Population Pharmacokinetics (PPK) and Optimal Dosing of Oseltamivir Administered IV and Orally to Healthy Subjects and Subjects with Renal Impairment

Leonid Gibiansky1, Mylène Giraudon2, Craig R. Rayner3,4, Barbara Brennan5, Vishak Subramoney5, Richard Robson6, Mohamed A. Kamal6

1QuantPharm LLC, North Potomac, MD, USA; 2Roche, Basel Switzerland; 3’d Medicine LLC, NJ, USA; 4Monash University, Melbourne, Australia; 5Roche, New York, NY; 6Christchurch Clinical Studies Trust, Christchurch, New Zealand.

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. While conversion to OC in the liver is rapid, release of OC from the hepatocyte is the rate-limiting step. Data from two studies that evaluated oseltamivir pharmacokinetics (PK) following oseltamivir i.v. administration to healthy volunteers and patients with normal and impaired renal function were available. There were too few subjects with severe renal impairment in the i.v. studies to reliably estimate the impact of severe renal impairment on OC pharmacokinetics. Therefore, following completion of the analysis of the i.v. studies, data from eight studies with oral oseltamivir administration that included patients with renal impairment were added to confirm the influence of renal impairment on OC pharmacokinetics.

OBJECTIVES
• To characterize the pharmacokinetics of oseltamivir phosphate (OP) and its active metabolite OC following IV and oral administration in patients with normal renal function and with various degrees of renal impairment;
• To propose oseltamivir IV dosing regimens for treatment of influenza in patients with normal renal function and with various degrees of renal impairment.

METHODS
Initially, data of 149 subjects with normal renal function and mild to severe renal impairment administered 40 to 200 mg oseltamivir IV were described by a 4-compartment model. Two compartments described OP, one compartment described OC, and one compartment described OP to OC metabolism (Figure 1). Then, data of 128 subjects administered 20 to 1000 mg oseltamivir orally were added. The absorption model consisted of absorption and recirculation compartments with the direct (via first-pass) and indirect (via oseltamivir) input in the OC compartment.

RESULTS
The i.v. data contributed 1,597 and 1,873 plasma concentrations of OP and OC, respectively, from 149 subjects. The oral data added 1,957 and 2,418 concentrations from 128 subjects. Although all renal impairment groups were represented in both datasets, there were only 4 subjects with severe renal impairment in the i.v. dataset. The oral data added 11 subjects with severe renal impairment. The addition of the oral dataset to the i.v. dataset also significantly increased the number of subjects in the other renal impairment groups.

The final covariate i.v. model included the effect of creatinine clearance (CLCR) on CLM and kmet, and the effect of age > 80 years old on CLM. The model used Hill function to describe the effect of CLCR on CLM:

$$CLM = \frac{CLM_{\text{MAX}} \cdot CLCR}{CLM_{\text{EC50}} + CLCR}$$

where CLM_{\text{EC50}} is the CLCR at which CLM is half of its maximally achievable value.

OBJECTIVE...

CONCLUSIONS
Similarly to oral dosing, IV dosing regimens of 75 mg BID, 75 mg BID, 30 mg BID, and 30 mg QD can be recommended for treatment of influenza in subjects with normal renal function, mild, moderate, and severe renal impairment, respectively.

REFERENCES