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MAJOR ARTICLE

SOLITAIRE-IV: A Randomized, Double-Blind, Multicenter Study Comparing the Efficacy and Safety of Intravenous-to-Oral Solithromycin to Intravenous-to-Oral Moxifloxacin for Treatment of Community-Acquired Bacterial Pneumonia

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Background. Solithromycin, a novel macrolide antibiotic with both intravenous and oral formulations dosed once daily, has completed 2 global phase 3 trials for treatment of community-acquired bacterial pneumonia.

Methods. A total of 863 adults with community-acquired bacterial pneumonia (Pneumonia Outcomes Research Team [PORT] class II–IV) were randomized 1:1 to receive either intravenous-to-oral solithromycin or moxifloxacin for 7 once-daily doses. All patients received 400 mg intravenously on day 1 and were permitted to switch to oral dosing when clinically indicated. The primary objective was to demonstrate noninferiority (10% margin) of solithromycin to moxifloxacin in achievement of early clinical response (ECR) assessed 3 days after first dose in the intent-to-treat (ITT) population. Secondary endpoints included demonstrating noninferiority in ECR in the microbiological ITT population (micro-ITT) and determination of investigator-assessed success rates at the short-term follow-up (SFU) visit 5–10 days posttherapy.

Results. In the ITT population, 79.3% of solithromycin patients and 79.7% of moxifloxacin patients achieved ECR (treatment difference, −0.46; 95% confidence interval [CI], −6.1 to 5.2). In the micro-ITT population, 80.3% of solithromycin patients and 79.1% of moxifloxacin patients achieved ECR (treatment difference, 1.26; 95% CI, −8.1 to 10.6). In the ITT population, 84.6% of solithromycin patients and 88.6% of moxifloxacin patients achieved clinical success at SFU based on investigator assessment. Mostly mild/moderate infusion events led to higher incidence of adverse events overall in the solithromycin group. Other adverse events were comparable between treatment groups.

Conclusions. Intravenous-to-oral solithromycin was noninferior to intravenous-to-oral moxifloxacin. Solithromycin has potential to provide an intravenous and oral option for monotherapy for community-acquired bacterial pneumonia.

Clinical Trials Registration. NCT01968733.

Keywords. pneumonia; solithromycin; community-acquired; *Streptococcus pneumoniae*; clinical trial.

Community-acquired bacterial pneumonia (CABP) remains a major public health concern, despite advances in patient care [1–4]. Macrolides are well-tolerated, target the causative pathogens of CABP, and have anti-inflammatory effects in addition to antibacterial activity. However, pneumococcal macrolide resistance in developed countries is approaching 50% [5, 6], concern over which has elevated preference for broad-spectrum combination or fluoroquinolone therapies.

Selection of the optimum empiric treatment for CABP remains controversial [7, 8], though first-line options in many guidelines include a respiratory fluoroquinolone or a β-lactam (with or without a macrolide). Respiratory fluoroquinolones affect normal gut flora and increase the risk for *Clostridium difficile* disease [9, 10]. Furthermore, these drugs might select for more broadly cross-resistant enteric bacteria [11, 12] and are associated with unique adverse events, such as neuropathy and tendinopathy [13, 14]. Consequently, use of fluoroquinolones in CABP is restricted in some countries. Alternatively, monotherapy with β-lactams leaves atypical pathogens untreated and combination therapy can be cumbersome, particularly in the outpatient setting. Restoring confidence in macrolide monotherapy with a next-generation macrolide active against resistant strains would be beneficial.

Solithromycin, a novel macrolide and the first fluoroketolide, has been developed as a therapy for CABP. Solithromycin binds

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to the 23S RNA of the 50S ribosomal subunit but interacts with 3 ribosomal sites (vs 1 for older macrolides) providing activity against macrolide-resistant bacteria [15, 16]. The spectrum of activity of solithromycin includes key typical and atypical CABP pathogens [17]. Solithromycin is bactericidal for the majority of pneumococcal isolates [18] and is active against macrolide-resistant strains of pneumococcus and *Mycoplasma pneumoniae* [19–21]. Macrolides have anti-inflammatory properties with solithromycin exhibiting potent effects in vitro and in a mouse model [22], which may be beneficial in treating CABP and, in particular, pneumococcal disease. Oral solithromycin administered as 5 once-daily doses was shown to be noninferior to 7 once-daily doses of oral moxifloxacin in a phase 3, double-blind, randomized study (SOLITAIRE-Oral) [23].

