A Randomized, Double-Blind, Multi-Center Study to Evaluate the Efficacy and Safety of Oral Solithromycin (CEM-101) Compared to Oral Levofloxacin in the Treatment of Patients with Community Acquired Bacterial Pneumonia

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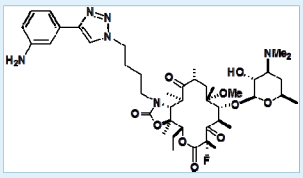
ABSTRACT

Trial Design:
This was a multi-center, Phase 2, double-blind, randomized, efficacy and safety study to evaluate oral solithromycin versus oral levofloxacin in the treatment of adults with moderate to moderately severe community-acquired bacterial pneumonia (CABP). [Clinical Trials registration NCT01168713]
Methods:
Patients with CABP were enrolled and randomized (1:1) to either: solithromycin 800 mg orally (PO) on Day 1 followed by 400 mg PO daily on Days 2 to 5 or levofloxacin 750 mg PO daily on Days 1 to 5. Randomization was stratified by age (<50 or ≥50 years) and pneumonia severity index (PORT) score. Co-primary efficacy outcome measures were Investigator's assessment of clinical success at test-of-cure (TOC; 4 to 11 days after the last dose of study drug) in the Intent-to-Treat (ITT) and Clinically Evaluable (CE) populations. Early response success (at Day 3) was defined as improvement in at least two cardinal symptoms (cough, sputum production, chest pain, or dyspnea) without worsening in any.
Results:
The 132 patients randomized were primarily (95%) from U.S. sites, 50.7% male, and 82.6% Caucasian, with a mean age of 55. Randomized patients had PORT scores of II (73%), III (20%), or IV (5%). Clinical success rates, presented in the table below, were comparable across the analysis populations, at both early response (Day 3) and TOC visits, as well as among subgroups with a baseline elevated procalcitonin (PCT) and with an identified pneumococcal infection.
More levofloxacin recipients experienced one or more treatment-emergent adverse events (TEAEs) during the study (45.6%) than did solithromycin recipients (29.7%). The majority of TEAEs were gastrointestinal, were of mild or moderate intensity, and included nausea (1.6% solithromycin; 10.3% levofloxacin), diarrhea (7.8% solithromycin; 5.9% levofloxacin), and vomiting (0% solithromycin; 4.4% levofloxacin). Six patients, all receiving levofloxacin, discontinued study drug due to an AE. There was one death in the trial, attributed to a pulmonary embolism, in a levofloxacin recipient.
Conclusions:
Solithromycin demonstrated efficacy comparable to levofloxacin and a favorable safety and tolerability profile, with a lower incidence of treatment-emergent adverse events than levofloxacin. These findings strongly support the further study of solithromycin in Phase 3 clinical trials for the treatment of CABP.

Funding: Cempra Pharmaceuticals

INTRODUCTION



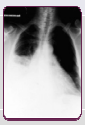
- Solithromycin
  - 4th generation macrolide, the first fluoroketolide
  - Binds bacterial ribosome at 3 loci (unlike azithromycin at 1)
  - Enhanced activity (lower MICs), reduced resistance
  - Potent activity against CABP and bacterial urethritis pathogens
  - Also active against mycobacteria, Helicobacter, malaria & biodefense pathogens

STUDY OBJECTIVES & TREATMENT

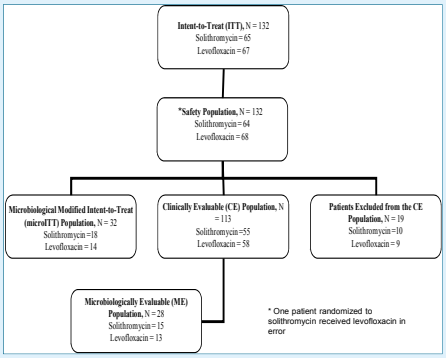
- Primary
  - To assess the clinical success rate at the Test-of-Cure visit (5-10 days post completion of therapy) of oral solithromycin versus oral levofloxacin in the treatment of CABP, in the intent-to-treat (ITT) and clinically-evaluable (CE) populations.
- Secondary
  - To assess the safety and tolerability of oral solithromycin compared to oral levofloxacin
  - To assess the per-patient microbiological success rates of oral soli compared to oral levofloxacin
  - To assess Day-3 Early Clinical Response of oral soli vs levofloxacin in the treatment of CABP
- Treatment (1:1 Randomization)
  - Solithromycin 800mg p.o. Day 1, 400 mg p.o. Days 2-5
  - Levofloxacin 750mg p.o. Days 1-5

