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SOLITAIRE-IV: Results of a Phase 3 IV to Oral Trial in Adults with Community-Acquired Bacterial Pneumonia Comparing Solithromycin to Moxifloxacin

*TM. File Jr[1], B. Rewerska[2], CM. Tanaseanu[3], V. Mihailovic-Vucinic[4], JR. Gonong[5], BD. Jamieson[6], D. Taylor[6], A. Sheets[6], K. Keedy[6], DW. Oldach[6], P. Fernandes[6]
1. Summa Health System, Akron, OH, USA *presenting author; 2. Diamond Clinic, Krakow, Poland; 3. St. Pantelimon Emergency Clinical Hospital, Bucharest, Romania; 4. Clinical Center of Serbia, Belgrade, Serbia; 5. Lung Center of the Philippines, Manila, Philippines; 6. Cempra, Inc., Chapel Hill, NC, USA

Brian D. Jamieson (corresponding author)
Cempra, Inc., Chapel Hill, NC
bjamieson@cempra.com

Introduction and Purpose

- Community-acquired bacterial pneumonia (CABP) is among the most common and serious infections requiring systemic antibiotic therapy[1-2] and is associated with significant morbidity and mortality, despite advances in therapeutic options[3]. The most common etiologic agents of CABP include *Streptococcus pneumoniae*, *Haemophilus influenzae* (mostly non-type B), *Staphylococcus aureus*, and *Moraxella catarrhalis*, along with atypical pathogens such as *Mycoplasma pneumoniae* and *Legionella pneumophila*.
- Solithromycin is a fourth-generation macrolide, the first fluoroketolide, and is being developed in oral, intravenous, and pediatric suspension formulations for the treatment of CABP. Solithromycin has potent in vitro activity against CABP pathogens, including atypical bacteria and macrolide-resistant strains.
- Unlike current macrolides, solithromycin interacts with three sites on the bacterial ribosome. This allows for increased antibacterial activity, bactericidal activity against key pathogens, and a lower likelihood of resistance development.
- Oral solithromycin demonstrated statistical non-inferiority (10% margin) to oral moxifloxacin in treating adults with CABP in the outpatient setting (SOLITAIRE-Oral trial)[4]. This Phase 3 trial evaluated the safety and efficacy of IV to oral solithromycin compared to IV to oral moxifloxacin (SOLITAIRE-IV trial).

Methods

Study Design/Outline

-Randomized, double-blinded study, with enrollment of 860 patients

-Stratified by geographic region, by history of asthma and/or COPD, and by PORT score/risk class II or III/IV

-PORT II severity pneumonia limited to 25%, while at least 25% of patients were to be PORT IV.

Enrollment Criteria

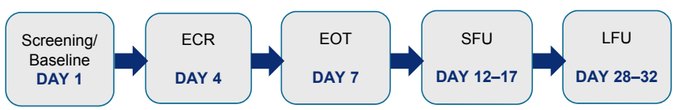
-Male or female ≥18 years of age, with acute onset or worsening of at least 3 of 4 cardinal symptoms of CABP: cough, dyspnea (SOB), chest pain, and sputum production.

-Must have fever or hypothermia and/or physical exam findings consistent with CABP (rales or pulmonary consolidation) and a chest X-ray or CT indicating lobar or patchy parenchymal pulmonary infiltrates. Health-care associated or hospital-acquired pneumonia was exclusionary.

-Up to 25% of patients could have received a single dose of a short-acting antibiotic in the 7 days prior to enrollment.

Visit Schedule

-The schedule of visits is outlined below in the diagram. All patients were followed through the Late Follow-Up (LFU) visit for all cause mortality. ECR = Early Clinical Response, EOT = End of Treatment, SFU = Short-term Follow-up.



Treatment Regimen

-Patients randomized to solithromycin received: 400 mg IV on all IV dosing days, 800 mg PO on the first oral dosing day, and 400 mg PO on subsequent days for total of 7 doses.

-Patients randomized to moxifloxacin received 400 mg IV or PO once-daily

-All patients received IV study drug on Day 1, and could be switched to oral study drug if criteria were met (based on investigator's discretion), or receive IV once-daily for 7 doses.

Microbiological Assessments

-Baseline blood cultures, sputum cultures (including for Legionella spp.), oropharyngeal swabs for *M. pneumoniae* culture, nasopharyngeal swabs for quantitative *S. pneumoniae* PCR, and acute and convalescent serologies.

Analysis Populations

-The ITT (intent-to-treat) population consists of all randomized patients; the mITT (microbiological ITT) population consists of all randomized patients with a baseline pathogen identified; the CE (clinically evaluable) population consists of patients who met inclusion/exclusion criteria without significant protocol deviations; the ME (microbiologically evaluable) population is the intersection of the mITT and CE populations. The modified-CE population was a post-hoc analysis which removed 5 patients without adequate IV study drug supply from the CE population.

