**Abstract**

ETX2514 is a novel deacetylpenicillin β-lactamase inhibitor with targeted spectrum activity against human Acinetobacter, and thus stands poised to address clinical resistance trends caused by XDR Acinetobacterbaumannii. Preclinical pharmacokinetic/pharmacodynamic (PK/PD) investigations determined exposure for both dogs and rats, and ETX2514 efficacy as a combination. In support of clinical dose projections, dog and rat PK of ETX2514 was used to predict human PK parameters.

**Methods**

Human PK prediction of ETX2514 was completed using single species allometry for volume of distribution (Vdss from dog PK and rat and dog allometry to predict non-renal clearance (CL̃ro)). Rat clearance of unchanged drug was fitted to be a linear model of elimination. Human Vdss (CL̃ro, 1000 L/kg) was predicted using dog-human renal replacement. Half-life was calculated as 3.59 (2.39-5.14) hours in Phase 1 dog data for selection of initial human PK study dose. ETX2514 was combined with Phase 2 population PK model parameters, with dog allometry applied to rat PK parameters. Markov chain Monte Carlo analysis processed the human PK dataset for key PK parameters. Predicted drug concentration was used to determine cumulative fraction of time (CFT) targets. Dose of a contemporary panel of clinical A. baumannii isolates was used to determine cumulative fraction of time (CFT) targets. ETX2514 dose predicted to exceed Vdss, but CFT was considered as criteria for success.

**Results**

Estimated incidence of multidrug resistant drug resistant (XDR) A. baumannii has become a worldwide healthcare concern. More daunting, issues of XDR strains proving poor susceptibility to colistin, once considered the drug of last resort, are finding their way into hospitals. The novel deacetylpenicillin β-lactamase inhibitor ETX2514 is active against a broad range of Class A, C, and D species β-lactamases and has been shown to effectively reverse the antibiotic resistance of strains against recent A. baumannii isolates within in-vivo efficacy studies. PK/PD targets derived from these studies were used along with allometric predictions of human PK to estimate dosing requirements of the combination. Use of available population PK data for dogs and projected inter subject variability of the target population were considered with susceptibility data from n=131 clinical A. baumannii strains to determine probability of target attainment.

**Conclusions**

In vitro and in vivo clearance, allometric predictions of ETX2514 PK in humans, and PK/PD targets derived from in vitro efficacy studies predicted ETX2514 doses for a combination regimen were considered. A strategy to translate in vitro and in vivo findings to clinical doses in a prospective target attainment study including patients who may have XDR pathogens is proposed. Preclinical PK/PD data for ETX2514 supports dosing of the drug in combination with sulbactam. The combination regimen supports PK/PD targets for XDR pathogens as predicted by the preclinical studies.}

---

**References**

(3) Fones et al. J. Anti Microbial Chemother. 71(10): 2693-2701.