RESULTS

CE01-200 Key Inclusion / Exclusion

Key Inclusion Criteria	Key Exclusion Criteria
Clinical (at least 3): cough, fever, dyspnea, purulent sputum, chest pain, consolidation, chills, ↑ or ↓ WBC	Hospital or ventilator-acquired pneumonia
No prior antibiotic treatment (unless documented failure following 2 days Rx or isolation of resistant pathogen)	Anatomical or pathological bronchial obstruction; FEV_1/FVC <70% or FEV_1 <50% predicted plus chronic respiratory failure.
PORT Class II-IV (not to exceed 105)	Known viral, fungal pneumonia, TB, PCP, aspiration or atypical pneumonia
	QTc greater than 450 msec or use of class Ia or III anti-arrhythmics
CXR/Chest CT scan: Lobar/multilobar infiltrates 	Current use of benzodiazepines, Ca channel blockers, immune modulators, antifungals, antipsychotics, phosphodiesterase inhibitors, methadone, fentanyl, rifampin, digoxin

Enrollment Overview



Study Population Demographic Data

		ITT Population		CE Population *	
Characteristic [Statistic]		Solithromycin 800/400 mg N=65	Levofloxacin 750 mg N=67	Solithromycin 800/400 mg N=55	Levofloxacin 750 mg N=58
Enrolled in United States		63 (96.9)	63 (94.0)	54 (98.2)	54 (93.1)
Enrolled in Canada		2 (3.1)	4 (6.0)	1 (1.8)	4 (6.9)
Age (years)	[n (%)]				
Mean±SD		56.0±13.0	55.2±14.1	56.5±13.2	54.8±14.4
<45		12 (18.5)	14 (20.9)	10 (18.2)	13 (22.4)
45-54		19 (29.2)	13 (19.4)	15 (27.3)	11 (19.0)
55-64		15 (23.1)	23 (34.3)	14 (25.5)	19 (32.8)
≥65		19 (29.2)	17 (25.4)	16 (29.1)	15 (25.9)
Race	[n (%)]				
White		55 (84.6)	54 (80.6)	45 (81.8)	46 (79.3)
Asian		5 (7.7)	6 (9.0)	5 (9.1)	5 (8.6)
Black		3 (4.6)	6 (9.0)	3 (5.5)	6 (10.3)
Other		2 (3.0)	1 (1.5)	2 (3.6)	1 (1.7)
Male	[n (%)]	28 (43.1)	39 (58.2)	25 (45.5)	34 (58.6)
Mean Weight (kg) ±SD		84.6±24.3	82.1±20.7	85.2±24.2	80.2±19.3
PORT Score Risk Class	[n (%)]				
I (0-50)		2 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
II (51-70)		47 (72.3)	50 (74.6)	39 (70.9)	44 (75.9)
III (71-90)		12 (18.5)	15 (22.4)	12 (21.8)	13 (22.4)
IV (91-105)		4 (6.2)	2 (3.0)	4 (7.3)	1 (1.7)

* Principal factors censoring patients from CE population: chest radiograph interpretation, other antibiotics, and missed visits.

Disposition & Adverse Events Overview

	Solithromycin 800/400 mg QD (N=64)	Levofloxacin 750 mg QD (N=68)
Number of Patients Completing	64 (100.0)	67 (98.5)
Number of Patients Prematurely Withdrawing from Study	0 (0.0)	1 (1.5)
Reason for Premature Withdrawal- Death		
Number of Patients Prematurely Discontinuing Study Drug	0 (0.0)	6 (8.8)
Reason for Premature Drug D/C – Adverse Event(s)	0 (0.0)	6 (8.8)
Patients with any Treatment Emergent Adverse Event (TEAE)	19 (29.7)	31 (45.6)
Patients with any study drug-related TEAE	7 (10.9)	13 (19.1)
Patients with any SAE	2 (3.1)	7 (10.3)
TEAEs by System Order Class, with > 2% incidence in either arm		
Gastrointestinal Disorders	9 (14.1)	16 (23.5)
Cardiac Disorders	1 (1.6)	2 (3.0)
Musculoskeletal and Connective Tissue Disorders	5 (7.8)	3 (4.4)
Nervous System Disorders	6 (9.4)	8 (11.7)
Psychiatric Disorders	2 (3.1)	1 (1.5)
Ear & Labyrinth Disorders	1 (1.6)	2 (2.9)

Success at Test-of-Cure (TOC)

	ITT Population		CE Population	
Clinical Response	Solithromycin 800/400 mg QD (N=65)	Levofloxacin 750 mg QD (N=67)	Solithromycin 800/400 mg QD (N=55)	Levofloxacin 750 mg QD (N=58)
Success	55 (84.6 %)	58 (86.6 %)	46 (83.6 %)	54 (93.1 %)
95% CI	(73.5-92.4)	(76.0-93.7)	(71.2-92.2)	(83.3-98.1)
Failure	9 (13.8)	7 (10.4)	9 (16.4)	4 (6.9)
Indeterminate	1 (1.5)	2 (3.0)		
	microITT Population		ME Population	
Clinical Response	Solithromycin (N=18)	Levofloxacin (N=14)	Solithromycin (N=15)	Levofloxacin (N=13)
Success	14 (77.8%)	10 (71.4%)	12 (80.0%)	10 (76.9%)
95% CI	(52.4-93.6)	(41.9-91.6)	(51.9-95.7)	(46.2-95.0)
Failure	3 (16.7)	4 (28.6)	3 (20.0)	3 (23.1)
Indeterminate	1 (5.6)	0 (0.0)		

- Among ITT patients with a baseline procalcitonin >0.5 ng/mL, clinical success in 14 of 15 (93.3%) solithromycin recipients and 12 of 13 (92.3%) levofloxacin recipients.
- Among ITT patients: Early Clinical Response achieved in 47/65 (72.3%) of solithromycin recipients versus 48/67 (71.6%) of levofloxacin recipients.

