

Multiple Dose Pharmacokinetics and Safety of CEM-101, a New Fluoroketolide, in Healthy Subjects

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Abstract

Objectives: CEM-101 is a potent new fluoroketolide under development for the treatment of bacterial respiratory tract infections. CEM-101 pharmacokinetics (PK) and safety at single doses up to 1600 mg have been reported previously. Safety and PK following escalating multiple oral doses were investigated in this study.

Methods: This was a randomized, double-blind, placebo-controlled, dose escalation study. Escalating doses (200, 400, and 600 mg) were administered once daily for 7 days to healthy adult subjects (5, 2, active placebo, 200 mg [n=7], 400 mg [n=4] and 600 mg [n=4]). Physical examinations, vital signs, ECGs, clinical laboratory tests, and adverse events were monitored throughout the study. Blood samples for CEM-101 concentrations and PK assessments were collected pre-dose and at frequent intervals to 24 h post-dose on Day 1 and to 72 h post-dose on Day 7.

Results: CEM-101 mean C_{max} values on Days 1 and 7 were 0.113 and 0.248 $\mu\text{g/mL}$ for the 200 mg group, 0.579 and 1.09 $\mu\text{g/mL}$ for the 400 mg groups, and 0.862 and 1.50 $\mu\text{g/mL}$ for the 600 mg groups. Corresponding AUC_{0-24} values on Days 1 and 7 were 0.888 and 2.31 $\mu\text{g}\cdot\text{h/mL}$, 4.85 and 13.30 $\mu\text{g}\cdot\text{h/mL}$, and 7.64 and 18.40 $\mu\text{g}\cdot\text{h/mL}$. Increases in C_{max} and AUC_{0-24} were more than dose proportional from 200 to 400 mg and then approximately dose proportional from 400 to 600 mg. At all doses CEM-101 exposures were higher on Day 7 than Day 1, indicating that accumulation occurred over the dosing period. Across the doses the mean T_{max} ranged from 3.0 to 4.0 hours, and the mean $T_{1/2}$ increased from 3.64 to 5.45 hours on Day 1 and from 5.39 to 8.07 hours on Day 7. All doses of CEM-101 were safe and generally well tolerated. Gastrointestinal AEs, mostly mild, occurred in each dose group. Low-level hepatic transaminase increases occurred in 4 of 10 subjects that received 600 mg CEM-101; all were transient, reversible, and not associated with signs or symptoms of toxicity.

Conclusion: Over the 200 to 600 mg dose range, multiple doses of CEM-101 were safe and well tolerated in healthy adult subjects. C_{max} and AUC increases were more than dose proportional from 200 to 400 mg, and approximately dose proportional from 400 to 600 mg. CEM-101 showed moderate accumulation over 7 days of dosing.

Introduction

CEM-101 is a novel fluoroketolide under development for the treatment of patients with community-acquired bacterial pneumonia (CABP), with potential to extend to other types of bacterial infections. It demonstrates a unique 50S ribosomal binding pattern that provides for multiple tight sites of interaction, even to ribosomes from cells carrying *erm* methyltransferase, which may explain its activity against *erm*-resistant bacteria.

CEM-101 is highly active against common bacterial respiratory tract infection pathogens (*S. pneumoniae*, *B. hemolyticus*, *H. influenzae*, *M. catarrhalis*) as well as atypical bacteria (*M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila*). CEM-101 demonstrates potent bactericidal activity against macrolide-resistant pneumococci (*ermB*, *mefA*, *ermB-mefA*, penicillin-resistant, all MICs ≤ 1 $\mu\text{g/mL}$) and is 2-4 fold more potent than telithromycin. Against multi-drug resistant *S. pneumoniae* serotype 19A, CEM-101 exhibited excellent activity (MIC₉₀ 0.5 $\mu\text{g/mL}$) with potency >32-fold better than azithromycin, clindamycin, or tetracycline. CEM-101 exhibits post-antibiotic effects 1.5 to 2.5 times longer than telithromycin for *S. pyogenes*, *S. pneumoniae*, and *H. influenzae*. It has an extended antimicrobial spectrum that includes bifidens pathogens (*B. anthracis*, *Y. pestis*, *F. tularensis*), STD pathogens (*Mycoplasmas*, ureaplasmas, *C. trachomatis*, *N. gonorrhoeae*), and intracellular pathogens (*Mycobacterium*, *Legionella*, *Listeria*, *Plasmodium*). CEM-101 has low potential for induction of resistance based on the results of multi-step in vitro passaging and single-step mutational analysis studies.