Methods (Continued)

Primary and Secondary Objectives

Primary Endpoint: Non-inferiority in the Early Clinical Response (ECR) responder rate in the intent-to-treat (ITT) population [10% margin].

-An ECR responder was defined as an improvement at 72 hrs (-13/+36) in at least two of the following symptoms: chest pain, cough, difficulty with sputum production, and dyspnea, without worsening of any symptom.

Key Secondary Endpoints: 1) Non-inferiority in ECR responder rate in the mITT population [15% margin]; 2) Non-inferiority at ECR with improvement of vital signs in the ITT population; 3) Investigator-assessed clinical success rates at SFU; 4) Safety and tolerability of IV to oral solithromycin compared to IV to oral moxifloxacin; 5) Sustained ECR - defined as response for the primary efficacy outcome that was maintained through SFU, and required chest pain and sputum production to be absent, and cough and dyspnea to be absent or improved since baseline.

Results

A total of 863 patients were enrolled from 147 sites in 22 countries between Jan 2014 and July 2015. Patients were primarily treated as inpatients, with 44% of patients ≥65 years of age and 21% having a history of COPD or asthma. PORT scores were balanced between treatment arms; in the solithromycin treatment arm, 24.4% of patients were PORT II, 45.2% PORT III, 30.0% PORT IV, and 0.5% PORT V.

Safety

- Five (1.2%) solithromycin patients and 7 (1.6%) moxifloxacin patients died. Serious adverse events (SAEs) (6.9% solithromycin; 5.4% moxifloxacin) and study drug discontinuations due to adverse events (AEs) (5.8% solithromycin; 4.0% moxifloxacin) were comparable. Infusion site AEs, mostly mild, were more common in solithromycin patients (31.3% solithromycin; 5.4% moxifloxacin); other AEs were comparable between treatment arms (see **Table 1**). With infusion site AEs included, 51.6% of solithromycin patients and 34.7% of moxifloxacin patients experienced any AE.
- One moxifloxacin patient had *Clostridium difficile* colitis and one moxifloxacin patient had persistent peripheral neuropathy for more than 6 months after two IV doses.

Table 1: Treatment-Emergent Adverse Events (Excluding Infusion Site Events) in ≥3% of Patients in Either Treatment Group (Safety Population)

System Organ Class (Preferred Term)	Solithromycin N, 432 n (%)	Moxifloxacin N, 426 n (%)
Patients with at least 1 TEAE (excluding infusion site events)	149 (34.5)	140 (32.9)
Gastrointestinal disorders	54 (12.5)	42 (9.9)
Diarrhea	19 (4.4)	25 (5.9)
Nausea	14 (3.2)	7 (1.6)
Nervous system disorders	29 (6.7)	25 (5.9)
Headache	15 (3.5)	18 (4.2)

TEAE, treatment-emergent adverse event Note: Patients reporting a particular AE (preferred term) more than once were counted only once by preferred term and SOC.

- More moxifloxacin than solithromycin patients experienced a QTcF change from baseline of >30 msec (25.4% vs. 16.3%) and >60 msec (6.3% vs 4.1%).
- Elevations in alanine aminotransferase (ALT) to >3 × ULN were observed in 9.1% of solithromycin recipients and 3.6% of moxifloxacin recipients. No elevations to >10 × ULN were observed. These elevations were asymptomatic, reversible, and not associated with bilirubin elevation.
- Elevations in ALT and aspartate aminotransferase (AST) among solithromycin recipients generally peaked on Day 4 and were improving on Day 7. These elevations declined with continued dosing or soon after the end of therapy.

Efficacy

- Solithromycin was non-inferior [10% margin] to moxifloxacin in the ITT population in ECR responder rates (79.3%; 79.7%) and SFU success rates (84.6%; 88.6%) (**Table 2**). Solithromycin was also non-inferior [15% margin] to moxifloxacin in the mITT population in ECR rate (80.3%; 79.1%) (**Table 2**).

- In the subset of patients with the highest quartile baseline white blood cell count, C-reactive protein, and procalcitonin (all three parameters), ECR responder rates were 82.9% for solithromycin patients (n=35) and 77.5% for moxifloxacin patients (n=40). At SFU, success rates in this subgroup were 91.4% for solithromycin patients and 85% for moxifloxacin patients.

