human immunodeficiency virus 1 (HIV-1) integrase strand transfer inhibitor and is mainly metabolized by UDP-glucuronosyltransferases (UGT) 1A1 and UGT1A9. The objective of this study was to develop a physiologically based pharmacokinetic (PBPK) model to predict Raltegravir PK in pediatric patients across all age groups.

Methods: Simcyp simulator version 15 release 1 (Simcyp, A Certara Company), Sheffield, UK) was used to conduct all simulations. A full PBPK model with first order absorption was constructed for raltegravir based on physicochemical properties and clinical observations. Absorption rate constants of three formulations (tablet, chewable tablet and suspension) were optimized using PK data observed in clinical studies in adults. Following appropriate verification in adult populations, pediatric PK was predicted for raltegravir across all age groups using Simcyp pediatric module with application of physiological-based ontogeny. The predicted AUC, CL and Cmax were then compared with available clinical data in pediatric subjects for each age group.

Results: Pediatric PBPK models reasonably predicted the AUC values of raltegravir in infants (1~6 months), toddlers (6 month - 2 years), young children (2 - 6 years), school-aged children (6 - 12 years) and adolescents (12 - 19 years). All predicted AUC values are within 2-fold of observed values (Figure 1). Large inter subject variability was observed in children and adults taking tablet formulation.

Figure 1: Predicted over observed ratios of mean AUC ± 90% CI for raltegravir in different age and adult studies following oral administration of suspension, chewable tablet or tablet. The dashed line represents line of unity and grey shading the 0.5 to 2-fold window. For the last two studies in hepatic (HI) and renal (RI) impairment, data is only presented from the control arms.

Conclusions: Pediatric PK of raltegravir can be reasonably described using the developed PBPK model by considering ontogeny profiles of UGT1A1 and UGT1A9 built in the Simcyp pediatric model. This approach represents a general strategy for projecting drug exposure in children, a priori to guide pediatric clinical trial design.