

Abstract

Background: Solithromycin (CEM-101) is a potent new fluoroketolide for treatment of bacterial respiratory tract and other infections.

Methods: In a randomized, double-blind, placebo-controlled study, escalating oral doses (200 [n=7], 400 [n=14], and 600 [n=14] mg) were administered once daily for 7 days (5:2, active: placebo). Physical examinations, vital signs, ECGs, clinical laboratory tests, and adverse events were monitored throughout the study. Plasma PK samples were collected pre-dose and up to 24 h (Day 1) and 72 h (Day 7) post-dose. A separate randomized, 400 mg single-dose, two-period, fed/fasted crossover bioequivalence study assessed the effects of food [12 fasted, 12 high fat diet].

Results: PK: Mean C_{max} values on Days 1 and 7 were 0.113 and 0.248 mg/L (200 mg), 0.579 and 1.09 mg/L (400 mg) and 0.862 and 1.50 mg/L (600 mg). Corresponding $AUC_{(0-24)}$ values were 0.888 and 2.31 mg·h/L, 4.85 and 13.30 mg·h/L, and 7.64 and 18.40 mg·h/L on Days 1 and 7. Mean T_{max} ranged from 3.0 to 3.75 hours on Day 1 and from 3.5 to 4.0 hours on Day 7, and mean $T_{1/2}$ increased from 3.64 to 5.06 hours on Day 1 and from 5.39 to 7.64 hours on Day 7. After single oral doses of CEM-101 400 mg, differences in plasma C_{max} , $AUC_{(0-24)}$, and $AUC_{(0-72)}$ between fasted and fed subjects were insignificant ($p \geq 0.05$). **SAFETY:** Gastrointestinal (GI) AEs, mostly mild, occurred in each dose group. Mild, reversible, clinically insignificant ALT or AST increases occurred in 4 of 10 subjects (600 mg group). The incidence of GI AEs was slightly reduced following fed treatment.

Conclusion: Multiple daily doses (200 to 600 mg) of CEM-101 were safe and well tolerated. C_{max} and $AUC_{(0-24)}$ increases were more than dose proportional, and moderate accumulation of CEM-101 was noted after 7 days. Oral bioavailability of CEM-101 following a single oral dose of 400 mg was not affected by food.

Introduction

- Solithromycin (CEM-101) is the first fluoroketolide being developed in oral and intravenous (IV) formulations for treatment of patients with community-acquired bacterial pneumonia (CABP).
- Solithromycin is highly active against common typical respiratory tract pathogens (*S. pneumoniae*, β -hemolytic streptococci, *H. influenzae*, *M. catarrhalis*, *S. aureus* and *CA-MRSA*) as well as atypical bacteria (*M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila*).
 - Solithromycin has potent bactericidal activity against macrolide resistant pneumococci (*S. pneumoniae*, *ermB*, *meiA*, *ermB* + *meiA*, penicillin resistant, all MICs ≤ 1 μ g/mL) and is 2- to 4-fold more potent than telithromycin.
 - Solithromycin MIC₉₀ was equal to azithromycin and 2-fold lower than telithromycin against β -lactamase producing *H. influenzae*.
- Solithromycin was significantly more potent in vitro than azithromycin against intracellular pathogens such as *S. aureus*, *L. monocytogenes*, or *L. pneumophila*.
- Solithromycin was efficacious in experimental murine infection models caused by key CABP pathogens.
- Solithromycin achieved higher concentrations in human lung epithelial lining fluid (~10-fold) and alveolar macrophages (~200-fold) compared with plasma when administered at 400 mg for 5 days.
- Solithromycin's extended spectrum of activity and pharmacological properties provided potential for future clinical use in other therapeutic areas with unmet medical need: gonococcal and nongonococcal urethritis, *M. avium* infections, biodefense threats (*Bacillus anthracis* and *Francisella tularensis*), mycobacterial infections, and malaria.
- Solithromycin has been administered orally to 115 healthy adults as single and multiple doses for 5 to 7 days. Results of the multiple dose and food effect studies are presented here.

