P1945

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 antimicrobial, 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 2 ABSSSI patient data following intravenous (IV) and oral (PO) administration revealed a complex disposition, with the following elements[1]:
  - A 3-compartment distribution,
  - First-order elimination,
  - Saturable plasma protein binding,
  - An absorption lag following oral dosing,
  - Biphasic absorption following oral dosing,
  - A food effect on fast and slow absorption rates, and
  - A food effect on overall bioavailability.
- These analyses were undertaken to refine the above-described population PK model and to determine whether LEF disposition is altered in patients manifesting CAP.

OBJECTIVES

- To refine a previously developed LEF population PK model, incorporating data from 2 phase 3 studies evaluating IV and PO administration in patients with CAP.
- To identify patient factors associated with the interindividual variability in LEF PK.
- To estimate exposure in patients enrolled in phase 2 ABSSSI and phase 3 CAP studies of LEF.

METHODS

Data

- 7 clinical studies were employed to refine the previously developed LEF population PK model[1]:
  - 4 phase 1 healthy volunteer studies with complete covariate information evaluating the PK of LEF following IV or PO (600 mg immediate-release tablet) administration,
  - 1 phase 2 study of IV LEF conducted in patients with ABSSSI, and
  - 2 phase 3 studies of IV and PO LEF conducted in patients with CAP.

Population PK Model

- Utilising the previously developed structural model as a base, candidate parameterisations were fit to the pooled phase 1–3 data using NONMEM Version 7.2 and the first-order conditional estimation algorithm with η-ε interaction.

METHODS (continued)

- The influence of various subject demographic and laboratory parameters in describing LEF disposition was evaluated using a stepwise forward inclusion (α=0.05), backwards elimination (α=0.001) procedure, including:
  - Age, weight, height, body surface area, gender, race, and study phase, and
  - Serum albumin, creatinine clearance, and baseline procalcitonin.
- The final covariate model was subjected to a prediction-corrected visual predictive check (pc-VPC) and nonparametric bootstrap to qualify its ability to describe the observed LEF PK data across phase 1–3 studies.
- Estimates of Day 1 LEF exposure in patients with ABSSSI and patients with CAP were produced using the final model and compared.

RESULTS

Data

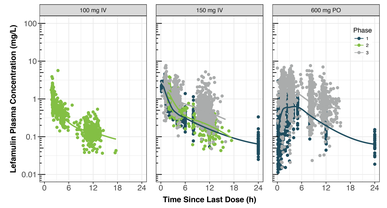
- The final pooled analysis dataset comprised 6205 LEF plasma concentrations from 849 individuals **(Figure 1)**.
  - 32.9% of plasma samples were collected in the included phase 1 studies.
  - 18.8% of plasma samples were collected in the phase 2 ABSSSI study.
  - 48.3% of plasma samples were collected in phase 3 CAP studies.
- Summary statistics of baseline subject demography and laboratory values are provided in **Table 1**.

Population PK Model

- No structural modifications to the previously developed model[1] were necessary to capture LEF disposition using the pooled phase 1–3 dataset.
- 5 statistically significant covariate relationships were discovered:
  - Systemic clearance (CL) and study phase,
  - CL and serum albumin,
  - Volume of distribution of the first peripheral compartment (Vp1) and study phase,
  - Vp1 and total body weight, and
  - Distributional clearance to the first peripheral compartment and study phase.
- Parameter estimates and associated standard errors for the final LEF population PK model are provided in **Table 2**.
  - Mean (%CV) LEF CL was estimated as 79.4 L/h (41.4%) in phase 3 CAP patients, whereas this value was approximately 1.8-fold higher in phase 2 ABSSSI patients and healthy volunteers.
- Goodness-of-fit diagnostic plots **(Figure 2)** and normalised prediction distribution errors **(Figure 3)** suggested an unbiased fit of the pooled data.
  - The final model was well qualified by pc-VPC **(Figure 4)** and the results of the nonparametric bootstrap **(Table 2)**.
- Model-derived estimates of Day 1 LEF exposure (area under the curve from time 0 to 24 hours [$AUC_{0\text{-}24}$]) revealed a geometric mean value 1.74-fold higher in patients with CAP versus patients with ABSSSI receiving the same 150 mg IV dosing regimen.

RESULTS (continued)

Figure 1. Lefamulin Plasma Concentrations Included in the PK Analysis Population vs Time Since Last Dose, Stratified by Study Phase and Faceted by Dose



Coloured lines represent loess smoothers through the data.
IV=intravenous; SPK=pharmacokinetic; PO=by mouth.

