Population Pharmacokinetic and Pharmacokinetic-Pharmacodynamic Target Attainment Analysis for Solithromycin to Support Intravenous Dose Selection in Patients with Community-Acquired Bacterial Pneumonia

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Abstract

Background: Solithromycin (CEM-101, SOL) is a novel fluoroketolide with activity against community-acquired bacterial pneumonia (CABP) bacterial pathogens including *Streptococcus pneumoniae* (MIC_{90}=0.125 mg/L). Population pharmacokinetic (PPK) and pharmacokinetic-pharmacodynamic (PK-PD) target attainment (TA) analyses were conducted to identify potential SOL intravenous (IV) dosing regimens for the treatment of CABP patients.
Methods: Using Phase 1 PK data for SOL 25-800 mg IV (n=40) and 50-1600 mg PO (n=113; n=30 for subjects with epithelial lining fluid (ELF) PK) and Phase 2 PK data (n=22), a previous PPK model (ICAAC 2010, A1-691) was refined. Using this model, PK-PD targets for *S. pneumoniae* from a murine-lung infection model (ELF and free-drug (*f*) plasma AUC_{0-24}:MIC ratios of 1.26 and 1.65 for net bacterial stasis, and 15.1 and 6.31 for a 1-log_{10} CFU reduction from baseline, respectively (ICAAC 2010, A1-688)), and Monte Carlo simulation, PK-PD TA analyses were conducted.
Results: A 3-compartment PPK model (central, peripheral and ELF) with auto-inhibition of clearance via an effect compartment fit the data well (r^2=0.974 for observed vs. individual fitted plasma concentrations; r^2=0.984 for observed vs. individual fitted ELF concentrations). PK-PD TA probabilities by MIC on Days 1 and 5 based on ELF and *f* plasma AUC_{0-24} for the dosing regimens evaluated are presented in the table below.
Conclusions: For ELF PK-PD targets, high PK-PD TA probabilities for MIC ≤ 1 mg/L were seen for dosing regimens 1, 2 and 5; using the *f* plasma PK-PD target for net bacterial stasis, high probabilities were seen for MIC ≤ 0.5 mg/L for these same dosing regimens. Unlike for SOL PO (ICAAC 2010, A1-692), front-loading was not required for SOL IV 400 mg Q24h to achieve a high PK-PD TA probability at MIC = 1 mg/L for the ELF PK-PD target for 1-log_{10} CFU reduction. These data will be used to support Phase 3 SOL IV dose selection.

Probability of PK-PD target attainment by MIC value for SOL IV dosing regimens based on both ELF and free-drug plasma exposures (ELF/free-drug plasma)

Dosing regimen (#)	Day	MIC = 0.25 mg/L		MIC = 0.5 mg/L		MIC = 1 mg/L	
		Bacterial reduction endpoint[a]					
		Net bacterial stasis	1-log_{10} CFU reduction	Net bacterial stasis	1-log_{10} CFU reduction	Net bacterial stasis	1-log_{10} CFU reduction
800 mg IV x 1 on Day 1 followed by 400 mg IV Q24h for 4 days (1)	1	1/1	1/0.914	1/0.993	1/0.45	1/0.897	0.994/0.06
	5	1/0.998	1/0.919	1/0.99	0.998/0.487	1/0.907	0.986/0.082
400 mg IV x 1 on Day 1 followed by 200 mg IV Q24h for 4 days (2)	1	1/0.988	1/0.396	1/0.857	0.991/0.048	0.999/0.364	0.892/0.002
	5	1/0.962	0.994/0.431	0.999/0.822	0.966/0.072	0.994/0.394	0.866/0.004
300 mg IV x 1 on Day 1 followed by 150 mg IV Q24h for 4 days (3)	1	1/0.967	0.999/0.191	1/0.667	0.961/0.017	0.999/0.171	0.75/0
	5	1/0.864	0.981/0.224	0.999/0.629	0.905/0.024	0.978/0.194	0.709/0.001
200 mg IV x 1 on Day 1 followed by 100 mg IV Q24h for 4 days (4)	1	1/0.805	0.988/0.037	0.999/0.302	0.859/0.001	0.981/0.032	0.478/0
	5	0.999/0.615	0.915/0.053	0.988/0.274	0.708/0.003	0.904/0.046	0.407/0
400 mg IV Q24h for 5 days (5)	1	1/0.988	1/0.396	1/0.857	0.991/0.048	0.999/0.364	0.892/0.002
	5	1/0.998	1/0.911	1/0.989	0.997/0.481	1/0.898	0.986/0.082
200 mg IV Q24h for 5 days (6)	1	1/0.805	0.988/0.037	0.999/0.302	0.859/0.001	0.981/0.032	0.478/0
	5	1/0.949	0.994/0.412	0.999/0.797	0.959/0.07	0.994/0.377	0.842/0.004