This phase 3 study (SOLITAIRE-IV) was designed to evaluate the efficacy and safety of intravenous (IV)–to-oral solithromycin in comparison with IV-to-oral moxifloxacin in adult patients with CABP.

METHODS

Study Conduct

This randomized, double-blind, active-controlled phase 3 study enrolled patients from January 2014 through July 2015 at 147 sites. All centers received approval to conduct the study from their institutional review boards or ethics committees, and all patients provided written informed consent for participation. The study was conducted in accordance with Good Clinical Practice, including International Council for Harmonisation guidelines, and in general conformity with the most recent version of the Declaration of Helsinki.

Study Population

Eligible patients were ≥18 years of age with clinically and radiographically confirmed pneumonia of Pneumonia Outcomes Research Team (PORT) [24] risk class II to IV (with pneumonia severity index scores from 51 to 130; see Supplementary Materials). Enrollment of PORT II patients was ≤25% of enrollment and PORT IV ≥25% of enrollment. Patients had an acute onset or worsening of at least 3 of 4 cardinal symptoms of CABP (cough, dyspnea, chest pain, or production of purulent sputum) and 1 of the following: fever, hypothermia, or presence of pulmonary rales and/or pulmonary consolidation. Exclusion criteria included prior systemic antibacterial therapy during the prior 7 days, with the exception of a single dose of a short-acting antibiotic prior to randomization in ≤25% of patients. Other major exclusion criteria included hospitalization within 90 days or residence in a nursing home/healthcare facility within 30 days prior to onset of symptoms; immunosuppression; QTcF (QT interval corrected by Fridericia correction formula) >450 ms (amended to 460 ms); current therapy with inducers of cytochrome P450 (CYP) enzymes and certain drugs metabolized by CYP3A4 (see Supplementary Materials).

Randomization and Intervention

Following informed consent, all patients underwent a physical examination, an electrocardiogram, and collection of specimens (Supplementary Materials).

Patients were randomized 1:1 to receive either solithromycin or moxifloxacin (400 mg IV) (Figure 1), with randomization stratified by geographic region, PORT II vs PORT III/IV, and history of asthma or chronic obstructive pulmonary disease (COPD). Patients could complete 7 days of IV therapy or be switched to oral dosing at the investigator's discretion based on defined criteria (Supplementary Materials). The initial oral dose of solithromycin was 800 mg; subsequent oral doses were 400 mg once daily. The oral dose of moxifloxacin was 400 mg daily. IV and oral study drug dosing was blinded.

Study Evaluation Schedule and Endpoints

Patients were evaluated at the following time points: early clinical response (ECR) assessment; end-of-treatment (EOT) visit; short-term follow-up (SFU) visit; and late follow-up (LFU) visit (Figure 1). All-cause mortality (fatalities and patients lost to follow-up) was recorded up to the LFU visit. Safety laboratory tests and electrocardiograms were monitored throughout. An independent data monitoring committee assessed the safety of patients at specified intervals.

All blood and sputum samples (≥10 polymorphonuclear leukocytes/low-power field [LPF] and <10 squamous epithelial cells/LPF required) were cultured at a local microbiological laboratory, with isolates confirmed and antimicrobial sensitivity tested by the central laboratory. Cultures for *Legionella* and *M. pneumoniae* and other microbiological testing are described in the Supplementary Materials.

The primary endpoint was ECR within the intent-to-treat (ITT) population. ECR responder was defined as improvement at 72 [−13/+36] hours after the first dose in at least 2 of the 4 cardinal symptoms and did not receive another antibiotic.

Secondary endpoints were ECR with improvement in vital signs (ITT population); ECR in the microbiological ITT (micro-ITT) population; and investigator's assessment of clinical response at SFU in the ITT and clinically evaluable (CE) SFU populations. Safety and tolerability were compared.

