Effect of Clinical Study Design on Estimation of Pharmacokinetic Parameters in Pediatric Populations Using Pharmacokinetic Parameters from Adult Populations as Bayesian Priors: Application to Target Mediated Drug Disposition Models (TMDD)

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Objective: To assess the accuracy and precision of clearance estimates obtained from sparse pediatric data using adult population pharmacokinetic parameters as Bayesian priors and to evaluate the frequency of Type 1 and Type 2 errors.

Methods: Pediatric population data were allometrically simulated using Michaelis Menten (MM) simplification of target mediated disposition model with known proportional differences (True-Δ= 0.6x, 0.8x, 1.0x, 1.2x, 1.4x) between adult and pediatric clearance parameters. In total, 25 scenarios were comprised of different numbers of patients (n=3 to 15) and samples (2 to 10 per subject) at five dose levels per subject with concentrations spanning the nonlinear region. Clearance parameters and estimates of differences in linear (Δ-CLL) and non-linear (Δ-CLN) clearance s were assessed from simulated data. Accuracy and precision were calculated as mean prediction error (MPE) and root mean square error (RMSE).

Results: The accuracy and precision of estimates of Δ-CLL and Δ-CLN were high (MPE <25%; RMSE <0.3) for all studied scenarios and conditions (True-Δ). The precision of both parameters increased with increases in sample size and number. However, an increase in the number of samples did not substantially alter the accuracy in the estimation of Δ-CLL and Δ-CLN. Across scenarios, Δ-CLN estimates were more accurate and precise than Δ-CLL estimates. Type II error was near zero in cases Δ= 0.6 and 1.4, and greatest in sparsest data.

Conclusions: Despite sparse sampling and limited subjects, clearance parameters in pediatric populations can be estimated with reasonable accuracy and precision by leveraging adult data as Bayesian priors. Results demonstrate pediatric studies can be suitably designed using this approach in order to minimize the number of subjects and samples without compromising power to discriminate pediatric from adult clearances when differences exist.