Population Pharmacokinetic Analysis for Lefamulin Using Data From Healthy Volunteers and Infected Patients

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INTRODUCTION & PURPOSE

- Lefamulin (LEF), a first-in-class pleuromutilin antibiotic, is being developed for the treatment of community-acquired pneumonia (CAP) and acute bacterial skin and skin structure infections (ABSSSI).
- A previously developed population pharmacokinetic (PK) model based on phase 1 healthy volunteer and phase 1 ABSSSI patient data following intravenous (iv) and oral administration revealed complex disposition, with the following elements:
  - A 3-compartment distribution,
  - First-order elimination,
  - Saturable plasma protein binding,
  - Biphasic absorption following oral dosing,
  - Intrinsic disposition was estimated as 79.4 L/h (41.4%) in phase 3 patients receiving the same 150 mg IV dosing regimen.

OBJECTIVES

- To refine a previously developed Lefamulin PK model, incorporating data from 3 phase 2 and 3 phase 3 efficacy trials and ABSSSI patient data with CAP.
- To identify patient factors associated with the interindividual variability in Lefamulin disposition.
- To enable exposure in patients enrolled in phase 2 ABSSSI and phase 3 CAP studies of LEF.

METHODS

Data

- Clinical studies were employed to refine the previously developed Lefamulin population PK model.
  - Phase 1 healthy volunteer studies with complete covariate information evaluating iv and po disposition following iv and oral doses of 150 mg iv (n=622).
  - Phase 2 ABSSSI patients and healthy volunteers.
  - Phase 3 phase 2 ABSSSI patients and healthy volunteers.
- The final covariate model was subjected to a prediction-corrected visual predictive check.
- Summary statistics of the nonparametric bootstrap suggested an unbiased fit of the pooled data.

RESULTS

- The final post hoc analysis dataset comprised 4,020 LEF plasma concentrations from 849 individuals (Figure 3).
- 32.9% of plasma samples were collected in the included phase 1 studies.
- 62.4% of plasma samples were collected in the pooled phase 3-2 CAP studies.
- The final covariate model was subjected to a prediction-corrected visual predictive check (Figure 3).
- Summary statistics of the nonparametric bootstrap suggested an unbiased fit of the pooled data.

CONCLUSIONS

- The developed Lefamulin PK model is unbiased and capable of capturing the within-patient and interpatient variability in Lefamulin disposition observed in phase 1–3 clinical trials.
- Several statistically significant covariate relationships were identified, but only that of study phase and systemic clearance was considered clinically relevant.
- Average LEF Day 1 free-thru-1, Cmax was 1.74-fold higher in phase 3 patients treated with CAP versus 2-phase studies patients with ABSSSI.
- The developed model will be useful for the subsequent evaluation of pharmacokinetic/pharmacodynamic properties and relationships and for simulations to support LEF dose justification.