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

Authors: ¹S. Song, ¹S. Rohatagi, ¹P.K. Wickremasingha, ²T. Khariton, ²S. Kshirsagar, ²T.J. Carrothers, and ²J. Kuwabara-Wagg.

Institutions: (1) Daiichi Sankyo Pharma Development, Edison, NJ, USA; (2) Pharsight Corporation, Mountain View, CA, USA

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: \( \frac{d[Crn]}{dt} = ([Crn].GFR + RateCrnIn - RateCrnSec*[Crn])/VolCrn; \) 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 \( RateCrnSec = Vmax*[Crn]/(Km*(1 + [Q]/Ki) + [Crn]) \) 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 (Ki 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.