a. Bacterial reduction endpoints evaluated included ELF and free-drug plasma AUC_{0-24}:MIC ratio targets for *S. pneumoniae* from a murine-lung infection model of 1.26 and 1.65 for net bacterial stasis, and 15.1 and 6.31 for a 1-log_{10} CFU reduction from baseline, respectively [ICAAC 2010 A1-688].

Introduction

- Solithromycin (CEM-101) is a broad spectrum fluoroketolide antibiotic with activity against typical and atypical respiratory pathogens such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Legionella pneumophila*, including macrolide-resistant isolates [1, 2].
- Using data from three Phase 1 studies, a population pharmacokinetic (PPK) model was developed to describe the disposition of PO solithromycin in plasma and epithelial lining fluid (ELF) [3].
- Results of pharmacokinetic-pharmacodynamic (PK-PD) target attainment analyses based on the above-described PPK model, PK-PD targets in ELF from a neutropenic murine-pneumonia infection model for *S. pneumoniae* and ELF exposures, and Monte Carlo simulation (MCS), demonstrated that a front-loaded dosing regimen of solithromycin 800 mg PO on Day 1 followed by daily doses of 400 mg achieved a high probability of PK-PD target attainment for MIC values of ≤ 1 mg/L [4].
- Results of a Phase 2 study in patients with community-acquired bacterial pneumonia (CABP), the dosing strategy for which was based on the above-described results, demonstrated high and comparable efficacy for solithromycin 800 mg PO on Day 1 followed by 400 mg PO daily on Days 2 to 5 and levofloxacin 750 mg PO daily on Days 1 to 5 [5].
- As described herein, the above-described pharmacometric approach was carried out to identify potential solithromycin IV dosing regimens for evaluation in a Phase 3 study in patients with CABP.

Objectives

- The objectives of these analyses were the following:
  - To refine a previously-developed PPK model in order to describe the disposition of solithromycin after PO and IV doses using data from Phase 1 and 2 studies; and
  - Using the above-described refined PPK model, together with non-clinical PK-PD targets for *S. pneumoniae* and MCS, to conduct PK-PD target attainment analyses to identify potential IV solithromycin dosing regimens for the treatment of patients with CABP in future clinical studies.

Materials and Methods

Population Pharmacokinetic Analysis

- PK data obtained from subjects enrolled in Studies CE01-104 and CE01-200 were combined with that from a previous PPK analysis which included subjects from Studies CE01-101, CE01-102, CE01-103, and CE01-114 [3].
- Details of Studies CE01-101, -102, -103, and -114 have been presented in part elsewhere [3].
  - Study CE01-104 was a Phase 1 single- and multiple-dose IV dose-escalation study in healthy subjects. Subjects enrolled in the single-dose group received a single IV dose of 25 to 800 mg of solithromycin. Subjects who received the 100, 200, or 400 mg single IV dose of solithromycin were also administered a single 400 mg PO dose of solithromycin a minimum of 14 days after the single IV dose.
  - Study CE01-200 was a Phase 2, multiple-dose study conducted in patients with CABP. Patients received 800 mg PO x 1 of solithromycin on Day 1 followed by 400 mg PO Q24h for 4 days [5].
  - During the course of Studies CE01-104 and CE01-200, serial plasma samples for PK assessment were collected following drug administration.
- Candidate PK models were fit to plasma and ELF concentration data simultaneously using Monte Carlo Parametric Expectation Maximization, as implemented in S-ADAPT 1.57.
  - Weighting of the plasma and ELF concentrations was based on the reciprocal of the estimated observation variance (the error model standard deviation (SD) squared), which was predicted as a function of the fitted concentrations.

