Population Pharmacokinetic Analysis for Lefamulin Plasma and Epithelial Lining Fluid Exposures Using Data from Healthy Subjects

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INTRODUCTION

- 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 *Streptococcus pneumoniae* and methicillin-resistant *Staphylococcus aureus*.
- Lefamulin is currently in Phase 3 development for treatment of patients with CABP.

OBJECTIVES

- Refine a previously-developed population pharmacokinetic (PPK) model [1] for lefamulin using pooled plasma and epithelial lining fluid (ELF) data from healthy subjects, as well as to predict the ELF penetration ratio of lefamulin after IV or PO administration in the fasted and fed state.

METHODS

Data
- Phase 1, ELF penetration study [2] in males
- Dose: lefamulin 150 mg IV x 1

Population PK Analysis
- Previous Population PK Model:
  - Three-compartments, linear clearance
  - Non-linear protein binding
- Model Development Process:
  - Bayesian fit to plasma data from healthy subjects
  - Fit to the ELF data
  - Simulate ELF penetration after IV and PO dosing
- Sensitivity analyses used to assure appropriate simulation of ELF concentrations with varying conditions (patients, PO dosing, etc.)

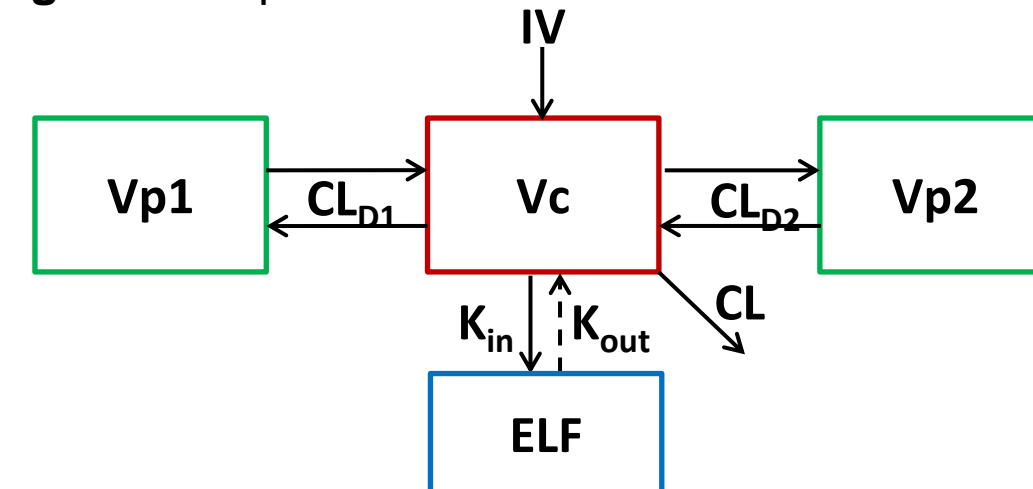## RESULTS

Population PK Model
- Observed data in **Figure 1.**
  - 12 male volunteers
  - 144 plasma concentrations
  - 12 ELF concentrations

