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Use of pharmacokinetic-pharmacodynamic (PK-PD) target attainment analyses to support the evaluation of intravenous and oral lefamulin dosing regimens for the treatment of patients with community-acquired bacterial pneumonia (CABP)

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Background: Lefamulin, a semi-synthetic intravenous (IV) and oral (PO) pleuromutilin antibiotic with activity against pathogens commonly associated with CABP, including multi-drug resistant *Streptococcus pneumoniae* (SP) and *Staphylococcus aureus* (SA), is currently in Phase 3 development for the treatment of patients with CABP. PK-PD target attainment analyses were undertaken to evaluate IV and PO lefamulin dosing regimens for patients with CABP using a refined population PK (PPK) model, non-clinical PK-PD targets for SP and SA efficacy, contemporary *in vitro* surveillance data, and Monte Carlo simulation.

Methods: Data used included a PPK model for IV and PO (fed and fasted) lefamulin developed using Phase 1 ELF and plasma data, PK-PD targets based on neutropenic murine-lung infection models (ICAAC 2015, Abstr A-037) and lefamulin MIC data for SP and SA isolates collected worldwide. The PPK model describing the disposition of lefamulin was a three-compartment model with nonlinear protein binding and two parallel first-order absorption processes. Two first-order rate constants were used to describe lefamulin into and out of the ELF compartment. Using the PPK parameter estimates, total-drug ELF and free-drug plasma concentration-time profiles were generated for 2000 simulated patients following lefamulin 150 mg IV q12h and 600 mg PO q12h under fed and fasted conditions;

Day 1 $AUC_{0\text{-}24}$ values were calculated. Percent probabilities of PK-PD target attainment by MIC and overall (i.e., weighted over SP and SA MIC distributions) were determined using median total-drug ELF and free-drug plasma AUC:MIC ratio targets associated with 1- and 2-$\log_{10}$ CFU reductions from baseline for SP and SA.

Results: Percent probabilities of PK-PD target attainment by MIC for SP (Figure 1) and SA (Figure 2) were similar after IV and PO dosing regimens at MIC values ≤ MIC_{90}. Percent probabilities of attaining total-drug ELF AUC:MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction for SP were ≥99.2% at the SP MIC_{90} of 0.12 mcg/mL and 96.7, 82.1, and 96.3% for IV and PO dosing regimens under fed and fasted conditions, respectively, at the SP MIC_{99} of 0.25 mcg/mL. For the free-drug plasma AUC:MIC ratio target for this endpoint and the SP MIC_{99}, percent probabilities were 100% for each dosing regimen. Percent probabilities of attaining total-drug ELF and free-drug plasma AUC:MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction for SA ranged from 92.7 to 100% for IV and PO (under fed or fasted conditions) dosing regimens at the SA MIC_{99} of 0.12 mcg/mL. Overall percent probabilities of attaining these AUC:MIC ratio targets for SP and SA were ≥98.3 and ≥98.6%, respectively.

Conclusion: These data provide support for lefamulin 150 mg IV q12h and 600 mg PO q12h for the treatment of patients with CABP and suggest that doses do not need to be taken under fasted conditions.

Figure 1. Percent probabilities of PK-PD target attainment by MIC for lefamulin dosing regimens based on the evaluation of total-drug ELF and free-drug plasma AUC:MIC ratio targets associated with a 1 $\log_{10}$ CFU reduction from baseline *for S. pneumoniae overlaid* on the MIC distribution for *S. pneumoniae* isolates collected from regions worldwide (n=1,835)

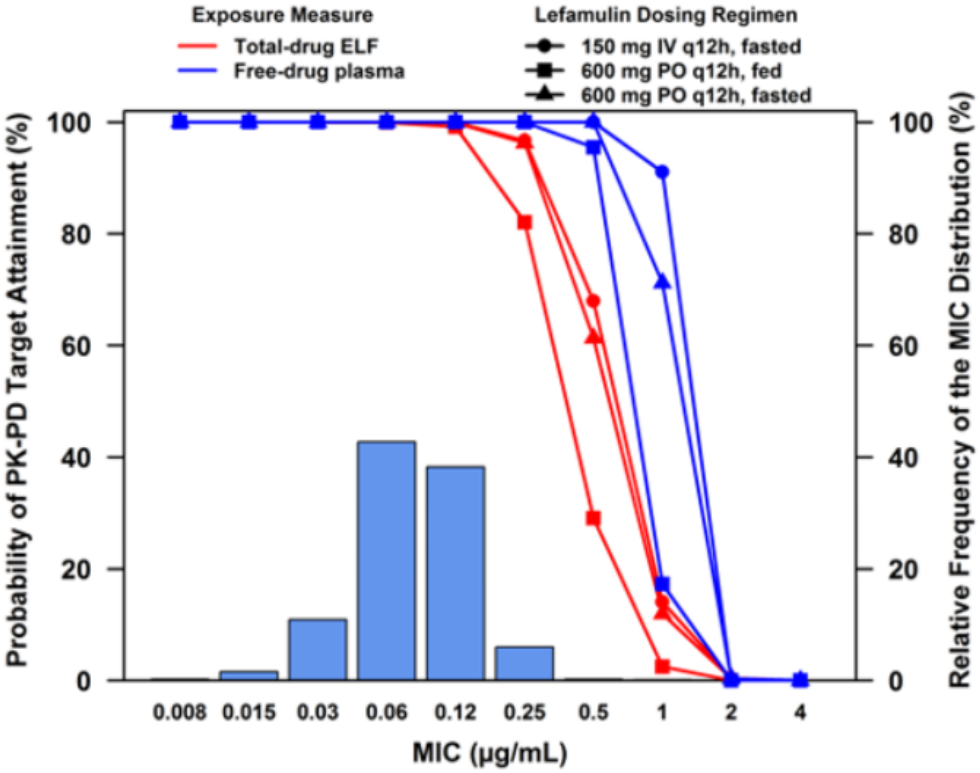

Figure 2. Percent probabilities of PK-PD target attainment by MIC for lefamulin dosing regimens based on the evaluation of the total-drug ELF and free-drug plasma AUC:MIC ratio targets associated with a 1 $\log_{10}$ CFU reduction from baseline for *S. aureus* overlaid on the MIC distribution for *S. aureus* isolates collected from regions worldwide (n=1,273)