Studies have shown higher concentrations of CEM-101 in tissues than in plasma, and that CEM-101 produces greater bacterial killing of phagocytized *S. aureus*, *L. monocytogenes* and *L. pneumophila* in macrophages than comparator macrolides tested. Studies in murine models have shown CEM-101 to be highly efficacious against infections caused by *S. pneumoniae*, *S. pyogenes*, and *S. aureus*, including in abscess and pneumonia models that used a highly virulent strain of pneumococcus. Pharmacokinetic data in rodents and monkeys have shown that CEM-101 achieves substantial concentrations in lung. In a murine lung infection model that concurrently measured CEM-101 levels in plasma and epithelial lining fluid (ELF), efficacy was best predicted by free-drug plasma and total-drug ELF AUC_{0-24} to MIC ratios.

Metabolism of CEM-101 in human hepatocytes is primarily a result of CYP3A4. CEM-101 also inactivated CYP3A4 in kinetic studies. As both a substrate for, and inhibitor of, CYP3A4, CEM-101 is predicted to inhibit its own metabolism, and may have clinically significant interactions with drugs that are substrates or inhibitors of CYP3A4. Like other macrolides, CEM-101 does not induce CYP3A4.

The toxicological profile of CEM-101 has been evaluated in acute oral toxicity studies in mice and monkeys, in repeat dose oral toxicity studies up to 13 weeks in rats and monkeys, and in a battery of genetic toxicology tests. The spectrum of toxicities was similar to that of the macrolide class of drugs. CEM-101 was not mutagenic or clastogenic. In vitro, CEM-101 inhibited the hERG channel current with a potency similar to clarithromycin and telithromycin, suggesting the potential to prolong cardiac repolarization. However, a telemetry study in conscious dogs showed no tendency for QTc prolongation after CEM-101 administration.

As reported previously, CEM-101 was safe and well-tolerated in the initial human single-dose study. The results of the subsequent multiple-dose, dose escalation study are discussed here.

Study Design

Objectives

- To determine the safety and tolerability of multiple escalating doses of oral CEM-101.
- To determine the pharmacokinetic (PK) profile of multiple escalating doses of oral CEM-101.

Study Design and Selection Criteria

- This was a single center, Phase 1, randomized, double-blind, placebo-controlled, flexible dose escalation study.
- Thirty-five healthy adult subjects were enrolled in 5 dosage groups.
- Subjects were admitted to the clinical research unit on the day prior to dosing and remained in the unit for 72 hours after the final dose of study drug. They were also assessed in a follow-up telephone call 7 days after completion of dosing.
- Key inclusion/exclusion criteria:
 - Healthy males and non-pregnant females 19 to 55 years of age with a body mass index 18 to 32 kg/m^2 and total body weight >60 kg were eligible for inclusion.
 - Negative pregnancy test and appropriate contraceptive methods for females of childbearing potential were inclusion requirements.
 - Subjects with clinically significant organ disease were excluded.
 - Drug or alcohol abusers and tobacco users were excluded.
 - Subjects with history of hypersensitivity to macrolides were excluded.
 - Subjects with QTc >450 msec (470 msec for females) were excluded.

Treatments

- Escalating multiple doses were administered (200, 400, 600, 400, 600) of CEM-101 or placebo were administered once daily to 5 groups of healthy adult subjects in capsules containing 200 mg CEM-101 or placebo.
- Within each dose group, 5 subjects received CEM-101 and 2 received placebo.
- The starting dose of 200 mg was based on estimated therapeutic C_{max} of ≤ 1 $\mu\text{g/mL}$ and the results of PK and safety assessments in a single dose Phase 1 study.
- Doses were increased in a flexible dose-escalation scheme; escalations were based on careful review of blinded clinical and PK data that confirmed the safety of the preceding dose; modifications to the dosage schedule were based on observed dose-limiting toxicity and strict stopping rules.

Safety Assessments

- Safety was assessed by monitoring of adverse events (AEs), physical examinations, vital signs, and clinical laboratory tests conducted pre-dose and post-dose. ECGs were obtained at baseline and anticipated time of peak plasma drug concentration.

Pharmacokinetic Assessments

- Blood samples for assay of CEM-101 concentrations and PK assessment were collected as follows:
 - Pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, and 16 hours post-dose on Day 1
 - Pre-dose on Days 2-5 (through determinations)
 - Pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours post-dose on Day 7 (through Day 10)
- The following PK parameter estimates were derived from the plasma concentration versus time curve:
 - Maximum measured plasma concentration (C_{max})
 - Area under the concentration versus time curve (AUC_{0-24} and AUC_{0-72})
 - Time to peak concentration (T_{max})
 - Apparent terminal elimination half life ($T_{1/2}$)
 - Volume of distribution (V_d)
 - Clearance (CL)

Statistical Methods and Data Analysis

- Sample size was based on clinical experience and judgment.
- No power calculations were performed.
- Data was summarized using descriptive statistics for continuous variables and frequencies and percentages for discrete variables.
- Graphs of mean plasma CEM-101 concentrations versus time were produced for each dose level. Standard PK parameters were calculated and summarized using descriptive statistics.

