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 (ε) effects: QTcF = Base + PCB + Effq + ε. LFT elevation was modeled using logistic regression equations: Logit(Pr(Day 13 LFTElevation => 1)) = K*EM + 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.