Pharmacokinetic-Pharmacodynamic Target Attainment Analyses

- Using the refined PPK model, previously-derived plasma and ELF AUC_{0-24} to minimum inhibitory concentration (MIC) ratio (AUC_{0-24}:MIC) targets for *S. pneumoniae* obtained from a neutropenic murine-pneumonia infection model [6] and MCS, PK-PD target attainment analyses were conducted to identify potential IV solithromycin dosing regimens.
- Using MCS implemented in S-ADAPT 1.57, PPK parameter estimates for 1,000 subjects were randomly selected from the population mean parameter vector and full variance-covariance matrix.
- ELF and free-drug plasma (based on plasma protein-binding of 82%) AUC_{0-24} values on Days 1 through 5 were calculated for each simulated subject by numerically integrating the individual predicted concentration-time profiles for each of the IV dosing regimens listed below:
  - 800 mg x 1 on Day 1 followed by 400 mg every 24 hours (Q24h) for 4 days;
  - 400 mg x 1 on Day 1 followed by 400 mg Q24h for 4 days;
  - 300 mg x 1 on Day 1 followed by 400 mg Q24h for 4 days;
  - 200 mg x 1 on Day 1 followed by 400 mg Q24h for 4 days;
  - 400 mg Q24h for 5 days;
  - 200 mg Q24h for 5 days.
- Probabilities of PK-PD target attainment by MIC value were assessed for each dosing regimen using the Day 1 and 5 ELF and free-drug plasma AUC_{0-24} values and MIC values ranging from 0.125 to 4 mg/L.
- A separate simulation which incorporated variability in both PK and MIC values was conducted.
  - MIC values for each of the 1,000 simulated patients were generated based on MIC distributions for *S. pneumoniae* taken from contemporary surveillance data [Data on File, Cempra Pharmaceuticals].
  - Daily ELF and free-drug plasma AUC_{0-24} values for each simulated patient were divided by the MIC value to determine the daily ELF and free-drug plasma AUC_{0-24}:MIC ratio on Days 1 to 5.

Results

Population Pharmacokinetic Analysis

- The final PPK model was a three-compartment model with central, peripheral, and ELF compartments.
  - The disposition of solithromycin was characterized using a hypothetical compartment to accommodate an auto-inhibition of the clearance process via an effect compartment, which was included in the model given the evaluation of the IV data, which indicated a delay in the onset of clearance inhibition.
  - Drug absorption was described by a Weibull absorption process, with a capacity-limited first-pass effect such that the fraction absorbed increased with dose.
- The final PPK model parameter estimates and associated %SEE are shown in **Table 1**.
  - The maximum increase in the rate of propagation of the hypothetical inhibition compartment (I_{max}) was estimated to be 65.7%, indicating that clearance was decreased by a maximum of 34.3%.

Results

- As evidenced by the r^2 values of 0.974 and 0.984 for the relationships between the observed vs. individual fitted plasma and ELF concentrations, respectively, the final PPK model fit the data well with good precision.

Table 1. Final PPK model parameter estimates

Parameter	Abbreviation	Population mean		Interindividual variability (%CV)	
		Final estimate	%SEE	Final estimate	%SEE
Effect compartment concentration for 50% maximal change in the propagation of the hypothetical inhibition compartment	IC_{50} (mg/L)	0.0554	23.6	47.1	135
First-order rate constant for dissipation (loss) of the hypothetical inhibition compartment	k_{out} (hr^{-1})	0.194	8.56	7.95	0
Volume of the central compartment	V_c (L)	38.4	6.43	19.0	78.1
Distributional clearance	CL_p (L/hr)	215	17.0	96.3	35.6
Volume of the peripheral compartment	V_p (L)	151	12.4	58.3	18.7
Apparent clearance	CL_t (L/hr)	62.4	4.36	46.9	16.3
Hill coefficient on the inhibition of clearance	Hill	2.28	9.63	35.6	23.9
Clearance into effect compartment	CL_{eff} (L/hr)	0.0318	37.2	64.8	37.4
Maximum fraction of drug absorbed	Fmax	0.823	5.31	8.68	0
Oral compartment amount for 50% Fmax	F50 (mg)	122	5.47	42.9	17.4
Hill coefficient for bioavailability	Hill_F	5.17	3.14	7.18	0
Rate constant for distribution into the ELF	kce (hr^{-1})	2.12	13.8	24.4	0
Rate constant for removal from the ELF	kec (hr^{-1})	0.233	20.9	24.4	0
Logistic transformation of the maximum increase in the rate of propagation of the hypothetical inhibition compartment	LgIM[a]	0.648	17.7	34.1[b]	29.3
Intercept term for the plasma error variance model	Sd_pP	0.0075	Fixed		
Slope term for the plasma error variance model	Sd_pP	0.168	4.29		
Intercept term for the ELF error variance model	Sd_eE	0.01	Fixed		
Slope term for the ELF error variance model	Sd_eE	0.180	Fixed		