Table 1. Summary Statistics of Baseline Subject Demography and Laboratory Values for the Pooled PK Analysis Population and Subjects Stratified by Study Phase

Variable	Phase 1 (n=98)	Phase 2 (n=129)	Phase 3 (n=622)	Total (N=849)
Age, median (range), y	50 (19–77)	41 (18–73)	61 (19–97)	57 (18–97)
Height, median (range), cm	173 (146–191)	173 (150–196)	168 (133–200)	170 (133–200)
Weight, median (range), kg	83.4 (54–124)	87.5 (43.8–161)	75 (31–175)	78 (31–174.6)
BSA, median (range), m^2	1.99 (1.53–2.44)	2.02 (1.4–2.68)	1.85 (1.13–2.73)	1.89 (1.13–2.73)
CLcr, median (range), mL/min/1.73 m^2	87.8 (5.4–130)	87.6 (24.1–171)	68.8 (14.1–192)	73.4 (5.4–192.4)
Albumin, median (range), g/dL	4.5 (2.8–5.6)	4.2 (2.8–5.2)	4 (2–5.3)	4.1 (2–5.6)
Gender, n (%)				
Male	74/98 (75.5)	86/129 (66.7)	360/622 (57.9)	520/849 (61.2)
Female	24/98 (24.5)	43/129 (33.3)	262/622 (42.1)	329/849 (38.8)
Race, n (%)				
White	74/98 (75.5)	97/129 (75.2)	493/622 (79.3)	664/849 (78.2)
Black	20/98 (20.4)	20/129 (15.5)	29/622 (4.66)	69/849 (8.13)
Asian	1/98 (1.02)	1/129 (0.775)	70/622 (11.3)	72/849 (8.48)
American Indian/Alaskan Native	2/98 (2.04)	6/129 (4.65)	23/622 (3.7)	31/849 (3.65)
Native-Hawaiian/Other Pacific Islander	0	4/129 (3.1)	0	4/849 (0.471)
Other	1/98 (1.02)	1/129 (0.775)	7/622 (1.13)	9/849 (1.06)
Procalcitonin, ng/mL, n (%)				
<0.1	—	—	340 (54.7)	340 (54.7)
0.1–0.25	—	—	117 (18.8)	117 (18.8)
>0.25	—	—	154 (24.8)	154 (24.8)

BSA=body surface area; CLcr=creatinine clearance; PK=pharmacokinetic.

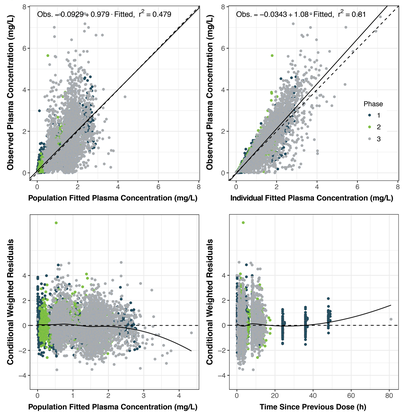
Table 2. Final Lefamulin Population PK Parameter Estimates, Associated Standard Errors, and Corresponding Nonparametric Bootstrap Results

	Final Model		Bootstrap Statistics (N=50)			
Parameter*	Final Estimate	%SEE	Mean	Median	%CV	90% CI
CL (L/h)	79.4	2.13	79.4	79.4	2.49	76.1–82.6
Vc (L)	46.3	6.87	48.2	48.3	17.9	32.1–60.4
CLd1 (L/h)	40.6	7.76	41	41.2	11.7	32.7–48.4
Vp1 (L)	249	9.13	257	259	15.3	185–314
CLd2 (L/h)	199 (fixed)	—	199	199	—	—
Vp2 (L)	259 (fixed)	—	259	259	—	—
Ka (h^{-1})	1.2 (fixed)	—	1.2	1.2	—	—
Ka2 (h^{-1})	2.12 (fixed)	—	2.12	2.12	—	—
F_{fst}	0.244 (fixed)	—	0.244	0.244	—	—
FS	0.802 (fixed)	—	0.802	0.802	—	—
ALAG (h)	0.15 (fixed)	—	0.15	0.15	—	—
$F_{sc\ min}$	0.0997 (fixed)	—	0.0997	0.0997	—	—
$F_{sc\ max}$	0.259 (fixed)	—	0.259	0.259	—	—
F_{sc50} (mg/L)	1.35 (fixed)	—	1.35	1.35	—	—
$Ka2_{fast}$ (h^{-1})	0.445	1.55	0.451	0.423	20	0.297–0.593
$F_{fst,\ fed}$	0.763	3.23	0.781	0.785	5.3	0.695–0.831
Ka_{fed} (h^{-1})	0.0541	6.15	0.0558	0.0544	28.9	0.0276–0.0806
CL, albumin†	1.214	9.21	1.215	1.217	15.1	1.161–1.268
CL, phase 2‡	1.827	12.5	1.838	1.827	9.23	1.7–1.954
CL, phase 1‡	1.766	20.5	1.754	1.743	9.95	1.642–1.889
CLd1, phase 2‡	1.44	32.8	1.449	1.416	35.4	1.178–1.701
CLd1, phase 1‡	2.12	20.5	2.11	2.1	22.3	1.714–2.53
Vp1, phase 2§	1.985	32.8	2.06	1.949	43.1	1.232–2.74
Vp1, phase 1§	2.75	43.6	2.73	2.63	27.9	1.958–3.54
Vp1, WTKG§	1.0129	24.4	1.0127	1.0127	28.4	1.0069–1.0188
ω^2_{CL}	0.171 (41.4% CV)	5.12	0.172	0.175	9.3	0.145–0.197
ω^2_{Vc}	0.39 (62.4% CV)	25.1	0.352	0.333	63.2	0.0236–0.756
ω^2_{CLd1}	0.119 (34.5% CV)	29.8	0.136	0.131	35.4	0.0393–0.198
ω^2_{Vp1}	0.623 (78.9% CV)	—	0.623	0.623	—	—
ω^2_{Ka}	0.800 (89.4% CV)	—	0.8	0.8	—	—
ω^2_{Ka2}	0.400 (63.2% CV)	—	0.4	0.4	—	—
ω^2_{Fst}	0.100 (31.6% CV)	—	0.1	0.1	—	—
ω^2_{FS}	0.170 (41.2% CV)	—	0.17	0.17	—	—
$\sigma^2_{Proportional}$	0.103 (32.0% CV)	1.37	0.102	0.102	5.45	0.0935–0.112
$\sigma^2_{Additive}$	0.0000343 (0.00586 mg/L)	17.6	0.00004	0.00003	62.1	0–0.00008

