Effect of Altered In Vitro Dissolution on Lamivudine, Tenofovir, and Emtricitabine Pharmacokinetic Parameters: A PBPK Model Based Simulation Study

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Objective: The primary objective of this analysis is to assess the effects of delayed in-vitro dissolution due to over-encapsulation (OE) on exposure parameters of Lamivudine (3TC), Emtricitabine (FTC), and Tenofovir (TFV). Additionally, effect of food and repeated dose administration on exposure parameters between marketed and OE formulations were evaluated.

Methods: A full PBPK model was developed for 3TC, FTC, and TFV in Simcyp® v15 and validated by comparing the observed data to the simulated plasma concentration time profiles [N=2500; 50 trials and 50 sub/trial] after single dose administration. Simulations were repeated with in vitro dissolution data of OE formulation using advanced dissolution, absorption, and metabolism (ADAM) model in Simcyp. Additional simulations were run under fed conditions and at steady-state for OE formulation. Simulated exposure parameters and concentration-time profiles were compared between marketed and OE formulations.

Results: Simulated PK parameters (Cmax, Tmax, AUC0-τ, CL/F), based on dissolution profiles of 3TC, FTC, and TFV were comparable to the parameters from observed data. Simulated Cmax values of 3TC, FTC, and TFV in marketed formulation and OE formulation were: 3TC: 2.14 & 2.10 µg/mL; FTC: 1.75 & 1.74 µg/mL; TFV: 0.39 & 0.39 µg/mL respectively. Similarly, simulated AUC0-τ values of 3TC, FTC, TFV were: 11.98 & 11.75 µg*h/mL; FTC: 1.75 & 1.74 µg*h/mL; TFV: 2.92 & 2.90 µg*h/mL. Simulated concentration-time profiles for both marketed and OE formulations were nearly identical under fasted and fed conditions. Simulated PK parameters for three compounds in marketed and OE formulations were similar after single or multiple dose administration. A sensitivity analysis with lowest dissolution of OE formulation showed less than 5% variation in PK parameters of FTC and TFV as compared to marketed formulation.

Conclusions: The PBPK model based simulations showed no significant effect of delayed dissolution on exposure parameters of 3TC, FTC, and TFV. These simulations can support the waiver of BE study for OE formulation.