Analysis Populations

The ITT population is all randomized patients; the safety population is all randomized patients who received study drug; the CE population is the subset of ITT patients adherent to key inclusion/exclusion criteria and procedures; the micro-ITT population is all patients in the safety population with a baseline bacterial pathogen (identified by culture, molecular diagnostic assay, antigen detection, or host serologic response). A modified CE-SFU population was determined after unblinding and excludes 5 solithromycin patients, classified as failing treatment, who discontinued study drug solely due to insufficient supply of IV study drug (unrelated to safety or efficacy).

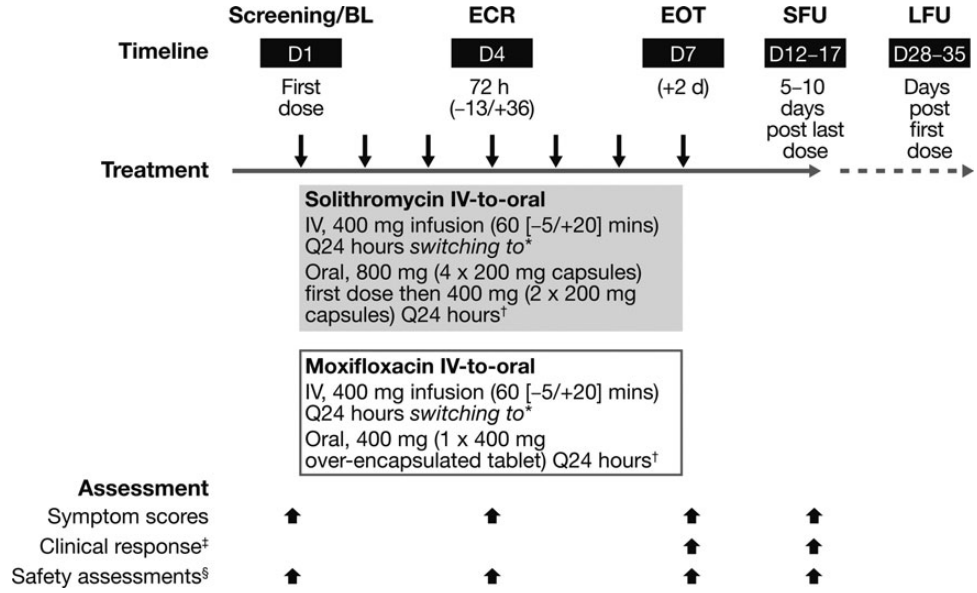

Figure 1. Dosing and evaluation schedule. *Criteria for switching: improved signs and symptoms vs baseline, afebrile, respiratory rate ≤24 bpm, systolic blood pressure ≥90 mm Hg, oxygen saturation ≥90%. †Plus placebo capsules for comparator regimen at each time point. ‡Investigator assessment. §Included electrocardiogram and blood chemistries; adverse events were assessed at every visit. Abbreviations: BL, baseline; ECR, early clinical response; EOT, end of treatment; IV, intravenous; LFU, long-term follow-up; Q24 hours, every 24 hours; SFU, short-term follow up.

Statistical Analysis

The planned sample size of 860 patients ensured sufficient power for the primary efficacy analysis and secondary efficacy analyses of investigator-assessed clinical response at SFU (see Supplementary Materials for assumptions). Noninferiority was concluded if the lower limit of the 2-sided 95% confidence interval (CI) for the difference in ECR was >−10% (using an unadjusted continuity corrected Z-statistic). This noninferiority margin was based on historical data as summarized in the current US Food and Drug Administration CABP guidance [25]. Due to the smaller numbers in the micro-ITT population, a noninferiority margin of 15% was used.

RESULTS

Patient Population

This study enrolled 863 patients from 147 centers in 22 countries: Eastern Europe (n = 449), Europe (n = 132), Asia-Pacific (n = 123), North America (n = 103), South Africa (n = 40), and Latin America (n = 16) (Figure 2). Demographic characteristics were balanced between the treatment groups (Table 1), with >40% of subjects ≥65 years of age. Baseline pathogens were identified in 37.8% of all patients and are described by treatment group in Table 2. Against the most common pathogen, *Streptococcus pneumoniae,* the minimum inhibitory concentration required to inhibit 50% of isolates (MIC_{50})/ minimum inhibitory concentration required to inhibit 90% of isolates (MIC_{90}) was 0.008/0.06 μg/mL for solithromycin vs 0.12/0.12 μg/mL for moxifloxacin (Table 3).

