Single Oral Dose Pharmacokinetics and Safety of CEM-101 in Healthy Subjects

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Abstract

Background: CEM-101 is a potent new ketolide currently under development for treatment of respiratory tract infections. CEM-101 pharmacokinetics and safety following escalating single oral doses administered under fasting conditions were investigated in this first-in-human study.

Methods: This was a Phase 1, randomized, double-blind, placebo-controlled, dose escalation study. Escalating single doses (50, 100, 200, 400, 800, 1200, and 1600 mg) were administered to seven groups of healthy adult subjects using 50, 100, or 200 mg CEM-101 or matching placebo capsules. Within each dose group, 5 subjects received CEM-101 and 2 received placebo. Dose escalation proceeded only after the safety of the previous dose was determined. Physical examinations, vital signs, ECGs, clinical laboratory tests, and adverse events (AEs) were monitored throughout the study. Blood samples for assay of CEM-101 concentrations and pharmacokinetic assessment were collected pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, 48, and 72 h post-dose.

Results: Over the dose range studied, the mean CEM-101 $T_{1/2}$ ranged from 2.2 to 7.9 h. The median T_{max} increased from 1.5 h at 50 mg to 6 h at 1600 mg. The mean C_{max} and $AUC_{0\text{-}inf}$ ranged from 22.3 ng/mL and 81.5 ng•h/mL to 1970 ng/mL and 28900 ng•h/mL over the dose range. The C_{max} and $AUC_{0\text{-}inf}$ increases were more than proportional across the dose range. These doses of CEM-101 were safe and generally well tolerated. AEs were reported in 12 of the 49 (24%) study subjects, all mild or moderate in severity. The most common AE was headache, occurring in 9 subjects. Nausea and/or diarrhea were seen in 2 subjects in the 1200 and 1600 mg dose cohorts, suggesting possible gastrointestinal intolerance beginning at these doses.

Conclusion: Over the 50 mg to 1600 mg dose range, CEM-101 was safe and generally well tolerated in healthy male and female subjects. C_{max} and $AUC_{0\text{-}inf}$ increases were more than dose proportional across the dose range administered.

Introduction

CEM-101 (Figure 1) is a new macrolide antibiotic of the ketolide subclass under development for treatment of patients with community-acquired bacterial respiratory tract infections, in particular those caused by multi-drug resistant *Streptococcus pneumoniae*. CEM-101 binds to the 50S unit of bacterial ribosomes and inhibits bacterial protein synthesis. It has physicochemical and pharmacologic properties similar to other macrolides, but differs in having enhanced antibacterial activity against susceptible and resistant organisms including *S. pneumoniae*, β-hemolytic streptococci, *H. influenzae*, CA-MRSA, enterococcal spp. (*E. faecium* and *E. faecalis*), and atypicals (*Mycoplasma*, *Chlamydophila*, *Legionella*). CEM-101 binds to ribosomes from cells with the *erm* phenotype, which may account for its activity against macrolide-resistant bacteria. The tendency for CEM-101 to induce resistance among key respiratory pathogens is very low.

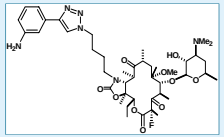
Studies of experimental infections in murine models have shown CEM-101 to be highly effective against infections caused by *S. pneumoniae*, *S. pyogenes*, and *S. aureus*. CEM-101 was also effective in a mouse abscess model and in a mouse pneumonia model using a highly virulent strain of pneumococcus. Pharmacokinetic (PK) data from these studies indicates good tissue distribution of CEM-101. Activity in these animal models suggests that CEM-101 will be effective in human respiratory tract infections.

CEM-101 appears to be metabolized primarily in the liver. Analysis by reaction phenotyping using both a chemical inhibitor and recombinant CYP450 indicates that CYP3A4 is likely the major CYP450 enzyme governing the metabolism of CEM-101. CYP interaction studies indicate that CEM-101 is a substrate of and inhibitor of CYP3A4 similar to most other macrolides. Accordingly, CEM-101 is expected to have clinically significant interactions with drugs that are substrates or inhibitors of CYP3A4. It is also possible that CEM-101 may cause clinically significant inhibition of CYP2C8 and/or CYP2D6. CEM-101 does not appear to be an inducer of CYP3A4.

The potential for CEM-101 to prolong cardiac repolarization (long QTc) is suggested by the results of an in vitro study that showed inhibition of the hERG channel similar to that of clarithromycin and telithromycin. However, a telemetry study in conscious dogs showed no tendency for QTc prolongation after CEM-101 administration.