Study Design and Objectives

	Multiple Ascending Dose Study (CE01-102)	Food Effect Study (CE01-103)
Objectives	<ul style="list-style-type: none"> To determine safety and tolerability of multiple escalating doses of oral solithromycin To determine the pharmacokinetic (PK) profile of multiple escalating doses of solithromycin. 	<ul style="list-style-type: none"> To assess the effects of food on the bioavailability of a single oral 400 mg dose of solithromycin. To assess the effects of food on the safety and tolerability of a single oral 400 mg dose of solithromycin.
Study Design	<ul style="list-style-type: none"> Single center, Phase 1, randomized, double-blind placebo-controlled, flexible dose escalation trial. 35 healthy adult subjects were enrolled into 5 dosage cohorts (200 mg, 400 mg [2 cohorts], and 600 mg [2 cohorts]). 	<ul style="list-style-type: none"> Single center, Phase 1, randomized, 2-period, 2-sequence crossover trial 24 healthy adult subjects received solithromycin in both the fed and fasted states.
Key Inclusion Criteria	<ul style="list-style-type: none"> Healthy males and non-pregnant females 19 to 55 years of age with a body mass index of 18 to 32 kg/m² and total body weight > 60 kg Negative pregnancy test and appropriate contraception required 	<ul style="list-style-type: none"> Healthy males and non-pregnant females 19 to 55 years of age with a body mass index of 18 to 32 kg/m² and total body weight > 60 kg Negative pregnancy test and appropriate contraception required
Key Exclusion Criteria	<ul style="list-style-type: none"> Subjects with clinically significant organ disease Drug, alcohol, or tobacco use History of hypersensitivity to macrolides or ketolides QTc>450 msec (470 msec for males) 	<ul style="list-style-type: none"> Subjects with clinically significant organ disease Drug, alcohol, or tobacco use History of hypersensitivity to macrolides or ketolides
Treatment Regimen	<ul style="list-style-type: none"> Solithromycin 200, 400, 600 mg or a matched placebo Within each cohort, 5 subjects received solithromycin and 2 received placebo. Flexible dose escalation based on blinded safety and PK data review; strict termination rules followed. 	<ul style="list-style-type: none"> Treatment A: Single oral dose of solithromycin 400 mg under fasted conditions Treatment B: Single oral dose of solithromycin 400 mg under fed conditions (2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk).
Statistical Analysis	<ul style="list-style-type: none"> Data summarized using descriptive statistics for continuous variables and frequency and percentages for discrete variables. 	<ul style="list-style-type: none"> Bioequivalence of drug exposure in fasted and fed conditions based on the 90% CIs of the ratios of least-squares means (LSMs) for the natural log (ln)-transformed exposure measurements ($AUC_{(0-24)}$ and C_{max}) of the fed to fasted drug exposures. Standard PK parameters were summarized using descriptive statistics.
PK Sampling	<ul style="list-style-type: none"> Day 1: 7 Pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, and 16 hours post-dose Day 2-6: Pre-dose Day 8-10: 26, 36, 48, 72 hrs post dose 	<ul style="list-style-type: none"> Day 1 (Periods 1 & 2): Pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16 hrs post-dose Days 2-3, 4 (Periods 1 & 2): 24, 36, 48, 72 hrs post-dose
PK Parameter Measurements (derived from plasma vs. time curve)	<ul style="list-style-type: none"> 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 ($t_{1/2}$) Apparent first-order terminal elimination rate constant (k_{el}) Volume of distribution (VdF) and clearance (CL/F) 	<ul style="list-style-type: none"> 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 ($t_{1/2}$) Apparent first-order terminal elimination rate constant (k_{el}) Volume of distribution (VdF) and clearance (CL/F)
Safety Assessments	<ul style="list-style-type: none"> Monitoring of AEs, physical examinations, vital signs, and clinical laboratory tests conducted pre-dose and post-dose. Triplicate ECGs were obtained at baseline and anticipated time of peak plasma levels. 	<ul style="list-style-type: none"> Monitoring of AEs, physical examinations, vital signs, and clinical laboratory tests conducted pre-dose and post-dose. Triplicate ECGs were obtained at baseline and anticipated time of peak plasma levels.