Results (Continued)

Table 2: Treatment Outcomes: Early Clinical Response and Clinical Success at Short-term Follow-up

Outcome Measure	Solithromycin, % (n/N)	Moxifloxacin, % (n/N)	Delta, % (95% CI)
Early Clinical Response (ECR) Rate			
ITT Population	79.3 (344/434)	79.7 (342/429)	-0.46 (-6.1, 5.2)
mITT Population	80.3 (139/173)	79.1 (121/153)	+1.26 (-8.1, 10.6)
ECR with vital sign normalization (ITT)	42.4 (184/434)	38.9 (167/429)	+3.47 (-3.3, 10.3)
Clinical Success at SFU Visit			
ITT Population	84.6 (367/434)	88.6 (380/429)	-4.02 (-8.8, 0.8)
ITT, PORT III/IV patients	85.7 (281/328)	88.0 (293/333)	-2.32 (-7.8, 2.7)[1]
mITT Population	83.2 (144/173)	88.2 (135/153)	-5.00 (-13.2, 3.2)
Other Outcomes at SFU Visit			
Sustained ECR (ITT)	68.4 (297/434)	67.6 (290/429)	0.8
Sustained ECR (CE Population)	69.6 (272/391)	70.1 (272/388)	-0.5

CE, Clinically Evaluable; CI, Confidence Interval; ITT, Intent to Treat; PORT, Pneumonia Outcomes Research Team; SFU, short-term follow-up.
[1]Adjusted CIs were calculated using the Miettinen and Nurminen method with adjustment for the randomization stratification factors of geographical region and asthma/COPD. Other CIs (without this footnote) presented here were calculated using an unadjusted continuity corrected Z-test.

- Overall, a baseline pathogen was identified in 37.8% of patients (the mITT population). The most common baseline pathogens identified were *S. pneumoniae* (47.5% of mITT), *M. pneumoniae* (21.2%), *H. influenzae* (11.7%), *S. aureus* (11.3%), and *L. pneumophila* (11.0%). By-pathogen outcomes at ECR and SFU are shown in **Table 3**.
- In the ME population, 100% of solithromycin recipients (10/10) with macrolide-resistant pneumococcus were considered successes at SFU by the Investigator.

Table 3: By-pathogen ECR and Investigator-assessed Clinical Success at SFU in the mITT Population

	ECR, n/N (%)		Clinical Success at SFU, n/N (%)	
	Solithromycin	Moxifloxacin	Solithromycin	Moxifloxacin
Gram-positive bacteria				
Streptococcus pneumoniae	62/79 (79%)	64/76 (84%)	65/79 (82%)	66/76 (87%)
MDRSP	10/11 (91%)	10/14 (71%)	9/11 (82%)	12/14 (86%)
Macrolide-resistant	10/12 (83%)	10/14 (71%)	10/12 (83%)	11/14 (79%)
Staphylococcus aureus	15/21 (71%)	13/16 (81%)	17/21 (81%)*	16/16 (100%)
Gram-negative bacteria				
Haemophilus influenzae	14/18 (78%)	17/20 (85%)	15/18 (83%)	19/20 (95%)
Moraxella catarrhalis	4/4 (100%)	3/3 (100%)	4/4 (100%)	3/3 (100%)
Klebsiella pneumoniae	7/9 (78%)	2/3 (67%)	6/9 (67%)	2/3 (67%)
Pseudomonas aeruginosa	4/4 (100%)	5/6 (83%)	4/4 (100%)	5/6 (83%)
Atypical Pathogens				
Mycoplasma pneumoniae	34/39 (87%)	23/30 (77%)	32/39 (82%)	27/30 (90%)
Legionella pneumophila	16/18 (89%)	11/17 (67%)	17/18 (90%)	16/17 (94%)

ECR, early clinical response; MDRSP, multidrug-resistant *Streptococcus pneumoniae*; mITT, microbiological intent-to-treat; SFU, short-term follow-up.
*Of the 4 patients in the solithromycin group positive for *S. aureus* and considered failures at SFU (assessment independent to ECR outcome), 3 patients were ECR responders: 1 patient with macrolide-resistant MRSA but solithromycin MIC >32 µg/mL; 1 patient with macrolide-resistant MSSA (solithromycin MIC 0.03 µg/mL) withdrew consent "for personal reasons" unrelated to an adverse event; 1 patient with MSSA (solithromycin MIC 0.03 µg/mL) worsened on Day 5, and 1 patient with macrolide-resistant MSSA (solithromycin MIC 0.12 µg/mL) also had co-infection with *Serratia marcescens*.

Discussion/Conclusions

IV to oral solithromycin demonstrated statistical non-inferiority to IV to oral moxifloxacin in the ITT population for both ECR responder and SFU success rates, as well as in the mITT population for ECR responder rate. Systemic adverse events (excluding local infusion site reactions) were comparable between solithromycin and moxifloxacin treatment arms. *S. pneumoniae* was the most common pathogen and success rates were comparable, with 100% success against macrolide-resistant pneumococcus at SFU in the ME population. IV to oral solithromycin is a promising potential monotherapy for empiric treatment of adults with CABP.

References

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Disclosures

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