Oral Solithromycin Versus Oral Moxifloxacin for Treatment of Adult Community-Acquired Bacterial Pneumonia (CABP): Results of the Global Phase-3 Trial SOLITAIRE-ORAL

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INTRODUCTION AND PURPOSE

Community-acquired bacterial pneumonia (CABP) is associated with considerable morbidity and mortality worldwide and is the number one cause of death from infectious disease in the US [**1**]. Due to the rising threat of microbial resistance, along with concerns over antibiotic tolerability and impact on intestinal microflora, new CABP treatments are needed.

Solithromycin (CEM-101), a 4th generation macrolide, is being developed as oral, intravenous, and pediatric suspension formulations for the treatment of CABP. Solithromycin has potent antibacterial activity against 'typical' and 'atypical' CABP pathogens, including macrolide-resistant strains. Solithromycin has limited activity against anaerobic gram negative flora and is therefore not expected to have the risk of *C. difficile* infection often associated with fluoroquinolones and broad-spectrum β-lactams antibiotics. Solithromycin was definitively negative in a thorough QT study [**2**].

Moxifloxacin, being available in IV and oral formulations was chosen as the comparator for both Phase 3 trials. Azithromycin could not be used as the comparator since it is not approved in monotherapy for PORT II-IV pneumonia.

The purpose of this Phase 3 trial was to evaluate the safety and efficacy of oral solithromycin compared to oral moxifloxacin in the treatment of adult patients with CABP.

METHODS

Study Outline

- 1:1 randomization of 860 CABP patients to oral solithromycin (5 days) or oral moxifloxacin (7 days)
- Stratified by geographic region, by history of asthma and/or COPD, and by PORT score (II vs III/IV)
- PORT II severity pneumonia capped at 50%. PORT IV enrollment limited to PSI score < 105

Enrollment Criteria

- Acute onset or worsening of at least 3 of 4 cardinal symptoms: cough, dyspnea, chest pain, and sputum production
- Must have fever or hypothermia, and/or physical examination findings consistent with CABP
- Chest radiograph with lobar or patchy parenchymal pulmonary infiltrates
- Pneumonia should not be hospital or health care associated; no long-acting antibiotic use during the prior 7 days

Visit Schedule

The schedule of visits is outlined in the diagram below. All patients were followed through to the Long-term Follow-Up (LFU) visit for all cause mortality.

Treatment Regimen

	SOLITHROMYCIN	MOXIFLOXACIN
Days of Dosing	5 days	7 days
Regimen	800 mg loading dose on Day 1 400 mg on Days 2-5, placebo on days 6-7	400 mg on Days 1-7

METHODS (CONTINUED)

Primary objective and endpoint (for FDA)

- Non-Inferiority (NI) in Early Clinical Response (ECR) rate in the ITT population

Improvement at 72 hours (-12/+36) in at least two of the following symptoms: chest pain, cough, difficulty with sputum production, and dyspnea, without worsening in any

Primary objective and endpoint (for EMA)

- NI in success rate at SFU (short term follow-up visit, 5 to 10 days after end of therapy) in the ITT and clinically-evaluable (CE) populations

Success or failure as determined by the investigator

Secondary objectives

- NI in early clinical response rate at 72 (-12/+36) hours in the pooled mITT population from the two Phase 3 trials
- NI in early clinical response rate at 72 (-12/+36) hours in the individual study mITT population
- Safety and tolerability of oral solithromycin vs oral moxifloxacin

RESULTS

Study Populations and Subgroups

	SOLITHROMYCIN	MOXIFLOXACIN
Intent to Treat Population [ITT] N	426	434
PORT II	209 (49.1%)	223 (51.4%)
PORT III/IV	168 (39.4%) / 48 (11.3%)	173 (39.9%) / 38 (8.8%)
CURB-65 SCORE 0 1 ≥ 2	 135 (31.7%) 175 (41.1%) 106 (24.9%)	 138 (31.8%) 166 (38.2%) 125 (28.7%
Safety (%)	424 (99.5)	432 (99.5)
Microbiological ITT Population [mITT] (%)	235 (55.2)	226 (52.1)
Clinically Evaluable at SFU [CE-SFU] (%)	388 (91.1)	390 (89.9)