Efficacy Outcomes

The primary endpoint, ECR in the ITT population, was achieved in 79.3% of patients in the solithromycin group and 79.7% of patients in the moxifloxacin group (Table 4). The lower bound of the 95% CI for the treatment difference was greater than −10%, demonstrating noninferiority of IV-to-oral solithromycin to IV-to-oral moxifloxacin.

ECR rates with the inclusion of criteria for improvement from abnormal at baseline to normal at ECR in vital signs were also comparable between groups in the ITT population. Noninferiority of solithromycin to moxifloxacin was also demonstrated in the micro-ITT population and in subgroup analysis of PORT III/IV patients. Comparable ECR rates between treatment groups were demonstrated for subgroups according to sex, age, history of asthma/COPD, prior antibiotic use, PORT risk class, CURB-65 score, and baseline symptoms of CABP (Table 5). Among patients with bacteremia, 9 of 14 solithromycin recipients and 7 of 8 moxifloxacin recipients had ECR.

Clinical success at SFU based on investigator assessment was achieved by 84.6% of solithromycin patients and 88.6% of moxifloxacin patients in the ITT population and 83.2% and 88.2%, respectively, in the micro-ITT population (Table 4). In the CE-SFU population, 86.4% of solithromycin patients and 92.5% of moxifloxacin patients achieved clinical success at SFU based on investigator assessment; however, of the 43 patients excluded from the CE-SFU population in the solithromycin group, 20 had an SFU visit that occurred out-of-window compared with 11 in the moxifloxacin group. Most of these patients had a visit