Figure 1. Observed plasma (total) and ELF data
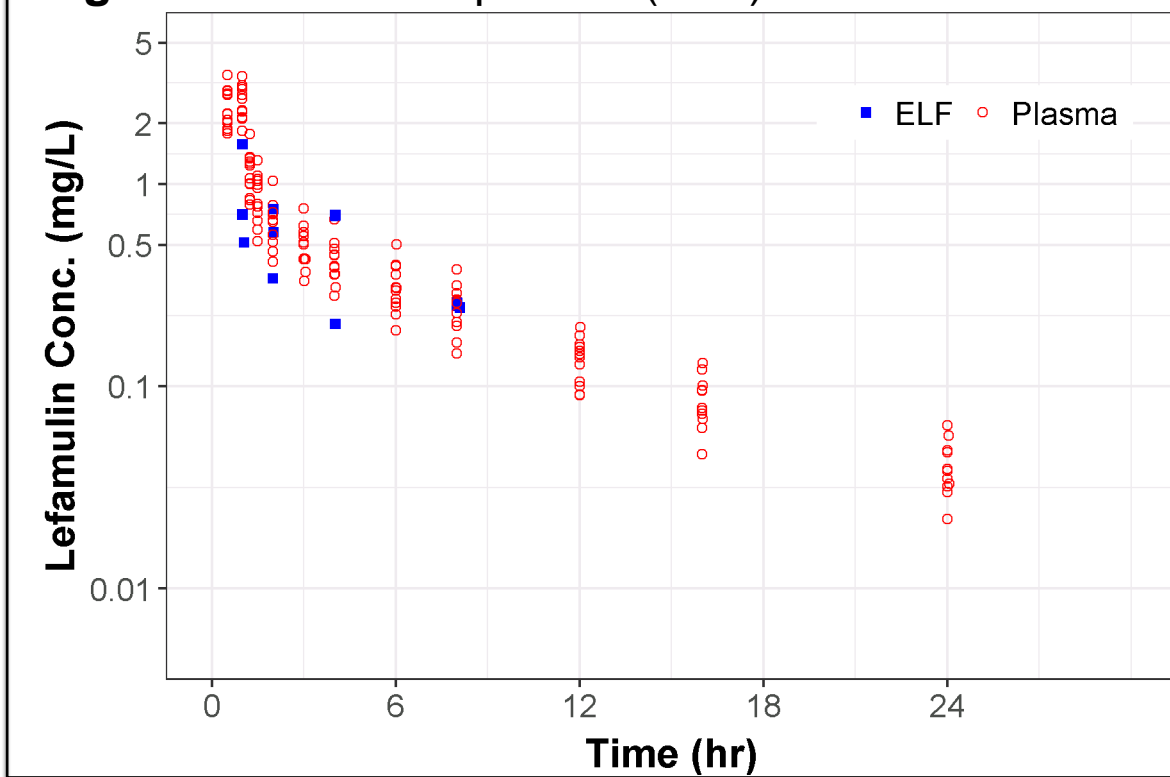
- The final PPK model is shown in **Figure 2**:
  - Robust fit to plasma using previous PPK model (r^2 of 0.983). Overall interindividual variability (IIV) was low (<40%).
  - The ELF data from these 12 subjects were well described using first-order rate constants into and out of the ELF compartment (r^2 of 0.966).

Figure 2. Population PK model schematic

RESULTS

- Visual predictive check plots indicated that the model was appropriately capturing the observed data (**Figure 3** and **Figure 4**).
- Using model-predicted exposures, the median lefamulin total-drug ELF AUC_{0-24}/free-drug plasma AUC_{0-24} ratio was approximately 5 after IV or PO administration among simulated patients (**Figure 5**).

