Population Pharmacokinetics (PPK) and Optimal Dosing of Oseltamivir in Patients with End Stage Renal Disease (ESRD) on Hemodialysis

Leonid Gibiansky1, Richard Robson2, Vishak Subramoney3, Mohamed A. Kamal3
1QuantPharm LLC, North Potomac, MD, USA; 2Christchurch Clinical Studies Trust, Christchurch, New Zealand; 3Roche, New York, NY.

BACKGROUND
Oseltamivir (Tamiflu®) is an ethyl ester pro-drug that is rapidly absorbed after oral administration and metabolized in the liver to form oseltamivir carboxylate (OC), a potent, stable and selective inhibitor of influenza A and B neuraminidase (NA) enzymes. OC is excreted by the kidney via glomerular filtration and active tubular secretion through the organic anion transport system. ESRD patients are at increased risk of influenza and its complications. There is no consensus on dosing of oseltamivir for treatment and prophylaxis of influenza in ESRD patients on hemodialysis (HD). Different regimens are recommended in US and EU.

OBJECTIVES
- To characterize the pharmacokinetics (PK) of oseltamivir (OP) and its active metabolite oseltamivir carboxylate (OC) in ESRD patients on HD;
- To propose oseltamivir dosing regimens for treatment and prophylaxis of influenza in ESRD patients on HD.

METHODS
Rich PK data of 24 subjects with ESRD on hemodialysis administered oral oseltamivir 30 mg or 75 mg doses were described by a 5-compartment PPK model. Two compartments with first-order absorption described OP, two compartments described OC, and one compartment described OP to OC metabolism. HD clearance was described by an additional clearance term that was turned on during HD sessions.

RESULTS
The data set contained 210 and 645 quantifiable plasma samples of OP and OC, respectively, from 24 subjects (Figure 2).

The population PK analysis was conducted via nonlinear mixed-effects modeling, using NONMEM software, version 7.2.0 (ICON Development Solutions). The first-order conditional estimation method with the interaction option (FOCEI) was employed for all model runs.

The extensive model evaluation was performed using diagnostic plots and various visual predictive check (VPC) procedures.

Simulations of several dosing regimens (30 mg after every or every other session) and PK bridging (comparison of exposures with exposures of subjects with normal renal function at recommended doses) were used to select the dosing regimen.

CONCLUSIONS
- The results of the analysis support a regimen of 30 mg oseltamivir administered after each dialysis session for treatment of influenza in subjects with ESRD on hemodialysis. The previously recommended dose of 30 mg after alternate sessions would provide sub-therapeutic Cmin coverage.
- A 30 mg dose administered after alternate hemodialysis sessions, as currently recommended, is sufficient for prophylaxis.
- If the treatment is initiated between the dialysis sessions, the post-HD session dose should be administered independently of the treatment initiation time.
- Dialysis had no clinically relevant influence on oseltamivir exposure.