Toxicology studies with CEM-101 have shown no significant unexpected toxicities after repeat dosing for 28 days in rats and 14 days in monkeys. CEM-101 was not mutagenic or clastogenic in multiple genetic toxicity assays, indicating that it is not genotoxic. No potential for unusual or severe adverse effects in humans was suggested by the nonclinical safety data on CEM-101 available to date.

Figure 1. Chemical Structure of CEM-101



Study Design and Methodology

Objectives

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

Study Design and Selection Criteria

- This was a Phase 1, randomized, double-blind, placebo-controlled, flexible dose escalation study.
- Forty-nine healthy adult subjects were enrolled in 7 dosage groups.
- Subjects were admitted to the clinical research unit on the day prior to dosing and remained in the unit for 72 hours post-dose. Safety follow-up was made by phone 7 days post-dose.
- Key selection criteria:
  - Healthy males and non-pregnant females 19 to 55 years of age.
  - Body mass index (BMI) 18 to 30 kg/m^2; total body weight >60 kg.
  - Negative pregnancy test and appropriate contraceptive methods for females of childbearing potential.
  - Subjects with clinically significant organ disease excluded.
  - Drug or alcohol abusers and tobacco users excluded.
  - Subjects with history of hypersensitivity to macrolides excluded.
  - Subjects with QTc >450 msec (470 msec for females) excluded.

Treatments

- Escalating single doses (50, 100, 200, 400, 800, 1200, and 1600 mg) of CEM-101 or placebo were administered to seven groups of healthy adult subjects using 50, 100, or 200 mg CEM-101 or matching placebo capsules.
- Dose escalation was designed to be flexible to allow for study of intermediate dose levels based on PK data from preceding doses and for addition or deletion of cohorts at specific dose levels.
- Within each dose group, 5 subjects received CEM-101 and 2 received placebo.
- Dose escalation proceeded only after the safety of the previous dose was determined following strict dose escalation stopping rules.

Safety Assessments

- Safety was assessed by monitoring of adverse events (AEs), physical examinations, vital signs, and clinical laboratory tests pre- 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 pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, 48, and 72 h post-dose.
- The following PK parameters were derived from the plasma concentration versus time curve:
  - Maximum measured plasma concentration (C_{max})
  - Area under the concentration versus time curve ($AUC_{0\text{-}t}$ and AUC_{inf})
  - Time to peak concentration (t_{max})
  - Apparent terminal elimination half life ($t_{1/2}$)
  - Apparent first-order terminal elimination rate constant (Kel)
  - 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 and standard PK parameters calculated and summarized using descriptive statistics.

Results

Subjects

- Forty-nine subjects (30 males and 19 females) between 19 and 55 years of age were enrolled; all completed the study.
- No significant differences were noted in demographics of CEM-101 and placebo groups.

Safety and Tolerability

- AEs were reported in 12 of the 49 study subjects (25%) following study drug administration; all AEs were of mild or moderate severity.
- The most common AE was headache, occurring in 9 subjects (5 received CEM-101 and 4 received placebo).
- For most of the AEs, no pharmacologic treatment was required. Five subjects received acetaminophen for headache, musculoskeletal pain, or low back pain.
- Complaints of nausea and/or diarrhea were seen in 2 CEM-101 subjects in the 1200 and 1600 mg dose cohorts (associated with dizziness, palpitations, and symptoms of gastroesophageal reflux in 1 subject in the 1600 mg cohort), suggesting possible gastrointestinal intolerance beginning at these dose levels.
- There were no clinically significant changes in physical examinations, vital signs, ECGs, or laboratory parameters.
- A summary of the AEs in the study is provided in Table 1.

