Population Pharmacokinetic/Pharmacodynamic Analysis of Intravenous Zanamivir in Healthy and Hospitalized Subjects with Influenza

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Objectives: Build a population pharmacokinetic model for IV zanamivir using healthy subjects and hospitalized influenza patients to explore dosing regimens and exposure-response relationship

Methods: Serum concentrations of zanamivir from 8 studies were pooled, including two studies of patients hospitalized with severe influenza. Population pharmacokinetic/pharmacodynamic analysis was performed using a nonlinear mixed-effects modelling approach in NONMEM VII (FOCE-I). Posthoc estimates (Cmax, AUC(0-τ) and Cτ) were generated for use in Cox-Proportional hazard model to assess impact of exposure on clinical and virological endpoints. Additional Monte Carlo simulations were performed for 300 and 600mg (QD & BID) dosing to determine percentage of infected subjects with steady-state concentrations above the in vitro IC₅₀ for zanamivir.

Results: A two-compartment model adequately described zanamivir PK in healthy (n=125, 19-77 years) and influenza-infected (n=533, 0.6-101 years) subjects. The estimated clearance was 5.16 L/hr in influenza patients, which decreased linearly with a reduction in creatinine clearance. The steady-state volume of distribution was 18.8 L for adult subjects and along with inter-compartmental clearance was positively correlated with body weight. The posthoc PK exposure estimates suggested current BID dosing regimen based on age, weight and creatinine clearance will achieve target exposure in adult and pediatric patients. Simulations indicated that 300 and 600mg BID dosing resulted in a saturated dose-response relationship with individual trough exposures substantially above the in vitro IC₅₀ values over the entire dosing interval. These results were confirmed by PK/PD analysis; the exposure achieved with 300 and 600mg doses did not show difference for the clinical or virologic endpoints in patients with severe influenza. Simulated QD dosing, however, appeared to be less effective at maintaining steady-state trough exposure above IC₅₀ levels.

Conclusions: The population PK/PD model supports a BID dosing regimen for IV zanamivir and suggests 300 and 600mg BID are superior to QD with both doses at the saturation range of the dose-response relationship.