Subjects

- Thirty-five healthy adult subjects between 20 and 55 years of age were enrolled (22 males and 13 females); all completed the study.
- There were no significant differences in the demographics of the CEM-101 and placebo subjects.

Safety and Tolerability Results

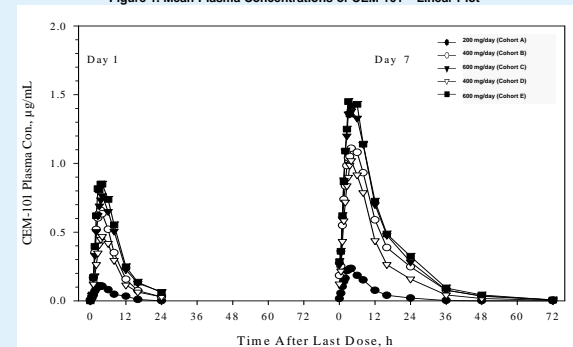
AEs were reported in 21 of the 35 (60%) subjects overall, and in 14 of 25 (56%) subjects administered CEM-101. Of the 64 AEs reported in subjects who received CEM-101, 58 were mild and 6 were moderate in intensity, none were considered clinically significant.

- The most common AE was headache, reported in 6 subjects who received CEM-101 and 5 subjects who received placebo. The other common AEs in CEM-101 subjects were loose stools (5 subjects), cramps/abdominal pain/stomach ache (7 subjects), and bad/metallic aftertaste (3 subjects).
- Most AEs did not require pharmacological treatment; 4 subjects received acetaminophen.
- There were no clinically significant changes in physical exams, vital signs, or electrocardiograms in study subjects.
- Four of 10 subjects administered 600 mg of CEM-101 (Cohorts C and E) had low-level hepatic transaminase increases during dosing (ALT, 3 at $\leq 2 \times \text{ULN}$ and 1 at $< 3 \times \text{ULN}$; AST, 2 at $< 2 \times \text{ULN}$); levels returned rapidly to normal after dosing was completed.
- No transaminase increases were observed in 10 subjects who received multiple doses of 400 mg.

Table 1. Mean PK Parameters for CEM-101 in Plasma after Multiple Doses

Parameter	200 mg/d (Cohort A)	400 mg/d (Cohort B)	400 mg/d (Cohort D)	600 mg/d (Cohort C)	600 mg/d (Cohort E)
Day 1					
C_{max} , $\mu\text{g/mL}$	0.11	0.68	0.48	0.79	0.93
T_{max} , h (median)	3.00	3.50	4.00	4.00	3.50
$T_{1/2}$, h (harmonic mean)	3.64	4.19	4.74	5.06	5.45
AUC_{0-24} , $\mu\text{g}\cdot\text{h/mL}$	0.89	5.54	4.15	7.22	8.08
AUC_{0-72} , $\mu\text{g}\cdot\text{h/mL}$	0.91	5.70	4.33	7.67	8.50
CL/F, L/h	285	250	192	378	173
V_d/F , L	1,520	1,400	1,520	2,900	1,660
Day 7					
C_{max} , $\mu\text{g/mL}$	0.25	1.15	1.03	1.42	1.58
T_{max} , h (median)	3.50	4.00	4.00	4.00	3.00
$T_{1/2}$, h (harmonic mean)	5.39	6.52	6.18	7.64	8.07
AUC_{0-24} , $\mu\text{g}\cdot\text{h/mL}$	2.31	14.80	11.80	18.10	18.70
CL/F, L/h	102	150	42.2	49.30	33.70
V_d/F , L	837	963	362	538	399
C_{max} Day 7/ C_{max} Day 1 (accumulation ratio)	2.19	1.69	4.95	5.04	4.86
AUC_{0-24} Day 7/ AUC_{0-24} Day 1 (accumulation ratio)	2.60	2.67	7.13	9.03	6.45

Figure 1. Mean Plasma Concentrations of CEM-101 – Linear Plot



Conclusions

CEM-101 was safe and generally well tolerated in healthy male and female adult subjects orally administered 7 daily doses of 200 mg, 400 mg or 600 mg. Low-level serum transaminase elevations were observed in 4 subjects administered 600 mg CEM-101; levels returned rapidly to normal after dosing was completed. C_{max} and AUC_{0-24} increases were more than dose proportional from 200 mg to 400 mg and dose proportional from 400 mg to 600 mg. Moderate accumulation of CEM-101 was observed after 7 days of oral dosing; this may reflect CEM-101 inhibiting its own metabolism. Based on its microbiological and PK profile, and the overall safety and tolerability of multiple-dose regimens observed in this study, CEM-101 appears to be a promising new agent for once-daily treatment of CABP and potentially other types of infections.