Reference

Still JG, Clark K, Degenhardt T, Scott D, Fernandes P. Multiple dose pharmacokinetics and safety of CEM-101, a new fluoroketolide, in healthy subjects. (ECCMID 2010; Vienna, Austria: poster 902.

Safety and Tolerability

Multiple Dose Study (CE01-102):

- AEs were reported by 60% (3/5) of subjects who received 200 mg, 50% (5/10) of subjects who received 400 mg, 60% (6/10) of subjects who received 600 mg, and 70% (7/10) of subjects who received placebo.
- No SAEs or deaths were reported and no subject was discontinued due to an AE.
- Most frequently reported AEs involved the gastrointestinal tract, occurring at similar rates in the solithromycin dosage cohorts and placebo group.
- Treatment-emergent AEs (TEAEs) reported by 4 ($\geq 10\%$) or more of the 35 subjects included headache, diarrhea, nausea, vomiting, abdominal pain, and dyspepsia.
- 4 of 10 subjects in the 600 mg cohort had asymptomatic, reversible, transient ALT elevations (1.1X to <3X ULN); bilirubin remained within normal range.

Food Effect Study (CE01-103):

- 33 TEAEs were reported by 8 (33%) of the 24 subjects; 25 of 33 AEs (75%) were considered treatment related; all AEs were mild in severity.
- More related TEAEs were reported by subjects following fasted (21) versus fed (4) treatment.
- A majority (24 of 33, 73%) of reported AEs were related to the GI tract (e.g. nausea, abdominal pain, loose stools, acid reflux, flatulence and burping).
- 3 of 24 subjects had asymptomatic, transient, reversible elevation of ALT (1.1X-1.4X ULN); bilirubin remained within normal range.

Pharmacokinetic Results

Multiple Dose Study (CE01-102)

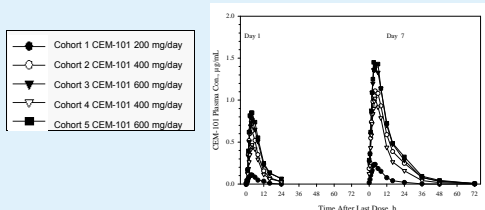
Mean PK Parameters for Solithromycin in Plasma after Multiple Doses (CE01-102)

Parameter	Cohort A 200 mg/d		Cohort B 400 mg/d		Cohort C 600 mg/d		Cohort D 400 mg/d		Cohort E 600 mg/d	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Day 1										
C_{max} (μ g/mL)	0.113	0.0482	0.681	0.452	0.709	0.534	0.477	0.290	0.934	0.582
T_{max} (hr)	3.00	2.4	3.50	3.4	4.00	2.4	4.00	3.4	3.50	(2.5-6)
k_{el} (h ⁻¹)	0.189	0.0188	0.165	0.0186	0.137	0.0215	0.146	0.0232	0.127	0.0263
$T_{1/2}$ (hr)	3.64	0.375	4.19	0.467	5.06	0.782	4.74	0.744	5.45	1.14
$AUC_{(0-24)}$ (μ g·h/mL)	0.888	0.442	5.940	3.400	7.220	4.900	4.150	2.960	8.08	4.80
$AUC_{(0-72)}$ (μ g·h/mL)	0.913	0.431	5.700	3.470	7.670	5.250	4.330	3.110	8.50	4.92
CL/F (L/h)	285	165	250	417	378	612	192	220	173	241
Vd/F (L)	1,520	963	1,400	2,300	2,900	4,810	1,520	2,060	1,660	2,580
Day 7										
C_{max} (μ g/mL)	0.248	0.839	1.150	0.640	1.420	0.493	1.030	0.436	1.58	0.329
T_{max} (hr)	3.50	2.5-3.5	4.00	3.5-6	4.00	2.5-6	4.00	2.5-4	3.00	(2.5-6)
k_{el} (h ⁻¹)	0.128	0.0194	0.106	0.0433	0.0907	0.0123	0.112	0.0221	0.0850	0.0197
$T_{1/2}$ (hr)	5.39	0.912	6.52	2.90	7.64	1.08	6.18	1.19	8.07	1.83
$AUC_{(0-24)}$ (μ g·h/mL)	2.310	0.773	14.800	8.780	18.100	6.790	11.800	6.230	18.7	4.78
CL/F (L/h)	102	59.8	150	285	49.3	17.5	42.2	19.7	33.7	8.36
Vd/F (L)	837	561	963	1,580	538	164	362	122	399	79.1
C_{max} accumulation										
ratio*	2.19	1.74	1.69	1.42	5.04	7.82	4.95	7.47	4.86	7.80
$AUC_{(0-24)}$ accumulation										
ratio*	2.60	1.75	2.67	2.58	9.03	15.6	7.13	11.4	6.45	10.2