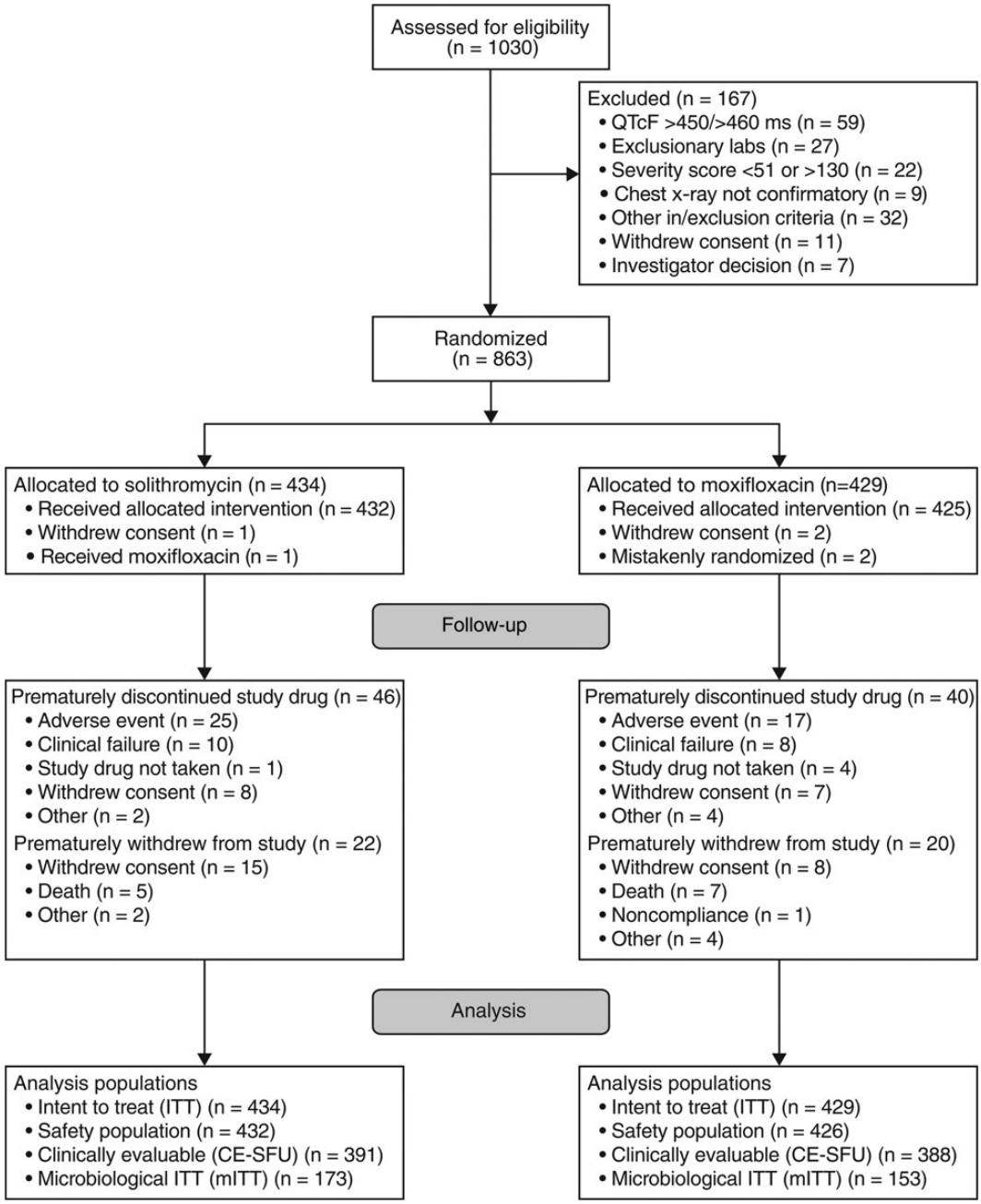

Figure 2. Trial profile. Abbreviations: CE-SFU, clinically evaluable short-term follow-up; ITT, intent-to-treat; mITT, microbiological intent-to-treat; QTcF, QT interval corrected by Fridericia correction formula.

<24 hours outside of the prespecified SFU window and were considered successes. Additionally, 5 patients (see "Analysis Populations") could reasonably be excluded from the CE population, as treatment failure was not due to safety or efficacy. In a post hoc analysis censoring these 5 patients (modified CE-SFU population), the treatment difference was −4.96%, and −3.99% in PORT III/IV/V patients.

Additional prespecified analyses assessed symptom-based outcomes at SFU (Table 4). Sustained ECR was comparable between the groups in both ITT and CE-SFU populations. Similar observations were made based on analysis of the major CABP symptoms. By-pathogen efficacy outcomes for typical and atypical pathogens are listed in Table 6.

Safety and Tolerability

Through LFU, 223 solithromycin patients (51.6%) and 148 moxifloxacin patients (34.7%) experienced at least 1 treatment-emergent adverse event (TEAE). TEAEs leading to premature

Table 1. Baseline Characteristics (Intent-to-Treat Population)

Characteristic	Solithromycin (n = 434)	Moxifloxacin (n = 429)
Age, y		
Mean ± SD	60.5 ± 15.5	61.1 ± 15.1
Median (min, max)	62.0 (19, 94)	63.0 (18, 92)
Age group, y		
<55	136 (31.3)	124 (28.9)
55–64	110 (25.3)	108 (25.2)
65–74	105 (24.2)	120 (28.0)
≥75	83 (19.1)	77 (17.9)
Race		
White	344 (79.3)	334 (77.9)
Black or African American	22 (5.1)	22 (5.1)
Asian	61 (14.1)	63 (14.7)
American Indian or Alaska Native	0	2 (0.5)
Other (mixed)	7 (1.6)	8 (1.9)
Ethnicity		
Hispanic or Latino	18 (4.1)	27 (6.3)
Sex		
Female	222 (51.2)	193 (45.0)
BMI, kg/m^2		
Mean ± SD	26.8 ± 6.2	27.4 ± 6.4
Median (min, max)	26.1 (14.1, 68.4)	26.5 (13.7, 53.1)
History of asthma and/or COPD from IWRS	95 (21.9)	92 (21.4)
PORT score from eCRF		
Mean ± SD	81.8 ± 18.3	82.6 ± 17.4
Median (min, max)	80.0 (51, 133)	81.0 (51, 139)
PORT risk class from eCRF		
II	106 (24.4)	96 (22.4)
III	196 (45.2)	204 (47.6)
IV	130 (30.0)	125 (29.1)
V[a]	2 (0.5)	4 (0.9)
CURB-65[b] score		
0	78 (18.0)	81 (18.9)
1	172 (39.6)	165 (38.5)
2	131 (30.2)	125 (29.1)
3	29 (6.7)	30 (7.0)
4	1 (0.2)	1 (0.2)
Met SIRS criteria[c]	313 (72.1)	294 (68.5)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; eCRF, electronic case report form; IWRS, interactive web response system; PORT, Pneumonia Outcomes Research Team; SD, standard deviation; SIRS, Systemic Inflammatory Response Syndrome.