Microbial Pathogens

	microITT Population	
Key CABP Pathogens	Solithromycin 800/400 mg QD	Levofloxacin 750 mg QD
Baseline Pathogen Identified	n=18	n=14
Staphylococcus aureus	1	3
Streptococcus pneumoniae	7	3
MDRSP	2	1
PSSP	5	3
Haemophilus influenzae	3	4
Haemophilus parainfluenzae	1	0
Moraxella catarrhalis	1	1
Chlamydophila pneumoniae	1	1
Mycoplasma pneumoniae	1	0
Legionella pneumophila	0	0

- Among patients with a diagnosis of pneumococcal pneumonia, success at TOC reported in 5 of 7 (71.4%) solithromycin recipients and 2 of 3 (66.7%) levofloxacin recipients.
- Among patients with a diagnosis of *H. influenzae* pneumonia, success at TOC reported in 2 of 3 (66.6%) solithromycin recipients and 3 of 4 (75%) levofloxacin recipients.

Treatment Emergent AEs, by Severity with > 2% Incidence in Either Arm

System Organ Class Preferred Term	Solithromycin (N=64) n (%)			Levofloxacin (N=68) n (%)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Subjects with at least one TEAE	10 (15.6)	6 (9.4)	3 (4.7)	14 (20.6)	11 (16.2)	6 (8.8)
Gastrointestinal Disorders	5 (7.8)	4 (6.3)	0 (0.0)	11 (16.2)	5 (7.4)	0 (0.0)
Abdominal discomfort	1 (1.6)	0 (0.0)	0 (0.0)	2 (2.9)	0 (0.0)	0 (0.0)
Diarrhea	4 (6.3)	1 (1.6)	0 (0.0)	1 (1.5)	3 (4.4)	0 (0.0)
Flatulence	0 (0.0)	1 (1.6)	0 (0.0)	2 (2.9)	0 (0.0)	0 (0.0)
Nausea	0 (0.0)	1 (1.6)	0 (0.0)	5 (7.4)	2 (2.9)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.9)	1 (1.5)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders	2 (3.1)	3 (4.7)	0 (0.0)	2 (2.9)	1 (1.5)	0 (0.0)
Arthralgia	1 (1.6)	2 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous System Disorders	3 (4.7)	2 (3.1)	1 (1.6)	5 (7.4)	2 (2.9)	1 (1.5)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.9)	0 (0.0)	0 (0.0)
Headache	2 (3.1)	1 (1.6)	0 (0.0)	3 (4.4)	0 (0.0)	0 (0.0)
Syncope	2 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Key Safety Outcomes

Cardiac Safety

- No patient, in either arm, had observed QTcF > 480 msec.
- No patient, in either arm, had mean QTcF change from baseline of > 60 msec.
- Only one patient, a solithromycin recipient, had both change from baseline of > 30 msec and a resultant QTcF of > 450 msec…..this patient's maximum QTcF was 454 msec

Liver Safety

- Grade 3 (3-8 x ULN) ALT elevations in 3 subjects (2-levofloxacin,1-solithromycin)
- The single solithromycin patient with a Grade-3 ALT had HCV infection, with elevation from a baseline ALT value of 90 IU/mL (abnormal) to a peak of 220 IU/mL (less than 3-fold over baseline)
- The two levofloxacin patients with Grade-3 ALTs had peak values of 154 and 170 IU/mL, elevations over their respective baseline ALT values of 20 and 23 IU/mL by 7-fold
- No concomitant elevation of bilirubin

CONCLUSIONS

- Solithromycin performed *very well* in this Phase 2 trial
- Efficacy
  - Comparable success rates in ITT, mITT and ME population, against a very effective comparator. Numerically comparable in Early Response, the endpoint of interest to FDA for Phase 3 trials
  - Numerically comparable in high procalcitonin patients, perhaps the best single marker of invasive/serious bacterial pneumonia
- Safety
  - Fewer drug discontinuations due to AEs (0 vs 6 subjects)
  - Fewer study subjects with SAEs (2 vs 7 subjects)
  - Fewer treatment emergent AEs (30% vs 46%)
  - Fewer GI related AEs (14% vs 26%)
  - No liver safety or QT signals of concern
  - No bitter aftertaste