%SEE=percent standard error of the estimate; %CV=coefficient of variation; ALAG=absorption lag time; CAP=community-acquired pneumonia; CL=clearance; CLd1=distributional clearance to the first peripheral compartment; CLd2=distributional clearance to the second peripheral compartment; FS=fraction of dose undergoing slow absorption; F_{sc}=total bioavailability; $F_{sc\ min}$=total bioavailability under fed state; $F_{sc\ max}$=maximum fraction unbound; $F_{sc\ min}$=minimum fraction unbound; $F_{sc\ 50}$=concentration at which unbound fraction is half-maximal; Ka=immediate absorption rate constant; Ka_{fed}=immediate absorption rate constant under fed state; Ka2=delayed absorption rate constant; $Ka2_{fed}$=delayed absorption rate constant under fed state; ω^2=interindividual variability in specified PK parameter; PK=pharmacokinetic; σ^2=residual unexplained variability; Vc=volume of the central compartment; Vp1=volume of distribution of the first peripheral compartment; Vp2=volume of distribution of the second peripheral compartment; WTKG=total body weight.

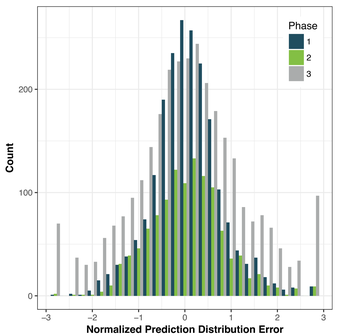
* Parameters represent population mean values for a typical CAP patient, and are in terms of unbound lefamulin disposition.
† Fold-change in lefamulin CL per every 1-g/dL deviation in albumin from the population median value of 4.1 g/dL.
‡ Fold-increase in pharmacokinetic parameter due to study phase.
§ Fold-change in lefamulin Vp1 per every 1-kg deviation in WTKG from the population median value of 78 kg.

Figure 2. Goodness-of-Fit Plots for the Final Lefamulin Population PK Model



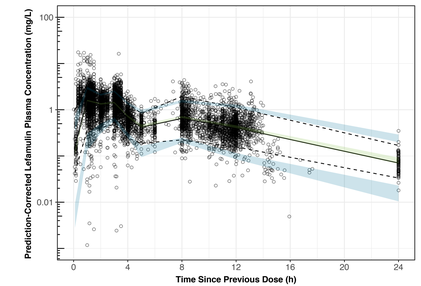
PK=pharmacokinetic.

Figure 3. Histogram of Normalised Prediction Distribution Errors of the Final Lefamulin Population PK Model, Stratified by Study Phase



PK=pharmacokinetic.

Figure 4. Prediction-Corrected Visual Predictive Check of Final Lefamulin Population PK Model



Black circles represent prediction-corrected lefamulin plasma concentrations. Black lines represent median (solid) and 5th/95th percentiles (dashed) of the observed data. Green shaded region represents 90% prediction interval around median of simulated values. Blue shaded regions represent 90% prediction intervals around 5th and 95th percentiles of simulated values.
PK=pharmacokinetic.

CONCLUSIONS

- The developed LEF population PK model is unbiased and capable of explaining both the central tendency and extent of variability in LEF disposition observed in phase 1–3 clinical trials.
- Several statistically significant covariates were identified, but only that of study phase and systemic clearance was considered clinically relevant.
  - Average LEF Day 1 free-drug $AUC_{0\text{-}24}$ was 1.74-fold higher in phase 3 studies in patients with CAP versus phase 2 studies in patients with ABSSSI.
- The developed model will be useful for the subsequent evaluation of pharmacokinetic-pharmacodynamic efficacy and safety relationships and for simulations to support LEF dose justification.

REFERENCES

(1) Zhang L, et al. *J Antimicrob Chemother.* 2019:In press.

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