Pharmacokinetic-Pharmacodynamic (PK-PD) and Dose Selection Analyses for Eravacycline Using Phase 2 Data from Patients with Community-Acquired Complicated Intra-Abdominal Infections (cIAI)

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Introduction: Eravacycline is a novel IV tetracycline with *in vitro* activity against pathogens associated with cIAI. Using Phase 2 data from patients with community-acquired cIAI treated with eravacycline (1.5 mg/kg q24h or 1 mg/kg q12h), PK-PD and dose selection analyses were undertaken.

Methods: PK data were fit to a previous population PK model (3-compartment model with zero-order drug administration and linear elimination). Relationships between clinical response and Day 1 free-drug (*f*) AUC, *f*AUC:MIC ratio, or MIC, were evaluated using Fisher's exact test and logistic regression. Relationships for time to defervescence were examined using log rank tests and Cox regression. Using Day 1 *f*AUC for 2000 simulated patients and PK-PD analysis results, average predicted % probabilities of clinical success and % probabilities of PK-PD target attainment (TA) by *E. coli* MIC values and distributions were determined for eravacycline 1 mg/kg q12h and 1.5 mg/kg q24h.

Results: Using the previous structural PK model, an acceptable fit to the data from 107 patients was obtained (r^2=0.917 for observed versus individual fitted concentrations). Based on the 79 evaluable patients, a relationship between clinical response and *f*AUC:MIC ratio was identified; clinical success was 100% for *f*AUC:MIC ratio ≥1.87 and 80% for *f*AUC:MIC ratio <1.87 (p=0.015). The time for 50% of patients to achieve defervescence was 47 hours earlier for those with *f*AUC ≥ 1.11 vs those with lower *f*AUC (p=0.04). Across MIC distributions for all and levofloxacin-resistant *E. coli* isolates, average predicted % probabilities for clinical success were ≥95.6% for both regimens (table).

Conclusions: Results of these analyses support further evaluation of eravacycline 1.0 mg/kg q12h and 1.5 mg/kg q24h for patients with cIAI.

Average predicted % probabilities over *E. coli* MIC distributions by eravacycline dosing regimen

***E. coli* isolate group**[a]	**Dosing regimen**	**Average predicted % probability**[b]	
		Clinical success	**PK-PD target attainment**
All isolates (n=445)	1.5 mg/kg q24h	97.3	86.5
	1.0 mg/kg q12h	98.0	90.2
Subset of levofloxacin-resistant isolates (n=143)	1.5 mg/kg q24h	95.6	77.8
	1.0 mg/kg q12h	96.7	83.6
Subset of levofloxacin-non-resistant isolates (n=302)	1.5 mg/kg q24h	98.1	90.6
	1.0 mg/kg q12h	98.7	93.3

a. Based on a collection of demographically diverse clinical *E. coli* isolates, the minimum, MIC_{50}, MIC_{90} and maximum values for which were ≤ 0.0156, 0.25, 0.5, and 4 mg/L, respectively, for all isolates and the subset of levofloxacin-resistant isolates. These values were ≤ 0.0156, 0.125, 0.5, and 2 mg/L, respectively, for the subset of levofloxacin non-resistant isolates.

b. Represents the weighted average which was calculated over the specified MIC distribution.

Key words: Eravacycline (TP-434), pharmacokinetics-pharmacodynamics, Complicated Intra-Abdominal Infections

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