# Pharmacokinetic-Pharmacodynamic Target Attainment Analysis Supporting Solithromycin (CEM-101) Phase 2 Dose Selection

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## Abstract

**Background**: CEM-101 is a novel broad spectrum fluoroketolide with activity against typical and atypical bacterial respiratory pathogens. A pharmacokinetic-pharmacodynamic (PK-PD) target attainment (TA) analysis was conducted to evaluate Phase 2 CEM-101 dosing regimens for the treatment of patients with community-acquired bacterial pneumonia (CABP).

**Methods**: Monte Carlo simulation (n=1,000) using Phase 1 PK and non-clinical PK-PD data were utilized to determine the probability of PK-PD TA by MIC for various CEM-101 dosing regimens. Parameter estimates and the variance-covariance matrix from a population PK model, developed using data from 91 healthy subjects in 3 Phase 1 studies, was used to simulate plasma and epithelial lining fluid (ELF) profiles. Resultant ELF $AUC_{0-24}$ values were divided by fixed MIC values (0.125 to 2 mg/L). Using ELF $AUC_{0-24}$:MIC targets (%SE) associated with net bacterial stasis and a 1-$log_{10}$ CFU change from baseline in neutropenic murine-pneumonia infection models evaluating CEM-101 against *Streptococcus pneumoniae* of 1.3 (51) and 15.1 (29), respectively, probabilities of PK-PD TA by MIC were computed for each CEM-101 dosing regimen evaluated.

**Results**: Probabilities of PK-PD TA by MIC (ranging from 0.125 to 2 mg/L) based on Day 1 ELF $AUC_{0-24}$ for each dosing regimen evaluated are presented (see table).

| CEM-101 dosing regimen | Probability of PK-PD target attainment by MIC value (Stasis/↓1-$log_{10}$ CFU) | | | |
|---|---|---|---|---|
| | 0.125 mg/L | 0.25 mg/L | 0.5 mg/L | 1 mg/L |
| 800 mg Q24h on Day 1 followed by 400 mg Q24h | **1.00/0.998** | **1.00/0.996** | **1.00/0.969** | **0.999/0.909** |
| 600 mg Q24h on Day 1 followed by 300 mg Q24h | **1.00/0.997** | **1.00/0.985** | **1.00/0.946** | 0.998/0.836 |
| 500 mg Q24h on Day 1 followed by 250 mg Q24h | **1.00/0.996** | **1.00/0.975** | **0.999/0.916** | 0.998/0.776 |
| 400 mg Q24h on Day 1 followed by 200 mg Q24h | **1.00/0.993** | **1.00/0.955** | 0.999/0.870 | 0.997/0.692 |
| 300 mg Q24h on Day 1 followed by 150 mg Q24h | **1./0.97000** | **0.999/0.906** | 0.997/0.771 | 0.989/0.528 |
| 400 mg Q12h on Day 1 followed by 400 mg Q24h | **1.00/0.999** | **1.00/0.997** | **1.00/0.975** | 1.00/0.893 |
| 400 mg Q24h | **1.00/0.993** | **1.00/0.955** | 0.999/0.870 | 0.997/0.692 |

Note: ELF $AUC_{0-24}$:MIC targets of 1.26 and 15.1 for net bacterial stasis and a 1-$log_{10}$ CFU reduction from baseline for *S. pneumoniae*, respectively.

**Conclusions:** High probabilities of PK-PD TA based on the ELF $AUC_{0-24}$:MIC target associated with net bacterial stasis were demonstrated for all CEM-101 dosing regimens evaluated. A high probability of PK-PD TA at an MIC of 1 mg/L (0.91) based on the PK-PD target associated with a 1-$log_{10}$ CFU decline was observed for the 800 mg on Day 1 followed by 400 mg Q24h regimen. These results will be utilized to support dose decisions for a Phase 2 study in patients with CABP.

## 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).
- Monte Carlo simulations, using a population pharmacokinetic (PK) model for CEM-101 based on healthy volunteer plasma and epithelial lining fluid (ELF) data [1] and previously-determined murine ELF and free-drug plasma AUC:MIC targets [2], were utilized to evaluate the probability of pharmacokinetic-pharmacodynamic (PK-PD) target attainment (TA) for potential CEM-101 dosing regimens.