Safety Outcomes

	SOLITHROMYCIN (N=424)	MOXIFLOXACIN (N=432)
Any Treatment-Emergent Adverse Event (TEAE)	155 (36.6%)	154 (35.6%)
Any Study Drug Related TEAE	43 (10.1%)	54 (12.5%)
Any Serious Adverse Event (SAE)	28 (6.6%)	27 (6.3%)
Premature Discontinuation of Study Drug due to AE	16 (3.8%)	13 (3.0%)
Deaths	6 (1.4%)	6 (1.4%)

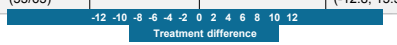
- Solithromycin demonstrated an acceptable safety and tolerability profile, comparable to moxifloxacin
- No SAEs attributed to Solithromycin

RESULTS (CONTINUED)

Treatment Emergent Adverse Events	SOLITHROMYCIN (N=424)	MOXIFLOXACIN (N=432)
Headache	4.5%	2.5%
Diarrhea	4.2%	6.5%*
Nausea	3.5%	3.9%
Emesis	2.4%	2.3%
Dizziness	2.1%	1.6%
ALT** - Grade 3	4.6%	2.1%
Grade 4	0.5%	1.2%

*2 patients, both of whom received moxifloxacin, developed *C. difficile* infection
**No patient in either arm of the study developed treatment emergent elevation of both ALT and bilirubin that met Hy's Law criteria. Observed ALT elevations were reversible and asymptomatic.

	Population	Solithromycin Success Rate %	Moxifloxacin Success Rate %	Favors Moxifloxacin	Favors Solithromycin	Difference (95% CI)
Early Clinical Response	ECR-ITT	78.2 (333/426)	77.9 (338/434)			+0.29 (-5.5, 6.1)
	PORT III/IV	75.9 (164/216)	74.9 (158/211)			+1.04 (-7.6, 9.7)
	Age <65	77.9 (211/271)	80.8 (240/297)			-2.95 (-10.0, 4.1)
	Age 65-74	75.3 (70/93)	73.0 (54/74)			+2.30 (-12.3, 16.9)
	Age ≥ 75	83.9 (52/62)	69.8 (44/63)			+14.03 (-2.1, 30.2)
SFU Success	SFU-ITT	84.5 (360/426)	86.6 (376/434)			-2.13 (-7.1, 2.8)
	PORT III/IV	82.9 (179/216)	83.9 (177/211)			-1.02 (-8.5, 6.5)
	Age <65	82.3 (223/271)	86.9 (258/297)			-4.58 (-10.9, 1.7)
	Age 65-74	90.3 (84/93)	87.8 (65/74)			+2.48 (-8.3, 13.3)
	Age ≥ 75	85.5 (53/62)	84.1 (53/63)			+1.36 (-12.8, 15.5)



DISCUSSION/CONCLUSIONS

Oral solithromycin demonstrated statistical non-inferiority to oral moxifloxacin for the treatment of CABP. Notably, solithromycin ECR and SFU rates were numerically higher than moxifloxacin in the elderly, the patients at greatest risk for CABP. Solithromycin was non-inferior to moxifloxacin on every pre-specified outcome measure. The safety outcomes between solithromycin and moxifloxacin were comparable, although there were more Grade 4 ALT elevations among patients who received moxifloxacin. In addition, there were two cases of *C. difficile* infection, both of which occurred in the moxifloxacin group. A global Phase 3 CABP trial evaluating IV to Oral solithromycin versus IV to Oral moxifloxacin is ongoing.

REFERENCES

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