

Intrapulmonary Penetration of Solithromycin (CEM-101) in Healthy Adult Subjects

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Abstract

Background: CEM-101 is a novel broad spectrum fluoroketolide with activity against typical and atypical bacterial respiratory organisms including *Streptococcus pneumoniae*. It is currently being evaluated for the treatment of patients with community-acquired bacterial pneumonia. The penetration of CEM-101 into the epithelial lining fluid (ELF) and alveolar macrophages (AM) were assessed in a Phase 1 clinical study.

Methods: 30 subjects received 400 mg of CEM-101 orally daily for 5 days. On Day 5, each subject underwent a single bronchoscopy and bronchoalveolar lavage at 1 of 5 time points (3, 6, 9, 12 or 24 h post-dose) to obtain ELF and AM samples (6 subjects/time point). Plasma samples were collected pre-dose on Days 1 to 5 and serially post-dose on Day 5 and 6. The samples collected were assayed for CEM-101 using LC/MS/MS. Urea in the plasma and ELF was used to correct the ELF CEM-101 concentrations. Non-compartmental pharmacokinetic (PK) analysis using the median concentrations at each time point was used to calculate Day 5 AUC₀₋₂₄. In addition, a population PK model (PPM) was used to determine Day 5 AUC₀₋₂₄ for each subject in plasma and ELF. Intrapulmonary penetration of CEM-101 into the ELF and AM was determined by dividing the Day 5 AUC₀₋₂₄ of each matrix by the Day 5 total plasma AUC₀₋₂₄.

Results: CEM-101 penetrated well into ELF and AM. Plasma (total), ELF and AM AUC₀₋₂₄ were 7.12, 63.2 and 1282 mg/L*hr, respectively. ELF and AM penetration ratios for CEM-101 were 8.88 and 180, respectively. Mean ELF penetration ratio determined by the PPM was 8.71.

Conclusions: CEM-101 achieved higher exposures in ELF (>8 times) and AM (≥180 times) compared to plasma concentrations during the 24 hour period after drug administration in healthy adults. CEM-101 provides a good intrapulmonary penetration profile for the treatment of bacterial pathogens associated with lower respiratory tract infections.

Introduction

- Solithromycin (CEM-101) is a broad spectrum fluoroketolide antibiotic with potent activity against Gram-positive, Gram-negative (*Haemophilus* spp., *Moraxella catarrhalis*), and atypical bacterial organisms.
- CEM-101 is active against key respiratory pathogens that are resistant to clarithromycin and azithromycin, and against strains that are resistant to telithromycin.
- For lower respiratory tract infections, epithelial lining fluid (ELF) and alveolar macrophages (AM) have been advocated as important infection sites for common extracellular and intracellular pathogens, respectively.
- The objectives of this study were to: 1) determine and compare the plasma, ELF, AM, and saliva concentrations of CEM-101 following multiple oral doses (400 mg daily for 5 consecutive days) in healthy adult subjects; and 2) determine the safety and tolerability of multiple oral doses of CEM-101 in healthy adult subjects.

Materials and Methods

- This was a Phase 1, multiple dose, open-label, pharmacokinetic study conducted in healthy male and female subjects who were between 18 to 55 years of age and had a body mass index between 18 and 32 kg/m².
- Blood samples for assay of plasma concentrations of CEM-101 were obtained before each dose and 1, 2, 3, 4, 6, 9, 12, and 24 hours after the last dose.
- Subjects were assigned to 1 of 5 bronchoscopy sampling times:

BAL and Saliva Sampling Times after the Fifth Dose					
Time	3 Hours	6 Hours	9 Hours	12 Hours	24 Hours
Subjects (n)	6	6	6	6	6