[a] Six patients were reclassified as PORT risk class V after randomization.

[b] CURB-65: 1 point each is assigned for the findings of confusion, blood urea nitrogen >19 mg/dL, respiratory rate >30 breaths/minute, systolic blood pressure <90 mm Hg or diastolic blood pressure ≤60 mm Hg, and age ≥65 years.

[c] SIRS criteria: defined as ≥2 of the following symptoms at baseline: temperature <36°C or >38°C, heart rate >90 beats/minute, respiratory rate >20 breaths/minute, white blood cell count <4000 cells/μL or >12 000 cells/μL, or immature polymorphonuclear leukocytes >10%.

Table 2. Patients With Pathogens Identified at Baseline from Blood Specimens, Respiratory Specimens, Urinary Antigen Tests, and/or Serology (Microbiological Intent-to-Treat Population)

	Micro-ITT	
Baseline Pathogen	Solithromycin, No. (% of Micro-ITT)[a]	Moxifloxacin, No. (% of Micro-ITT)[a]
Patients with any baseline pathogen, No. (% of ITT)	173 (39.9)	153 (35.7)
Patients with bacteremia[b]	14 (8.1)	8 (5.2)
Gram-positive bacteria	98 (56.6)	88 (57.5)
Any *Streptococcus pneumoniae*	79 (45.7)	76 (49.7)
Positive via urinary antigen	16 (9.2)	10 (6.5)
Positive via respiratory/ blood specimen	65 (37.6)	70 (45.8)
MDRSP[c]	11 (6.4)	13 (8.5)
Macrolide-resistant[c]	12 (6.9)	14 (9.2)
Staphylococcus aureus	21 (12.1)	16 (10.5)
MRSA	1 (0.6)	2 (1.3)
MSSA	20 (11.6)	14 (9.2)
β-hemolytic streptococci	2 (1.2)	1 (0.7)
Nocardia cyriacigeorgica	0	1 (0.7)
Gram-negative bacteria	41 (23.7)	38 (24.8)
Haemophilus influenzae	18 (10.4)	20 (13.1)
Klebsiella pneumoniae	9 (5.2)	3 (2.0)
Pseudomonas aeruginosa	4 (2.3)	6 (3.9)
Moraxella catarrhalis	4 (2.3)	3 (2.0)
Acinetobacter calcoaceticus	1 (0.6)	1 (0.7)
Alcaligenes xylosoxidans	0	1 (0.7)
Escherichia coli	2 (1.2)	1 (0.7)
Haemophilus parainfluenzae	2 (1.2)	2 (1.3)
Pasteurella multocida	1 (0.6)	0
Serratia marcescens	1 (0.6)	1 (0.7)
Atypical pathogens	56 (32.4)	46 (30.1)
Any *Mycoplasma pneumoniae*	39 (22.5)	30 (19.6)
Positive via respiratory specimen	25 (14.5)	25 (16.3)
Macrolide-resistant	1 (0.6)	0
Positive via serology	29 (16.8)	17 (11.1)
Any *Legionella* spp	19 (11.0)	17 (11.1)
Legionella pneumophila	18 (10.4)	17 (11.1)
Positive via serology	18 (10.4)	17 (11.1)
Positive via urinary antigen	1 (0.6)	0
Legionella longbeachae	1 (0.6)	0

Abbreviations: MDRSP, multidrug-resistant *Streptococcus pneumoniae*; micro-ITT, microbiological intent-to-treat; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

[a] Percentages calculated as 100 × (no./No.), where no./No. = number of patients with the specified pathogen/number of patients in the micro-ITT population.

[b] Of the 14 patients in the solithromycin group positive for bacteremia, 3 had *S. aureus*, 7 had *S. pneumoniae*, 2 had *H. influenzae*, 1 had *E. coli*, and 1 had *P. multocida*. Of the 8 patients in the moxifloxacin group, 1 had *S. aureus*, 6 had *S. pneumoniae*, and 1 had *P. aeruginosa* bacteremia.