a. LgIM is the logistic-transform of the maximum increase in the rate of propagation of the hypothetical inhibition compartment (I_{max}). I_{max} = 1/(1 + exp(-LgIM)].
b. Square-root of the variance in the transformed domain (logistic for LgIM).

Pharmacokinetic-Pharmacodynamic Target Attainment Analyses

- Probabilities of PK-PD target attainment by MIC for each dosing regimen, evaluated based on ELF and free-drug plasma exposures and AUC_{0-24}:MIC ratio targets, for MIC values ranging from 0.25 to 1 mg/L are presented in **Table 2**.
  - PK-PD target attainment probabilities based the ELF AUC_{0-24}:MIC ratio target associated with net bacterial stasis approached or exceeded 0.9 on Day 1 for all dosing regimens at MIC ≤ 1 mg/L. At a MIC of 4 mg/L, such probabilities were 0.993, 0.878 and 0.878 for dosing regimens 1, 2, and 5, respectively, and remained high on Day 5 (0.986, 0.857, and 0.985, respectively) [Data not shown].
  - PK-PD target attainment probabilities based the free-drug plasma AUC_{0-24}:MIC ratio target associated with net bacterial stasis were 0.993, 0.857, and 0.857 for dosing regimens 1, 2, and 5, respectively, at a MIC = 0.5 mg/L, and remained high on Day 5 (0.99, 0.822, and 0.989, respectively).

Table 2. Probability of PK-PD target attainment by MIC value for solithromycin IV dosing regimens based on ELF and free-drug plasma exposures (ELF/free-drug plasma)

Dosing regimen (number)	Day	MIC = 0.25 mg/L		MIC = 0.5 mg/L		MIC = 1 mg/L	
		Bacterial reduction endpoint[a]					
		Net bacterial stasis	1-log_{10} CFU reduction	Net bacterial stasis	1-log_{10} CFU reduction	Net bacterial stasis	1-log_{10} CFU reduction
800 mg x 1 on Day 1 followed by 400 mg Q24h for 4 days (1)	1	1/1	1/0.914	1/0.993	1/0.45	1/0.897	0.994/0.06
	5	1/0.998	1/0.919	1/0.99	0.998/0.487	1/0.907	0.986/0.082
400 mg x 1 on Day 1 followed by 200 mg Q24h for 4 days (2)	1	1/0.988	1/0.396	1/0.857	0.991/0.048	0.999/0.364	0.892/0.002
	5	1/0.962	0.994/0.431	0.999/0.822	0.966/0.072	0.994/0.394	0.866/0.004
300 mg x 1 on Day 1 followed by 150 mg Q24h for 4 days (3)	1	1/0.967	0.999/0.191	1/0.667	0.961/0.017	0.999/0.171	0.75/0
	5	1/0.864	0.981/0.224	0.999/0.629	0.905/0.024	0.978/0.194	0.709/0.001
200 mg x 1 on Day 1 followed by 100 mg Q24h for 4 days (4)	1	1/0.805	0.988/0.037	0.999/0.302	0.859/0.001	0.981/0.032	0.478/0
	5	0.999/0.615	0.915/0.053	0.988/0.274	0.708/0.003	0.904/0.046	0.407/0
400 mg Q24h for 5 days (5)	1	1/0.988	1/0.396	1/0.857	0.991/0.048	0.999/0.364	0.892/0.002
	5	1/0.998	1/0.911	1/0.989	0.997/0.481	1/0.898	0.986/0.082
200 mg Q24h for 5 days (6)	1	1/0.805	0.988/0.037	0.999/0.302	0.859/0.001	0.981/0.032	0.478/0
	5	1/0.949	0.994/0.412	0.999/0.797	0.959/0.07	0.994/0.377	0.842/0.004