- Assays for CEM-101 concentrations were performed with a validated HPLC tandem mass spectrometry (LC/MS/MS) method at MicroConstants, Inc., San Diego, CA. The coefficient of variation (CV) for total plasma CEM-101 samples ranged from 3.35% to 6.10%.
- The urea concentrations in plasma and bronchoalveolar lavage (BAL) were performed with the Urea Assay Kit (BioChain). The CV for the plasma and BAL samples ranged from 2.47% to 3.81% and 0.72% to 1.05%, respectively.
- The concentration of CEM-101 (ABX_{ELF}) in ELF was determined as follows: ABX_{ELF} = ABX_{BAL} × (Urea_{Plasma} / Urea_{BAL}). The concentration (ABX_{AM}) in alveolar macrophages (AM) was determined as follows: ABX_{AM} = ABX_M / V_{AM}, where ABX_M is the measured concentration of CEM-101 and V_{AM} is the volume of alveolar cells in the 1-ml cell suspension.
- The mean and median concentrations of CEM-101 from the plasma and bronchopulmonary sampling times were used to estimate the mean AUC₀₋₂₄ by the linear trapezoidal method (WinNonlin Professional, version 5.2). The ratio of AUC₀₋₂₄ of ELF to plasma, AM to plasma, and saliva to plasma were calculated.

Results

- A total of 31 subjects (Table 1) were enrolled and received five oral doses of CEM-101 during the study. One subject was withdrawn from the study prior to the bronchoscopy because of an upper respiratory tract infection.

Table 1. Characteristics of Study Subjects

Sampling Time	Sex	Age (years)	BMI (kg/m ²)	Total Cell Count in BAL Fluid (mm ³)	Macrophages (%)
3-hour	6 M	36 ± 10	26.9 ± 3.0	182 ± 106	85 ± 9
6-hour	7 M	40 ± 7	27.0 ± 2.3	215 ± 76	83 ± 3
9-hour	6 M	32 ± 4	27.4 ± 2.1	163 ± 58	82 ± 6
12-hour	3 M, 3 F	32 ± 11	26.2 ± 4.6	218 ± 276	61 ± 22
24-hour	3 M, 3 F	30 ± 11	25.7 ± 3.0	332 ± 514	74 ± 15

Data are expressed as mean ± SD except for sex; M = males; F = females
BMI = body mass index = weight [kg] ÷ (height [m])²

Results

- The mean (± SD) total plasma concentrations of CEM-101 in the 24-hour interval following the last dose are displayed in Figure 1. The mean (± SD) plasma C_{max} and AUC₀₋₂₄ were 0.92 ± 0.47 mg/L and 8.16 ± 4.52 mg·h/L.
- The mean (± SD) concentrations of CEM-101 in plasma (total), ELF, AM, and saliva during the intrapulmonary sampling times are presented in Table 2, and displayed in Figures 2 and 3.
- The AUC₀₋₂₄ values based on mean and median ELF concentrations and the ratio of site to total plasma based on AUC₀₋₂₄ values are shown in Table 3.
- Overall, 14/31 (45.2%) of subjects experienced treatment-emergent adverse events (TEAEs) that were considered to be related to study drug. The most frequent occurring TEAEs (occurring in ≥10% of subjects) included headache (6 subjects), diarrhea (4 subjects), and nausea (4 subjects). All other events occurred in 1 or 2 subjects.

