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# Population Pharmacokinetic (PPK) analysis for lefamulin plasma and Epithelial Lining Fluid (ELF) exposures using data from healthy subjects

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**Background:** Lefamulin is a semi-synthetic intravenous (IV) and oral (PO) pleuromutilin antibiotic with activity against pathogens commonly associated with community-acquired bacterial pneumonia (CABP), including multi-drug resistant *S. pneumoniae* and *S. aureus.* Lefamulin is currently in Phase 3 development for the treatment of patients with CABP. The objectives of these analyses were to refine a previously-developed PPK model [Zhang L *et al.* IDWeek 2016, Poster 1944] for lefamulin using pooled plasma and ELF data from healthy subjects as well as to predict the ELF penetration ratio of lefamulin after IV or PO administration.

**Material/methods:** Lefamulin plasma and ELF PK data were obtained from healthy subjects who received a single dose of 150 mg IV lefamulin. Model refinement was accomplished in a sequential fashion; first fit plasma data to the previous PPK model using Bayesian analysis, then fit to the ELF data from healthy subjects. By incorporating the previous PPK parameters describing the absorption of lefamulin under fed or fasted conditions into the refined ELF model, lefamulin $AUC_{0\text{-}24}$ on Day 1 and 5 was determined for 2000 simulated patients after administration of lefamulin 150 mg IV or 600 mg PO (with and without food) twice daily (Q12h) for 5 days. Using model-predicted free-drug plasma and total-drug ELF $AUC_{0\text{-}24}$ values, the ELF penetration ratio of lefamulin was determined for 2000 simulated patients after IV or PO administration.

**Results:** The PPK analysis dataset contained 144 plasma concentrations and 12 ELF concentrations of lefamulin from 12 male healthy subjects. The previous PPK model, which was a three-compartment model with non-linear protein binding, provided an unbiased fit to the plasma data after IV

administration ($r^2$ of 0.983). The ELF data from these 12 subjects were well described using first-order rate constants into and out of the ELF compartment ($r^2$ of 0.966). The final PPK model fit the observed plasma and ELF concentrations with a high degree of accuracy and precision. Additionally, the model simulations replicated the observed plasma concentrations after IV or PO (fed or fasted) administration, qualifying the applicability of the refined PPK model to describe lefamulin exposures irrespective of route of administration. Using model-predicted exposures, the median lefamulin total-drug ELF $AUC_{0\text{-}24}$/free-drug plasma $AUC_{0\text{-}24}$ ratio was approximately 5 after IV or PO administration among simulated patients (Figure 1).

**Conclusions:** The final PPK model allowed for a precise and unbiased characterization of lefamulin plasma and ELF exposures after IV and PO administration. The high ELF penetration ratio of lefamulin after IV or PO administration on Day 1 suggests that the penetration of lefamulin into the effect site is rapid and extensive irrespective of route of administration. This PPK model will be useful to evaluate lefamulin dosing regimens for patients with CABP.

**Figure 1.** Boxplots of total-drug ELF $AUC_{0\text{-}24}$/free-drug plasma $AUC_{0\text{-}24}$ ratio on Days 1 and 5 after administration of lefamulin 150 mg IV or 600 mg PO Q12h for 5 days among simulated patients