## Materials and Methods

- Using a previously-derived population PK model which was developed using plasma and ELF data from 91 healthy volunteers enrolled in 1 of 3 Phase 1 studies [1] and previously-derived PK-PD targets obtained from a murine-pneumonia infection model [2], Monte Carlo simulations were conducted to evaluate the PK-PD TA for different CEM-101 dosing regimens.
- The population PK model used for the Monte Carlo simulations 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 described the clearance of CEM-101 from the central compartment. Parameter estimates and associated coefficient of variation (%CV) based on this model are described elsewhere [1].
- Given that the population PK model was developed using Phase 1 data and since population PK parameter estimates for patients are usually more variable compared to those for healthy subjects, all inter-individual %CV for the population PK parameter estimates with a direct impact on clearance were assumed to be at least 30% if the effective %CV for the fitted plasma clearance parameter estimate (CL/f) was less than this threshold (30%).
- Using Monte Carlo simulation implemented in S-ADAPT 1.56, PK parameter estimates for 1,000 subjects were randomly selected from the population mean parameter vector and full variance-covariance matrix.
- ELF $AUC_{0-24}$ values on Days 1 through 5 were calculated for each simulated subject by numerically integrating the individual predicted ELF concentration-time profiles for each dosing regimen.
- CEM-101 dosing regimens evaluated in the Monte Carlo simulations included the following:
  - 800 mg once daily (Q24h) on Day 1 followed by 400 mg Q24h;
  - 600 mg Q24h on Day 1 followed by 300 mg Q24h;
  - 500 mg Q24h on Day 1 followed by 250 mg Q24h;
  - 400 mg Q24h on Day 1 followed by 200 mg Q24h;
  - 300 mg Q24h on Day 1 followed by 150 mg Q24h;
  - 400 mg twice daily (Q12h) on Day 1 followed by 400 mg Q24h;
  - 200 mg Q24h on Day 1 followed by 100 mg Q24h; and
  - 400 mg Q24h.
- PK-PD TA analyses were conducted using ELF $AUC_{0-24}$ to minimum inhibitory concentration (MIC) ratio ($AUC_{0-24}$:MIC) targets derived from a murine-pneumonia infection model for CEM-101 against *S. pneumoniae* [2]. ELF $AUC_{0-24}$:MIC targets (%SE) associated with net bacterial stasis, and a 1-$log_{10}$ colony forming units (CFU) reduction from baseline using pooled data from three *S. pneumoniae* isolates were 1.26 (51) and 15.1 (29), respectively.
- Probabilities of PK-PD TA, by MIC, were assessed for each of the CEM-101 dosing regimens using the Day 1 ELF $AUC_{0-24}$ values for MIC values ranging from 0.125 to 2 mg/L.

## Results

- As evidenced by the similarities in the parameter distributions of the healthy volunteers and the simulated subjects, the good agreement between these estimates and variance indicate that the Monte Carlo simulations replicated the expected distributions appropriately.
- A comparison of the distribution of the PK parameter estimates and %CV for the Phase 1 healthy volunteers and the simulated subjects used in the Monte Carlo simulations is provided in **Table 1**.
- Given that the variability on the population mean for CL/f was 68.8%, no empiric adjustments to the %CV of the population parameters which constitute the effective clearance were made.

**Table 1.** Comparison of distribution for the PK parameter estimates and %CV for the Phase 1 healthy volunteers and simulated subjects

| Parameter[a] | Phase 1 healthy volunteers | | Simulated subjects | |
|---|---|---|---|---|
| | Population mean | %CV | Geometric mean | %CV |
| $IC_{50}$ (mg/L) | 0.0558 | 25.5 | 0.0566 | 24.3 |
| kout ($hr^{-1}$) | 0.286 | 5.43 | 0.287 | 5.03 |
| LgIM | 1.38 | 14.6 | 1.37[b] | 13.3 |
| CL/f (L/hr) | 292 | 68.8 | 273 | 62.2 |
| Vc/f (L) | 166 | 28.0 | 161 | 25.8 |
| CLd/f (L/hr) | 14.6 | 69.2 | 13.9 | 63.3 |
| Vp/f (L) | 79.8 | 37.8 | 76.6 | 34.7 |
| gamma | 1.13 | 50.6 | 1.10 | 49.3 |
| cWB | 0.385 | 36.5 | 0.395 | 34.4 |
| ka ($hr^{-1}$) | 0.662 | 64.3 | 0.659 | 58.5 |
| Fm (mg/hr) | 10.0 | 70.9 | 9.41 | 65.0 |
| Fkm (mg) | 0.236 | 27.7 | 0.232 | 25.8 |
| $T_{lag1}$ (hr) | 0.219 | 52.4 | 0.225[b] | 47.2 |
| $T_{lag2}$ (hr) | 0.0709 | 55.1 | 0.0738[b] | 47.3 |
| IOVf | 0.947 | 46.8 | 0.930 | 45.3 |
| kce | 0.738 | 61.4 | 0.717 | 58.7 |
| kec | 0.0567 | 67.8 | 0.0576 | 66.7 |

a. $IC_{50}$ is total plasma concentration of CEM-101at 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: Imax = 1 / (1 + $e^{(-LgIM)}$); CL/f = 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 interoccassional 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.

b. Arithmetic mean reported given that the parameters were modeled as logit-transformed (LgIM) or as normally distributed ($T_{lag1}$ and $T_{lag2}$).

