

Title: Model Based Dose Selection of a Quinolone To Minimize Drug Induced Serum Creatinine Elevation

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Objectives: Reversible serum creatinine elevations were observed during development of a novel Q that may confound clinical safety monitoring. Glomerular filtration rate (GFR) remained constant while creatinine urinary clearance decreased suggesting the Q selectively inhibits creatinine renal tubular secretion. The objective of the present work was to utilize preclinical and phase I PK/PD data from a new quinolone (Q) and relevant public domain data to develop an exposure-response model for serum creatinine level increase by Q to support dose selection for subsequent clinical studies.

Methods: A population PK model was linked to a semi-physiological PD model of creatinine dynamics assuming competitive inhibition, consistent with preclinical data suggesting competitive inhibition of creatinine transport by Q. The PD model consisted of the following equation: $d[\text{Crn}]/dt = ([\text{Crn}].\text{GFR} + \text{RateCrnIn} - \text{RateCrnSec} \cdot [\text{Crn}]) / \text{VolCrn}$; where [Crn], GFR, RateCrnIn, RateCrnSec and VolCrn denote serum creatinine concentration (mg/dL), glomerular filtration rate (dL/Hour), zero order creatinine production rate (mg/Hour), creatinine tubular secretion rate (dL/Hour) and creatinine volume of distribution (dL). RateCrnSec was described as $\text{RateCrnSec} = V_{\text{max}} \cdot [\text{Crn}] / (K_m \cdot (1 + [Q]/K_i) + [\text{Crn}])$ where [Q] denotes the Q serum concentration. The resulting model was used to simulate Q dose dependent increase in serum creatinine. Creatinine dynamics parameters were derived from the literature.

Results: The model supported competitive inhibition of serum creatinine secretion (K_i 156 ng/mL, ED₅₀, 40 mg) by Q. Simulations showed that near maximal serum creatinine increase occurred at Q doses of about 200mg IV QD.

Conclusions: Q may competitively inhibit serum creatinine renal tubular secretion with near maximum increase at 200 mg IV QD. Hence IV Q doses above 200mg will not produce major additional increase in serum creatinine level.