a. Bacterial reduction endpoints evaluated included ELF and free-drug plasma AUC_{0-24}:MIC ratio targets for *S. pneumoniae* from a murine-pneumonia infection model of 1.26 and 1.65 for net bacterial stasis, and 15.1 and 6.31 for a 1-log_{10} CFU reduction from baseline, respectively [6].

Results

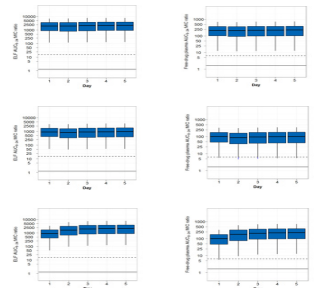
- **Figure 1**, which is based on the simulations incorporating variability in PK and MIC values, shows box plots for the daily ELF and free-drug plasma AUC_{0-24}:MIC ratios for simulated patients after the administration of dosing regimens 1, 2, and 5, which are currently being considered for evaluation in future Phase 3 studies.
  - Daily PK-PD target attainment probabilities based on ELF and free-drug plasma AUC_{0-24}:MIC ratio target for a 1-log_{10} CFU reduction from baseline were ≥ 95.4% and ≥ 85.9%, respectively, over the course of treatment for all six dosing regimens.
  - Using the same ELF and free-drug plasma AUC_{0-24}:MIC ratio targets, dosing regimens 1, 2 and 5 demonstrated daily PK-PD target attainment probabilities > 0.9 over the course of treatment.

Figure 1. Box plots for the daily ELF and free-drug plasma AUC_{0-24}:MIC for 1,000 simulated patients after the administration of solithromycin dosing regimens 1, 2, and 5 for 5 days

Dosing regimen 1, 800 mg IV on Day 1 followed by 400 mg IV Q24h for 4 days

Dosing regimen 2, 400 mg IV on Day 1 followed by 200 mg IV Q24h for 4 days

Dosing regimen 5, 400 mg IV Q24h for 5 days



The solid line represents the ELF and free-drug plasma AUC_{0-24}:MIC ratio of 1.26 and 1.65 associated with net bacterial stasis, respectively. The dashed line represents the ELF and free-drug plasma AUC_{0-24}:MIC ratio of 15.1 and 6.31 associated with a 1-log_{10} CFU reduction from baseline, respectively.

Conclusions

- Solithromycin plasma and ELF PK data were best described by a three-compartment model with auto-inhibition of clearance via an effect compartment; a Weibull function and a capacity-limited first-pass effect were used to describe drug absorption.
- Results of PK-PD target attainment analyses evaluating IV solithromycin dosing regimens demonstrated the following:
  - For ELF AUC_{0-24}:MIC targets, high PK-PD target attainment probabilities for MIC ≤ 1 mg/L (MIC_{100} for *S. pneumoniae*) were seen for dosing regimens 1, 2 and 5; using the free-drug plasma AUC_{0-24}:MIC target for net bacterial stasis, high probabilities of PK-PD target attainment were seen for MIC ≤ 0.5 mg/L ($MIC_{99.9}$ for *S. pneumoniae*) for these same dosing regimens.
  - Results of simulations based on variability in PK and MIC and ELF and free-drug plasma AUC_{0-24}:MIC targets for net bacterial stasis demonstrated probabilities of PK-PD target attainment > 0.9 over the course of treatment for dosing regimens 1, 2 and 5.
- Unlike the solithromycin 800 mg PO on Day 1 followed by 400 mg Q24h for 4 days dosing regimen [4], front-loading was not required to achieve a high probability of PK-PD target attainment for the 400 mg IV Q24h dosing regimen at a MIC of 1 mg/L for the ELF AUC_{0-24}:MIC target associated with 1-log_{10} CFU reduction.
- The data described herein will provide useful dose selection support for the future evaluation of IV solithromycin in Phase 3 studies in patients with CABP.

References

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