Interspecies Scaling in Pre-clinical Population Pharmacokinetics of CF-301

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Introduction: CF-301, the first bacteriophage-derived lysin to enter US clinical trials, completed the first Phase 1 trial recently (separate abstract). CF-301 exhibits rapid S. aureus-specific bacteriolysis, anti-biofilm activity, low propensity for resistance and pronounced synergy with antibiotics.

Objectives: Develop a pre-clinical population PK model to predict human target exposures. Data was pooled from 9 PK and toxicology studies in rats and dogs with various infusion regimens. Also, to predict exposures of CF-301 in rats following a single dose of 2.5 mg/kg 2-h infusion (the clinically relevant dose in toxicology studies).

Methods: 2- and 3-compartmental models with zero-order infusion were evaluated to characterize the concentration-time profiles of CF-301 in rats and dogs. Allometric scaling based on body weight was included a priori on all PK parameters. Covariates of interest (Sex, Age, Formulation) were evaluated for significance. Final model was evaluated using pcVPC. Primary species of interest in CF-301 toxicology studies were rats. Therefore, PK parameters for the 270 rats were used to predict exposures (Cmax, AUC) in rats following 2.5 mg/kg 2-h infusions.

Results: 1,969 concentrations from 270 rats and 78 dogs were included in the analysis. The pcVPC suggested that the final model (3-compartmental) adequately predicted CF-301 concentrations in both rats and dogs (Figure 1). Simulation of rat concentration profiles following 2.5 mg/kg 2-h infusions predicted a mean AUC=3,600 ng.h/mL and mean Cmax=1,750 ng/mL. Concentration-time profiles for typical male and female rats showed comparable AUC, Cmax and Tmax. There were no significant effect of age or formulation.

Conclusions: The population PK model for CF-301 described the plasma concentrations in rats and dogs parsimoniously, and was deemed appropriate for simulations. No relevant effect of covariates were found on the exposures. Simulations predicted a mean AUC of 3600 ng.h/mL and Cmax of 1750 ng/mL following 2.5 mg/kg 2-h infusion in rats.