

**Title:** Population Pharmacokinetics and Exposure-Response Modeling and Simulation To Support Quinolone Phase IIA Dose Selection.

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**Objectives:** Establish a quantitative framework to support Phase IIA dose selection for a novel quinolone, Q.

**Methods:** Preclinical and Phase I Q data were used to develop: (i) a population PK model; (ii) an exposure-efficacy response model based on preclinical data scaled to humans to predict the cumulative fraction of response (CFR); (iii) exposure-tolerability response models for QTc prolongation and liver function test (LFT) and serum creatinine elevations. Models were used to simulate likely efficacy and tolerability outcomes for dosing regimens of interest.

**Results:** The final Q PK model was a three-compartment model consisting of a single central compartment and two peripheral compartments. QTc prolongation was modeled as an additive combination of baseline, placebo, active treatment and residual variability ( $\epsilon$ ) effects:  $QTcF = \text{Base} + \text{PCB} + \text{Eff}_q + \epsilon$ . LFT elevation was modeled using logistic regression equations:  $\text{Logit}(\text{Pr}(\text{Day 13 LFT Elevation} \Rightarrow 1)) = K * \text{EM} + \text{Int}$ . A physiological, non-linear time dependent model of creatinine dynamics was used to model serum creatinine elevations. For Gram-positive infections, Q 400 mg QD IV was identified as the target dose. The predicted CFR was 90.4%, 88.3%, and 85.2% for a bacteriostatic, 1 log and 2 log kill, respectively. This dose was predicted to have an acceptable safety profile.

**Conclusions:** Given the safety and efficacy profile, an optimal dose range for IV Q administered once a day for Gram positive infections was identified.