[c] The overall percentage of MDRSP *S. pneumoniae* isolates was 25.5% and macrolide-resistant *S. pneumoniae* isolates was 26.5% among all isolated pneumococcus.

study drug discontinuation occurred in 5.8% of solithromycin patients and 4.2% of moxifloxacin patients.

Infusion site events (eg, infusion site pain, infusion site phlebitis, infusion site erythema) occurred in 31.3% of solithromycin recipients compared with 5.4% of moxifloxacin recipients (Table 7). Most infusion site events were mild or moderate,

Table 3. Minimum Inhibitory Concentrations for Key Pathogens in the Microbiological Intent-to-Treat Population

Pathogen	N1	MIC_{50}/MIC_{90}, μg/mL[a] Solithromycin	Moxifloxacin
Gram-positive bacteria			
Streptococcus pneumoniae	98	0.008/0.06	0.12/0.12
MDRSP	25	0.03/0.5	0.12/0.12
Macrolide-resistant	26	0.03/0.5	0.12/0.12
Staphylococcus aureus	37	0.06/0.12	0.03/2
MRSA	3	NA (0.06–>32)	NA (0.06–4)
MSSA	34	0.06/0.12	0.03/0.06
Gram-negative bacteria			
Haemophilus influenzae	35	2/2	0.015/0.06
Moraxella catarrhalis	7	NA (0.03–0.25)	NA (0.03–0.12)
Atypical pathogens			
Mycoplasma pneumoniae	26	≤0.000032/≤0.000032	0.125/0.125
Macrolide-resistant[b]	0	NA	NA
Legionella pneumophila	0	NA	NA

For patients with the same pathogen cultured from pleural fluid, bronchoalveolar lavage, blood, and/or sputum, a representative pathogen with the highest MIC to study drug received was selected for analysis; thus, patients were counted only once for that pathogen. MICs from nasopharyngeal swabs were used if MICs from blood or another respiratory specimen were unavailable.

Abbreviations: MDRSP, multidrug-resistant *Streptococcus pneumoniae*; MIC_{50}, minimum inhibitory concentration required to inhibit 50% of isolates; MIC_{90}, minimum inhibitory concentration required to inhibit 90% of isolates; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; N1, number of baseline pathogens with MIC available (treatment groups combined); NA, not applicable.

[a] MIC_{50} and MIC_{90} were derived only if there were ≥10 pathogens of a particular genus and species in each treatment group with baseline MIC data available. For <10 pathogens, the range of MIC values is provided in parentheses.

[b] A 23S RNA point mutation (A2063G) associated with macrolide resistance was detected by quantitative polymerase chain reaction and melting curve analysis of a positive broth culture; however, an isolate could not be recovered for MIC analysis.

Table 4. Treatment Outcomes: Early Clinical Response and Clinical Success at Short-term Follow-up

Outcome Measure	Solithromycin, % (no./No.)	Moxifloxacin, % (no./No.)	Delta, % (95% CI)
ECR rate			
ITT population	79.3 (344/434)	79.7 (342/429)	−0.46 (−6.1 to 5.2)
ITT, PORT III/IV/V patients	77.8 (253/325)	80.7 (260/322)	−2.90 (−9.4 to 3.6)
Micro-ITT population	80.3 (139/173)	79.1 (121/153)	+1.26 (−8.1 to 10.6)
ECR with vital sign normalization (ITT)	42.6 (185/434)	38.9 (167/429)	+3.70 (−3.1 to 10.5)
Clinical success at SFU visit			
ITT population	84.6 (367/434)	88.6 (380/429)	−4.02 (−8.8 to .8)
ITT, PORT III/IV patients	85.7 (281/328)	88.0 (293/333)	−2.32 (−7.8 to 2.7)[a]
Modified CE population	87.6 (338/386)	92.5 (359/388)	−4.96 (−9.4 to −.5)
Modified CE, PORT III/IV patients	88.0 (257/292)	92.0 (276/300)	−3.99 (−9.2 to 1.2)[a]
Symptom-based outcomes at SFU visit			
Sustained ECR[b] (ITT)	68.4 (297/434)	67.6 (290/429)	+0.8
Sustained ECR[b] (CE population)	69.6 (272/391)	70.1 (272/388)	−0.5
Major CABP symptoms[c] success (ITT)	79.7 (346/434)	76.9 (330/429)	+2.8
Major CABP symptoms[c] success (CE population)	81.1 (317/391)	79.9 (310/388)	+1.2

The Modified CE-SFU population was determined after unblinding and excludes 5 solithromycin patients (3 who were PORT class III/IV) who discontinued study drug due to insufficient supply of intravenous study drug. These 5 patients were defined as failing treatment at end of treatment and short-term follow-up due to receipt of nonstudy antibiotics.