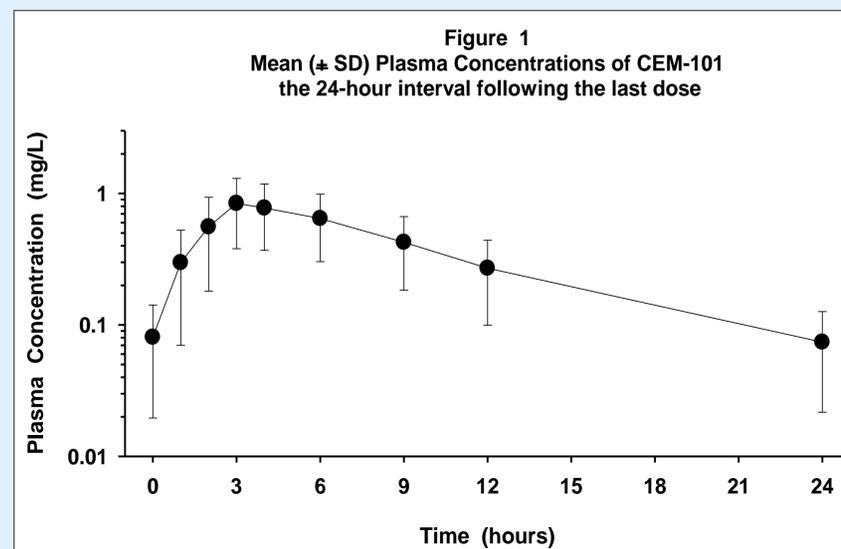


Table 2. CEM-101 Concentrations in Plasma, ELF, AM, and Saliva

Sampling Time ^a	Plasma (mg/L)	ELF (mg/L)	AM (mg/L)	Saliva (mg/L)
3-hour	0.730 ± 0.692	7.58 ± 6.69	99.4 ± 140.8	0.151 ± 0.086
6-hour	0.595 ± 0.325 ^b	6.50 ± 2.73	101.7 ± 52.6	0.240 ± 0.147 ^b
9-hour	0.301 ± 0.185	3.78 ± 4.32	64.1 ± 17.2	0.105 ± 0.026
12-hour	0.300 ± 0.171	2.54 ± 2.55	67.8 ± 24.6	0.140 ± 0.112
24-hour	0.086 ± 0.070	1.02 ± 0.83	25.9 ± 20.3	0.043 ± 0.041

Data are expressed as mean ± SD
^a 6 subjects per sampling period for all matrices
^b 7 subjects for plasma and saliva concentrations at 6-hour

Results

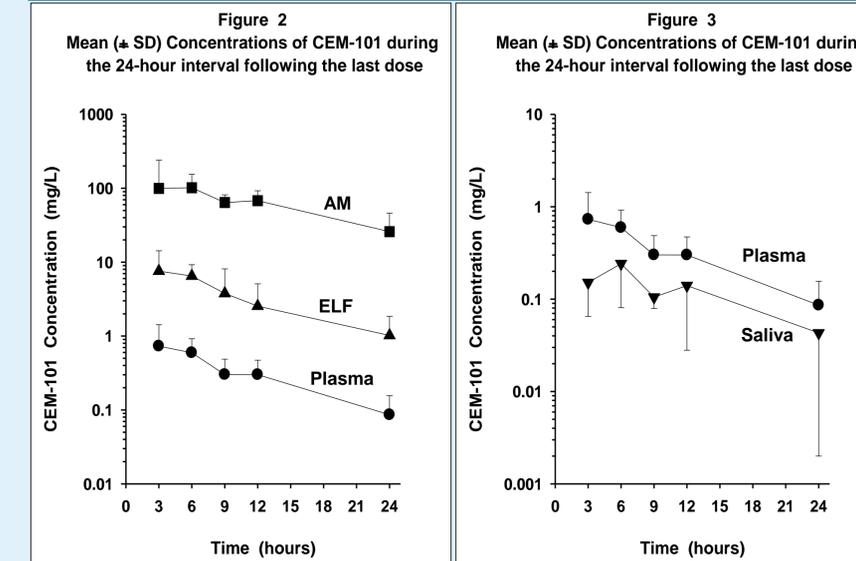


Table 3. AUC₀₋₂₄ and Site-to-Plasma Ratios for ELF, AM, and Saliva

	ELF	AM	Saliva
Mean Values:			
AUC ₀₋₂₄ (mg·h/L)	80.3	1498	3.13
Ratio Site:Plasma (ALL)	9.65	180	0.37
Ratio Site:Plasma (BAL)	10.3	193	0.39
Median Values:			
AUC ₀₋₂₄ (mg·h/L)	63.2	1282	2.23
Ratio Site:Plasma (ALL)	8.88	180	0.37
Ratio Site:Plasma (BAL)	9.96	202	0.39

ALL = Plasma AUC₀₋₂₄ determined with all available total plasma concentrations.
BAL = Plasma AUC₀₋₂₄ determined with total plasma concentrations obtained at bronchoscopy sampling times.

Conclusions

- Solithromycin (CEM-101) exposure, as measured by AUC₀₋₂₄ values, was higher in ELF (>8 times) and AM (≥180 times) compared to total plasma exposure after multiple oral doses.
- Solithromycin exposure in saliva was lower than the three other matrices and approximately 37% of the total plasma exposure.
- Solithromycin administered orally to 31 healthy adult subjects at 400 mg for 5 consecutive days was safe and well tolerated. The most frequently occurring treatment-emergent adverse events included headache, diarrhea, and nausea.
- This study supports progression to Phase 2 clinical trials evaluating solithromycin in community-acquired bacterial pneumonia.