Table 1. Adverse Events after Single Doses of CEM-101 or Placebo

Cohort/ Treatment	Subject #	Gender Age (Y)	Adverse Event	Frequency	Severity Grade	Relationship	Treatment	Outcome
50 mg								
CEM-101	002	M/25	Headache	Intermittent	2	Probably	Acetaminophen X1	Recovered
			Palpitations	Intermittent	1	Possibly	None	Recovered
			Left upper chest musculoskeletal pain	Constant	1	Not Related	Acetaminophen X1	Recovered
100 mg								
Placebo	026	F/54	Headache	Constant	1	Possibly	None	Recovered
Placebo	033	F/42	Headache	Constant	1	Possibly	None	Recovered
200 mg	-	-	None	-	-	-	-	-
400 mg								
CEM-101	072	M/30	Headache	Constant	1	Possibly	None	Recovered
800 mg								
CEM-101	081	M/46	Headache	Constant	2	Possibly	Acetaminophen X1	Recovered
Placebo	090	F/47	Headache	Constant	1	Possibly	None	Recovered
1200 mg								
CEM-101	114	M/34	Nausea	Constant	1	Possibly	None	Recovered
Placebo	119	F/49	Headache	Intermittent	2	Possibly	Acetaminophen X1	Recovered
CEM-101	123	F/28	Headache	Constant	2	Possibly	Acetaminophen X1	Recovered
			Headache	Constant	1	Possibly	Acetaminophen X1	Recovered
			Diarrhea	Intermittent	1	Possibly	None	Recovered
1600 mg								
CEM-101	126	M/32	Nausea	Constant	1	Probably	None	Recovered
			Nausea	Constant	1	Probably	None	Recovered
			Dizziness	Constant	1	Probably	None	Recovered
			Diarrhea	X1	2	Probably	None	Recovered
CEM-101	148	F/41	Dizziness	Constant	1	Probably	None	Recovered
			Headache	Constant	1	Probably	None	Recovered
			Epigastric Pain	Constant	1	Probably	None	Recovered
			Heartburn	Constant	1	Probably	None	Recovered
			Palpitations	X1	1	Possibly	None	Recovered
			Palpitations	X1	1	Possibly	None	Recovered
			Palpitations	Constant	1	Possibly	None	Recovered
			Diarrhea	Intermittent	2	Probably	None	Recovered
CEM-101	149	F/55	Low Back Pain	Constant	1	Unlikely	Acetaminophen X1	Recovered

Pharmacokinetics

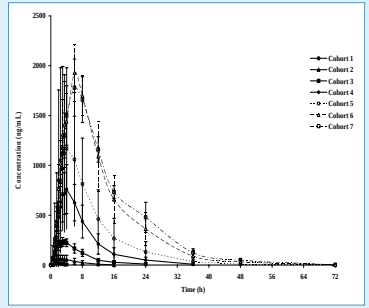
Descriptive statistics of pharmacokinetic results for CEM-101 in plasma are summarized in Table 2.

Table 2. Mean PK Parameters for CEM-101 in Plasma after Single Doses

Mean Parameter	Dose Levels (mg)						
	50	100	200	400	800	1200	1600
C_{max} (ng/mL)	22.3	68.3	255	784	1320	1960	1780
t_{max} (h)	1.5	2.0	3.0	4.0	3.5	6.0	6.0
$t_{1/2}$ (h) (median)	2.2	3.4	4.5	5.1	6.5	6.8	7.9
$AUC_{0\text{-}t}$ (ng•h/mL)	40.1	394	1730	6940	13700	26700	28600
AUC_{inf} (ng•h/mL)	81.5	457	1900	7110	13800	26900	28900
CL/F (mL/h)	619000	353000	116000	64000	101000	46800	106000

- Across the doses studied, the mean C_{max} and mean AUC_{inf} ranged from 22.3 ng/mL and 81.5 ng•h/mL to 1960 ng/mL and 28900 ng•h/mL.
- The C_{max} and AUC increases were more than proportional across the range of doses studied. However, in the 1600 mg cohort, the mean C_{max} was slightly lower than the mean C_{max} in the 1200 mg cohort and the mean AUC values were slightly higher and displayed less than dose proportional increases compared with the 1200 mg cohort. These results are due to markedly lower plasma CEM-101 concentrations in one subject relative to the other four subjects that received active drug in the 1600 mg cohort. When the data from the subject with outlying values is excluded, the mean C_{max} is 2153 ng/mL and the mean AUC_{inf} is 34775 ng•h/mL, which represents an approximately dose-proportional increase in exposure over the 1200 mg dose.
- The mean t_{max} increased from 1.5 h to 6.0 h and the mean terminal half life ($t_{1/2}$) increased from 2.2 h to 7.9 h over the 50 mg to 1600 mg dose range.
- Mean plasma concentrations of CEM-101 for each dose level are depicted in a linear plot in Figure 2.

Figure 2. Mean Plasma Concentrations of CEM-101 - Linear Plot



Conclusions

- CEM-101 was safe and generally well tolerated in healthy male and female adult subjects over the 50 mg to 1600 mg dose range.
- C_{max} and AUC increases were more than dose proportional across the dose range administered.
- At a projected therapeutic dose range of 400 to 500 mg, a t_{max} of 4 hours and a $t_{1/2}$ of 5-6 hours would be expected.
- Given the data from this single-dose study and based on its microbiological profile, CEM-101 appears to be a promising new agent for once-daily treatment of community-acquired bacterial respiratory tract infections.
- CEM-101 will next be evaluated in a study to determine the safety, tolerability and pharmacokinetics of multiple, ascending doses in healthy subjects.