## Results

- Probabilities of PK-PD TA by MIC value, based on murine ELF $AUC_{0-24}$:MIC targets associated with net bacterial stasis and a 1-$log_{10}$ CFU reduction from baseline for *S. pneumoniae* and using simulated Day 1 ELF $AUC_{0-24}$ values based on healthy subject population PK parameter estimates, are presented in **Table 2**.
- Based on the ELF $AUC_{0-24}$:MIC target for net bacterial stasis, probabilities of PK-PD TA at an MIC of 1 mg/L ≥ 0.947 were attained for all CEM-101 dosing regimens evaluated.
- When the probability of achieving the ELF $AUC_{0-24}$:MIC target for a 1-$log_{10}$ CFU reduction from baseline at an MIC of 1 mg/L was evaluated, the dosing regimen with a single 800 mg dose on Day 1 followed by daily doses of 400 mg was the only one among those evaluated to achieve a probability above 0.9 (0.909).

**Table 2**. Probability of PK-PD TA based on murine ELF $AUC_{0-24}$:MIC targets associated with net bacterial stasis and a 1-$log_{10}$ CFU reduction from baseline for *S. pneumoniae* and using simulated Day 1 ELF $AUC_{0-24}$ values based on data from healthy volunteers

| CEM-101 dosing regimen | Probability of PK-PD TA by MIC value | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0.125 mg/L | | 0.25 mg/L | | 0.5 mg/L | | 1 mg/L | | 2 mg/L | |
| | Stasis | ↓1-$log_{10}$ CFU | Stasis | ↓1-$log_{10}$ CFU | Stasis | ↓1-$log_{10}$ CFU | Stasis | ↓1-$log_{10}$ CFU | Stasis | ↓1-$log_{10}$ CFU |
| 800 mg Q24h on Day 1 followed by 400 mg Q24h | **1.00** | **0.998** | **1.00** | **0.996** | **1.00** | **0.969** | **0.999** | **0.909** | **0.998** | 0.750 |
| 600 mg Q24h on Day 1 followed by 300 mg Q24h | **1.00** | **0.997** | **1.00** | **0.985** | **1.00** | **0.946** | **0.998** | 0.836 | **0.996** | 0.626 |
| 500 mg Q24h on Day 1 followed by 250 mg Q24h | **1.00** | **0.996** | **1.00** | **0.975** | **0.999** | **0.916** | **0.998** | 0.776 | **0.995** | 0.526 |
| 400 mg Q24h on Day 1 followed by 200 mg Q24h | **1.00** | **0.993** | **1.00** | **0.955** | **0.999** | 0.87 | **0.997** | 0.692 | **0.978** | 0.388 |
| 300 mg Q24h on Day 1 followed by 150 mg Q24h | **1.00** | **0.97** | **0.999** | **0.906** | **0.997** | 0.771 | **0.989** | 0.528 | **0.945** | 0.242 |
| 400 mg Q12h on Day 1 followed by 400 mg Q24h | **1.00** | **0.999** | **1.00** | **0.997** | **1.00** | **0.975** | **1.00** | 0.893 | **0.998** | 0.701 |
| 200 mg Q24h on Day 1 followed by 100 mg Q24h | **0.998** | **0.908** | **0.995** | 0.782 | **0.983** | 0.568 | **0.947** | 0.295 | 0.866 | 0.097 |
| 400 mg Q24h | **1.00** | **0.993** | **1.00** | **0.955** | **0.999** | 0.87 | **0.997** | 0.692 | **0.978** | 0.388 |

Note: ELF $AUC_{0-24}$:MIC targets of 1.26 and 15.1 associated with net bacterial stasis and a 1- $log_{10}$ CFU reduction from baseline, respectively, were based on the PK-PD analysis of pooled data for *S. pneumoniae* [2].

## Conclusions

- Results of these PK-PD TA analyses demonstrated high probabilities of TA (≥0.906) for ELF $AUC_{0-24}$:MIC target associated with net bacterial stasis and a 1-$log_{10}$ CFU reduction at an MIC of 0.25 mg/L, the $MIC_{90}$ (range ≤0.008 to 1 mg/L) based on recent and robust surveillance data for CEM-101 against 1,738 *S. pneumoniae* isolates [3], for all CEM-101 dosing regimens evaluated with the exception of the lowest dosing regimen (200 mg on Day 1 followed by daily doses of 100 mg).
- At an MIC of 1 mg/L and based on the ELF $AUC_{0-24}$:MIC target associated with net bacterial stasis, high probabilities (≥0.947) of PK-PD TA at an MIC of 1 mg/L for all dosing regimens evaluated; when evaluated relative to the ELF $AUC_{0-24}$:MIC target associated with a 1-$log_{10}$ CFU reduction, a high probability of PK-PD TA (0.909) was demonstrated for CEM-101 800 mg on Day 1 followed by daily doses of 400 mg at an MIC of 1 mg/L.

## References

1. Okusanya OO, et al. [abstract A1-691] 50th ICAAC, Boston, MA, CA, Sept. 2010.
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3. Jones RN, et al. [abstract F1-2035] 49th ICAAC, San Francisco, CA, Sept. 2009.