

Population Pharmacokinetics of Solithromycin (CEM-101) Using Data from the Plasma and Epithelial Lining Fluid of Healthy Subjects

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Abstract

Background: CEM-101 is a broad spectrum fluoroketolide with activity against bacterial respiratory organisms including *S. pneumoniae*. The objective of this analysis was to characterize CEM-101 population pharmacokinetics (PPK) using plasma and epithelial lining fluid (ELF) Phase 1 data.

Methods: Subjects in 3 Phase 1 studies received CEM-101 as single (50 to 1600 mg) or multiple (200 to 600 mg) doses. Plasma samples were collected intensively in all 3 studies; ELF samples were collected on Day 5 via bronchoalveolar lavage at 1 of 5 time points in subjects who received CEM-101 400 mg daily for 5 days. Plasma and ELF samples were assayed for CEM-101 using LC/MS/MS. Urea in plasma and ELF was used to correct ELF concentrations. Candidate PPK models were fit to the data using the Monte Carlo parametric expectation maximization algorithm in S-ADAPT 1.56.

Results: The final PPK model, which was based on data from 91 subjects, was a 3-compartment model (central, peripheral and ELF) with auto-inhibition of clearance, a Weibull absorption process with fitted lag times and a capacity-limited first-pass effect. The mean (%CV) of the total clearance was 292 L/hr (69). The maximum extent of the inhibition of clearance (%CV) was 80% (3.1) and the IC₅₀ (%CV) associated with the inhibition process was 0.056 mg/L (26). Bi-directional rate constants (%CV) between ELF and plasma were 0.74 (61) and 0.057 (68) hr⁻¹, respectively. The PPK model provided excellent fits to the plasma and ELF data (r² = 0.94 and 0.99 for observed vs fitted concentrations, respectively). Goodness-of-fit diagnostics indicated an unbiased fit to the data. Mean (%CV) Day 5 ELF and plasma AUC₀₋₂₄ for 400 mg were 7.2 (51) and 62 (102), respectively.

Conclusions: A PPK model, which provided excellent data fits, was successfully developed for CEM-101. This model will be useful to support dose selection for future clinical trials.

Introduction

- Solithromycin (CEM-101) is a broad spectrum fluoroketolide antibiotic, a subclass of the macrolide family, with activity against typical and atypical bacterial respiratory organisms.
- CEM-101 is bactericidal against *Streptococcus pneumoniae* including macrolide-resistant isolates, suggesting its potential efficacy for the treatment of patients with community-acquired bacterial pneumonia (CABP).
- Using plasma concentration data from three Phase 1 studies and epithelial lining fluid (ELF) concentrations from one of three Phase 1 studies, a population pharmacokinetic (PK) model for CEM-101 was developed.

Methods

Study Design and Dose Administration

- Data from three Phase 1 studies (Studies 101, 102, and 114) were pooled for the population PK analysis.
- In Study 101, 35 subjects received a single CEM-101 oral dose ranging from 50 mg to 1600 mg. In Study 102, 25 subjects received 200, 400, or 600 mg of CEM-101 once daily for 7 days. In Study 114, 31 subjects received 400 mg of CEM-101 once daily for 5 days.

Materials and Methods

Study Design and Dose Administration (continued)

- Serial blood samples were collected at various times during the study after the administration of a single dose and multiple doses of CEM-101. In addition, subjects enrolled in Study 114 each underwent a single bronchoscopy and bronchoalveolar lavage at one of five time points (3, 6, 9, 12, and 24 hours post-dose) to obtain ELF samples for PK analysis (6 subjects/time point) on Day 5.
- CEM-101 concentrations in the plasma and ELF samples were determined using a validated high performance liquid chromatography tandem mass spectrometry (LC/MS/MS) method with a lower limit of quantification of 10.0 ng/mL and 0.1 ng/mL, respectively, with an inter-day coefficient of variation (%CV) of 6.10% for the plasma assay.
- Plasma and ELF urea concentrations were also measured and used to correct the measured ELF CEM-101 concentrations using the method described by Rennard *et. al*.

Population PK Analysis

- Candidate population PK models were fit to plasma and ELF concentration data using Monte Carlo parametric expectation maximization (MC-PEM), as is implemented in the open-source software program, S-ADAPT 1.56.
- Inter-individual variability was estimated for each PK parameter, where possible, using an exponential variability model (assuming log-normal distributions) or a logistic transform where appropriate (to constrain estimates to the allowed domain).
- Residual variability was described using an additive plus proportional residual error variance model.
- Model discrimination was performed by comparison of objective function for nested models or Akaike's Information Criterion for either nested or non-nested models.