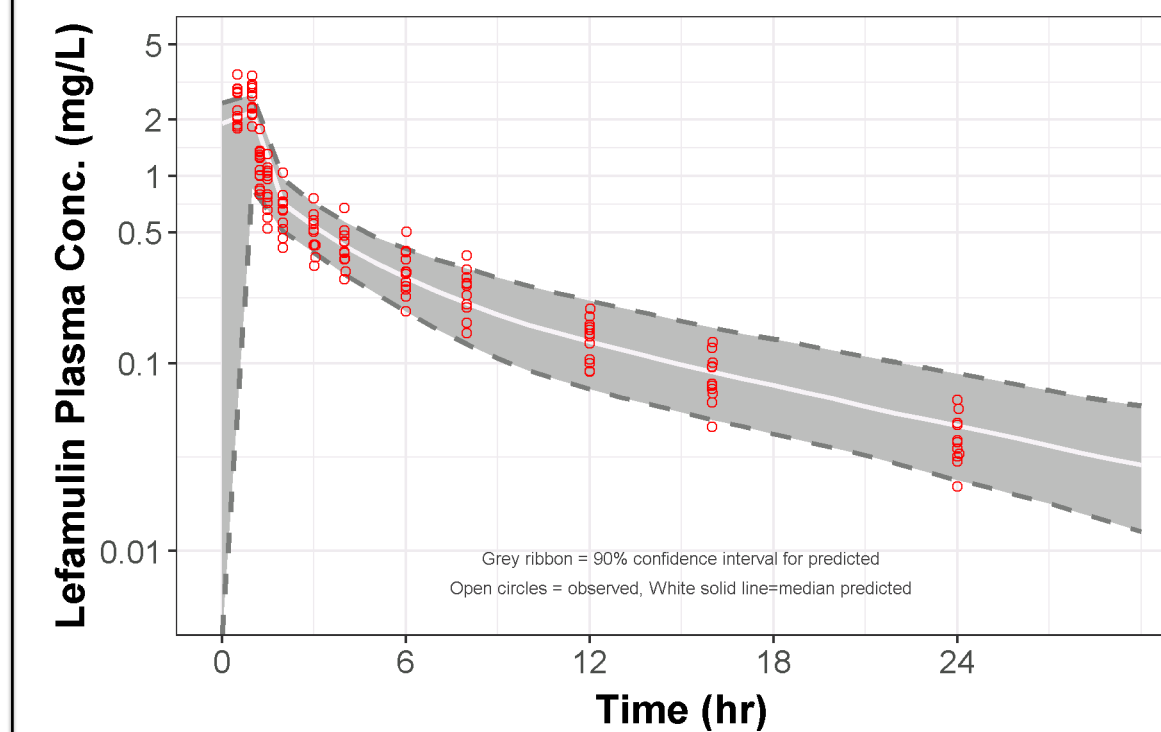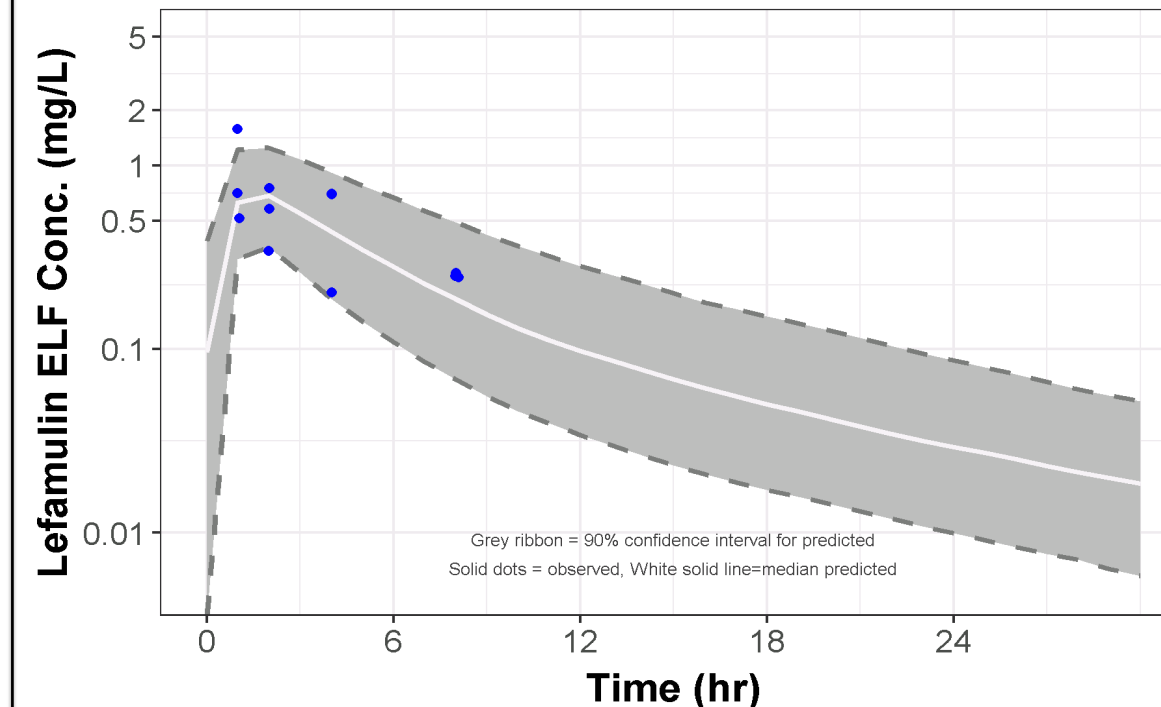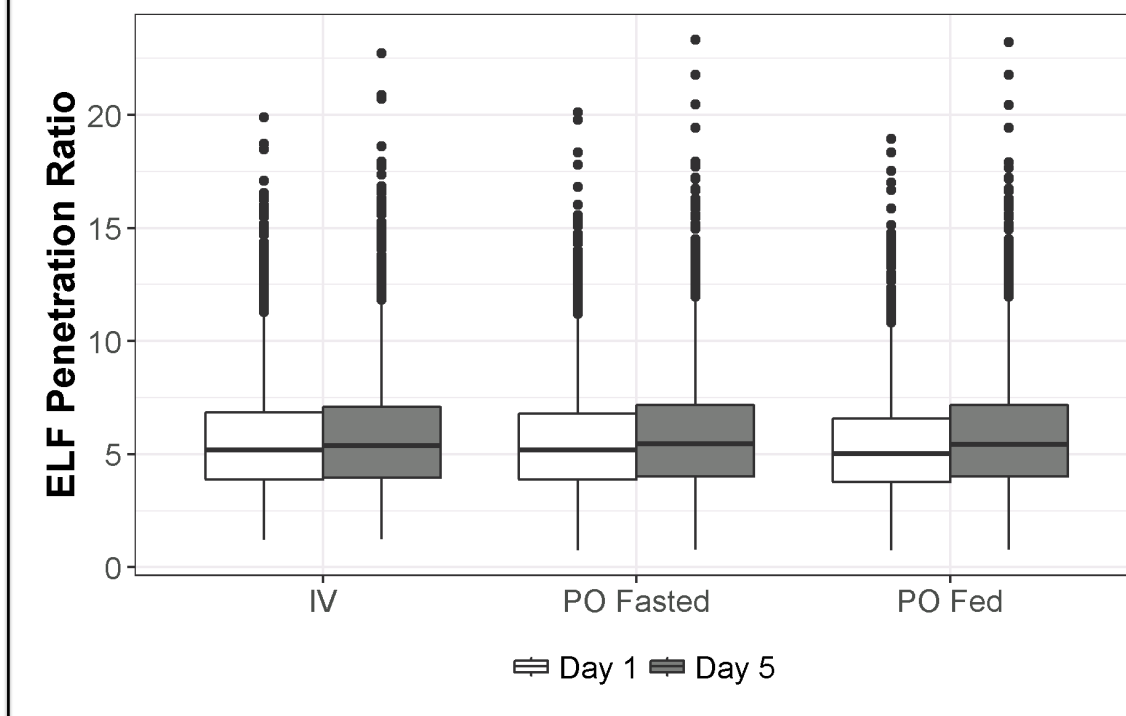**Figure 3**. Visual predictive check – Plasma (total)

Grey ribbon = 90% confidence interval for predicted
Open circles = observed, White solid line=median predicted

Figure 4. Visual predictive check - ELF

Grey ribbon = 90% confidence interval for predicted
Solid dots = observed, White solid line=median predicted

RESULTS

Figure 5. ELF:free-drug plasma AUC_{0-24} ratios

Sensitivity Analyses
- ELF PK highly sensitive to central volume of distribution (Vc) in a previous model, resulting in questionable ELF penetration predictions in patients and after PO dosing.
- Simulations from present model result in stable ELF PK across a broad range of Vc estimates.
- Allows for prediction of ELF penetration in patients after IV or PO dosing.

CONCLUSIONS

- The final PPK model allowed for a precise and unbiased characterization of lefamulin plasma and ELF concentrations after IV administration.
- The model was not sensitive to differences in drug absorption such that simulated ELF penetration after PO administration, irrespective of fasted/fed is expected to be reliable.

REFERENCES

1. Zhang L et al. Poster No. 1944. IDWeek. New Orleans, LA. October 26-30, 2016.
2. Zeitlinger M et al. *JAC* 2016;71(4):1022-6.