- a Expressed as median and range
- b Apparent first-order terminal elimination rate constant
- c Expressed as harmonic mean and pseudo SD
- d C_{max} , Day 7/ C_{max} , Day 1
- e $AUC_{(0-24)}$, Day 7/ $AUC_{(0-24)}$, Day 1

Results

Mean Plasma Solithromycin Concentrations after 200, 400 and 600 mg Multiple Oral Doses in Healthy Subjects (CE01-102)



Food Effect Study (CE01-103)

Mean PK Parameters for Solithromycin in Plasma: Fasted or Fed State

Solithromycin in Plasma Pharmacokinetic Parameters	Treatment A (Fasted)	Treatment B (Fed)	B/A (Fed vs. Fasted)
	Mean \pm SD	Mean \pm SD	% MR (90% CI)*
C_{max} (μ g/mL)	0.609 \pm 0.235	0.633 \pm 0.201	106.81 (97.56, 116.83)
$AUC_{(0-24)}$ (μ g·h/mL)	5.470 \pm 2.292	5.983 \pm 1.761	97.08 (86.86, 108.50)
$AUC_{(0-72)}$ (μ g·h/mL)	5.614 \pm 2.284	5.267 \pm 1.771	97.81 (87.89, 108.85)
$AUC_{(0-24)}$ (%)	3.048 \pm 1.571	3.770 \pm 1.437	N/A
T_{max} (hr)	3.50 (2.50, 6.00)	3.50 (2.50, 6.01)	N/A
$t_{1/2}$ (hr)	5.46 \pm 0.764	5.10 \pm 0.668	N/A
k_{el} (1/hr)	0.132 \pm 0.0164	0.138 \pm 0.0165	N/A
VdF (L)	676.0 \pm 356.9	610.5 \pm 187.4	N/A
CL/F (L/hr)	88.03 \pm 48.94	84.35 \pm 27.70	N/A

T_{max} is presented as Median (Minimum, Maximum); *Based on the ratio of least-squares means Treatment A=CEM-101 under Fasted Conditions; Treatment B=CEM-101 under Fed Conditions

- Solithromycin PK parameters were statistically bioequivalent for the fed and fasted states
- Ratios of least-squares means for the ln-transformed C_{max} , $AUC_{(0-24)}$, and $AUC_{(0-72)}$ of the fed to fasted drug exposures were 107%, 97.1%, and 97.8%, respectively, with the 90% CIs within the 80 to 125% range.
- No food effect on the bioavailability of solithromycin following a single 400 mg oral dose.

Conclusions

- Solithromycin was safe and generally well tolerated in healthy adult subjects orally administered a single 400 mg dose or 7 daily doses of 200 mg, 400 mg or 600 mg.
- Solithromycin can be administered without regard to food; tolerability may be improved when taken with food.
- Solithromycin exhibited non-linear PK over time with accumulation after repeat dosing (auto-inhibition). As a result, a daily loading dose (800 mg Day 1) / maintenance dose (400 mg Days 2-5) regimen was selected for evaluation in Phase 2 studies.
- Solithromycin is the first fluoroketolide in Phase 2 trials and is a promising agent for CABP and other infections due to its expanded and potent spectrum of activity and favorable PK profile.