Results

- As shown in **Figure 1**, the final population PK model was a three-compartment model with central, peripheral, and ELF compartments.
- Drug absorption was described by a Weibull absorption process, with fitted lag times delaying the onset of absorption and a capacity-limited first-pass effect.
- An indirect auto-inhibition process modeled using a hypothetical inhibition compartment (A5) described the clearance of CEM-101 from the central compartment.
- The parameter estimates and associated standard errors of the mean (%SEM) for the final population PK model are provided in **Table 1**.
- Based on the faster kce (0.738 hr⁻¹) relative to kec (0.0567 hr⁻¹), higher concentrations of CEM-101 are expected in the ELF relative to the plasma.

Results

Figure 1. Final population PK model for CEM-101

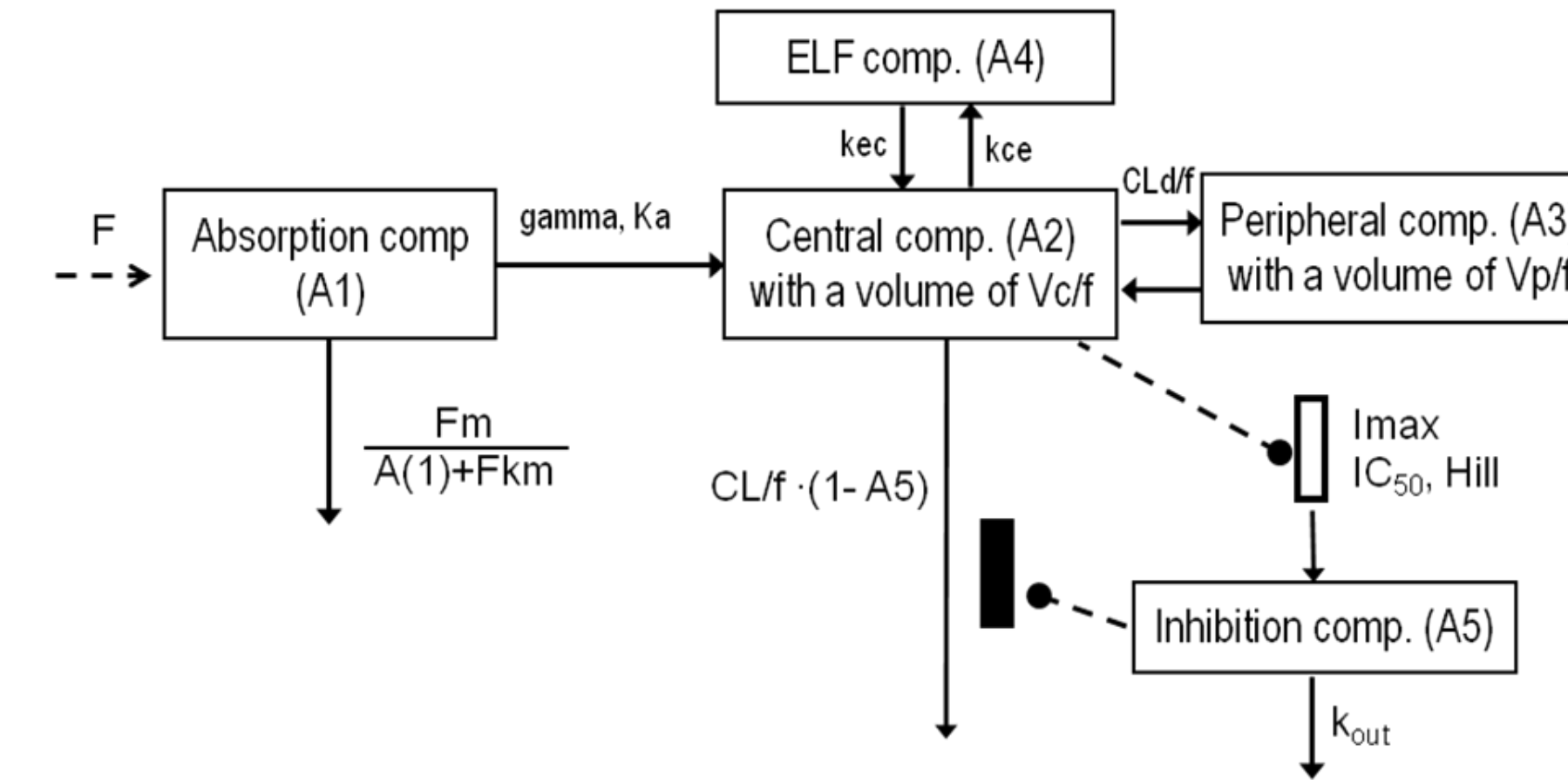


Table 1. Final CEM-101 population PK parameter estimates and %SEM

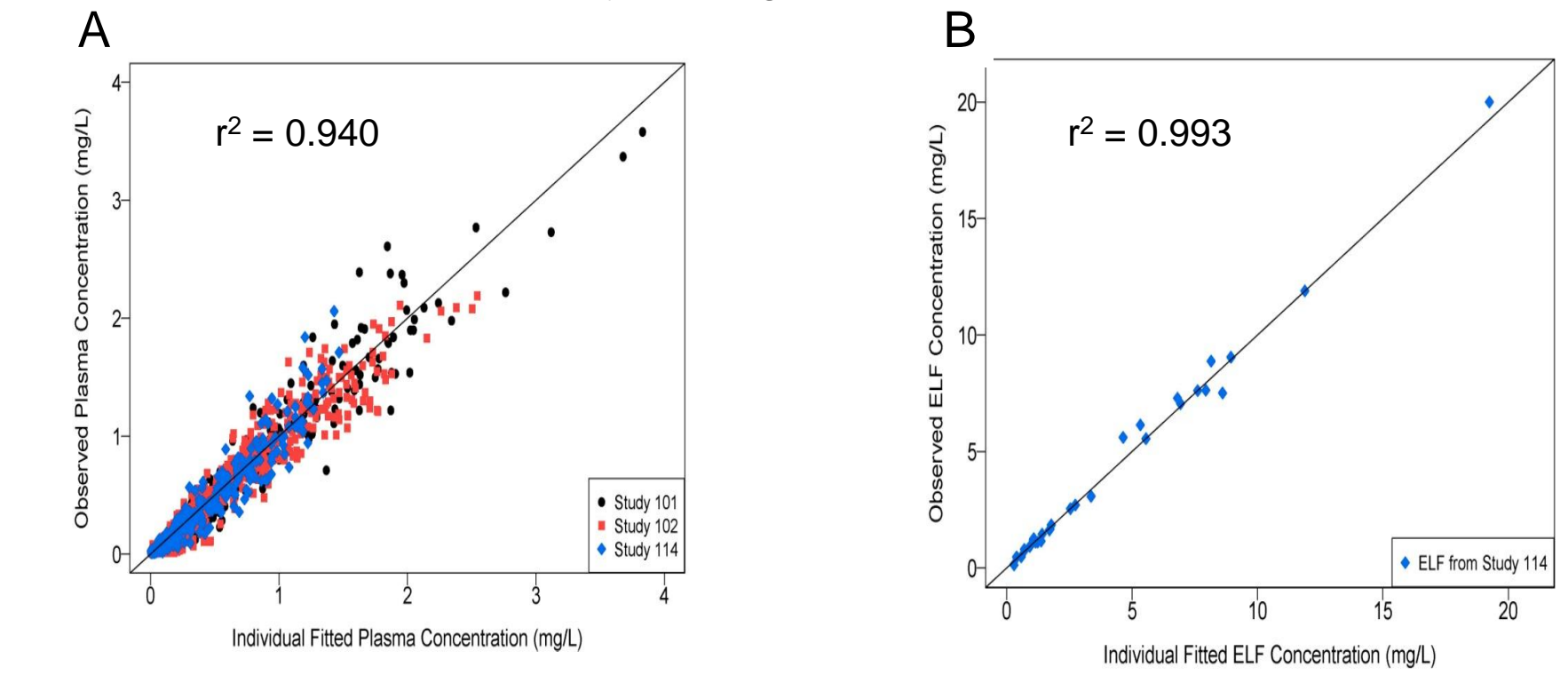
Parameter ^a	Population mean		Inter-individual variability (%CV)
	Final estimate	%SEM	Final estimate
IC ₅₀ (mg/L)	0.0558	7.25	25.5
k _{out} (hr ⁻¹)	0.286	0.827	5.43
LgIM	1.38	1.47	20.2 ^b
CL/f (L/hr)	292	2.50	68.8
Vc/f (L)	166	1.06	28.0
CLd/f (L/hr)	14.6	6.56	69.2
Vp/f (L)	79.8	1.83	37.8
gamma	1.13	13.1	50.6
cWB	0.385	5.76	36.5
ka (hr ⁻¹)	0.662	5.29	64.3
Fm (mg/hr)	10.0	6.12	70.9
Fkm (mg)	0.236	7.02	27.7
T _{lag1} (hr)	0.219	9.25	11.5 ^b
T _{lag2} (hr)	0.0709	11.4	3.91 ^b
IOVf	0.947	17.0	46.8
kce	0.738	8.70	61.4
kec	0.0567	14.7	67.8
SDslp Plasma	0.162	2.58	
SDint Plasma	0.00500	Fixed	
SDslp ELF	0.0500	Fixed	
SDint ELF	0.0500	Fixed	

Minimum value of the objective function = -3135
^a IC₅₀ is the total plasma concentration of CEM-101 at which the stimulation of A5 is half-maximal; k_{out} is the rate of loss from A5; LgIM is the logit-transformed of the maximum inhibitory effect on clearance: I_{max} = 1 / (1 + e^(-LgIM)); CL/f is plasma clearance; Vc/f is the volume of the central compartment; CLd/f is the distributional clearance between the Vc/f and Vp/f; Vp/f is the volume of the peripheral compartment; gamma is the shape parameter of the Weibull function; cWB is the Weibull coefficient; ka is the rate constant of the Weibull absorption; Fm is the maximum rate of the first-pass effect; Fkm is the value of A1 at which the first-pass effect is half-maximal; T_{lag1} and T_{lag2} are the lag-times; IOVf is the interoccasional variability on apparent bioavailability relative to Day 1; kce is the rate constant of drug transfer from the central compartment to the ELF compartment; kec is the rate constant of drug transfer from the ELF compartment to the central compartment. SDslp plasma is slope term for the intra-individual variability model for the plasma concentrations, corresponds to the proportional component of the model; SDint plasma is intercept term for the intra-individual variability model for the plasma concentrations, corresponds to the additive component of the model; SDslp ELF is slope term for the intra-individual variability model for the ELF concentrations, corresponds to the proportional component of the model; SDint ELF is the intercept term for the intra-individual variability model for the ELF concentrations, corresponds to the additive component of the model.
^b Square-root of the variance in the transformed domain expressed as a percentage.

Results

- Goodness of fit plots and other diagnostic plots demonstrated that the final population PK model provided an unbiased fit to the plasma data from all three studies and to the ELF data from Study 114.
 - As evidenced by the r² of 0.940 for observed vs. individual fitted plasma concentrations shown in **Figure 2A** and an r² of 0.993 for observed vs. individual fitted ELF concentrations shown in **Figure 2B** the model fit the data well.
 - The performance of the model was similar among the three studies, with r² values for the relationship between the observed and individual fitted plasma concentrations of 0.950, 0.938, and 0.921 for Studies 101, 102, and 114, respectively.
- The mean (%CV) Day 5 ELF and plasma AUC₀₋₂₄ values for 400 mg administered once daily to volunteers in Study 114 were 7.16 (51) and 62.3 mg/L•h (102), respectively.

Figure 2. Relationship between the observed and individual fitted plasma (A) and ELF (B) concentrations based on the final population PK model for CEM-101, with a line of identity through the data



Conclusions

- The population PK of CEM-101 was best described by a three-compartment model with auto-inhibition of clearance, a Weibull absorption process with fitted lag times, and a capacity-limited first-pass effect.
- Based on the faster rate of kce relative to kec, higher concentrations of CEM-101 are expected in the ELF relative to plasma. In addition, patients with low IC₅₀ values, faster kce, and/or those who receive higher CEM-101 doses are expected to achieve higher CEM-101 ELF concentrations earlier in therapy as compared to patients with high IC₅₀ values, slower kce, and/or those who receive lower CEM-101 doses.
- Parameter estimates based on the population PK model described herein will be useful to predict plasma and ELF concentration-time profiles for various CEM-101 dosage regimens, including front-loaded regimens, and thus, will be useful to support dose selection decisions in future clinical studies.

References

- Rennard S.L., et al. Estimation of volume of epithelial lining fluid recovered by lavage using urea as marker of dilution. J. Appl. Physiol 1986; 60:532-538.