Abbreviations: CABP, community acquired bacterial pneumonia; CE, clinically evaluable; CI, confidence interval; ECR, early clinical response; ITT, intent-to-treat; micro-ITT, microbiological intent-to-treat; PORT, Pneumonia Outcomes Research Team; SFU, short-term follow up.

[a] Adjusted CIs were used that were calculated using the Miettinen and Nurminen method with adjustment for the randomization stratification factors of geographical region and asthma/chronic obstructive pulmonary disease.

[b] Sustained ECR was 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.

[c] Major CABP symptoms: success required chest pain and sputum production to be absent, and cough and dyspnea to be absent or improved since baseline.

with study drug discontinuation in 11 patients (10 solithromycin and 1 moxifloxacin). Median duration of IV treatment (3.0 days) and oral treatment (4.0 days) was identical in both treatment arms, and similar percentages of patients remained on IV therapy for 7 days (22.0% solithromycin vs 25.6% moxifloxacin). In the subset of patients who received 5–7 days of IV study drug, no unique TEAEs were noted and the spectrum and incidence of events were comparable to the overall safety population.

Excluding infusion site events, the percentage of patients with TEAEs was similar between groups (Table 8). Systemic TEAEs common to antibiotic trials, such as diarrhea, nausea, and headache, were comparable between treatment arms. One episode of *C. difficile* colitis occurred in the moxifloxacin group, and another moxifloxacin recipient, who received 2 IV doses, discontinued due to peripheral neuropathy (bilateral hand tingling, preferred term of paresthesia) that persisted >6 months after discontinuing study drug. No visual disturbances were reported in solithromycin recipients. Syncope was reported in 1 moxifloxacin recipient and no solithromycin recipients.

The incidence of serious adverse events (SAEs) was comparable between groups (6.9% solithromycin vs 5.4% moxifloxacin), and most commonly was rehospitalization for pneumonia or its complications (acute respiratory failure). SAEs judged by the investigator to be related to study drug were experienced by 2 patients (0.5%; 1 urticaria, 1 anaphylactic reaction) in the solithromycin group and 1 patient (0.2%; anaphylactic reaction) in the moxifloxacin group, all occurring during the initial infusion. There were 12 deaths during the study—5 among solithromycin patients (1.2%) and 7 moxifloxacin patients (1.6%)—all unrelated to study drug. All deaths were considered efficacy failures at all timepoints and were attributable to underlying disease (septic shock, sepsis, respiratory failure, acute respiratory failure, influenza,

Table 5. Treatment Outcomes: Early Clinical Response by Subgroups of Intent-to-Treat Population

Outcome Measure	Solithromycin, % (no./No.)	Moxifloxacin, % (no./No.)	Delta, % (95% CI)
Sex/age			
Female	81.5 (181/222)	79.3 (153/193)	+2.26 (–5.9 to 10.4)
Male	76.9 (163/212)	80.1 (189/236)	–3.20 (–11.3 to 4.9)
<65 y	79.7 (196/246)	81.0 (188/232)	–1.36 (–8.9 to 6.2)
65–74 y	81.0 (85/105)	76.7 (92/120)	+4.29 (–7.3 to 15.8)
≥75 y	75.9 (63/83)	80.5 (62/77)	–4.62 (–18.6 to 9.4)
History			
History of asthma/ COPD	78.9 (75/95)	82.6 (76/92)	–3.66 (–16.0 to 8.7)
Prior antibiotic use	80.4 (82/102)	84.5 (93/110)	–4.15 (–15.3 to 7.0)
PORT risk class			
II	83.0 (88/106)	78.1 (75/96)	+4.89 (–7.0 to 16.8)
III/IV/V	78.0 (256/328)	80.2 (267/333)	–2.13 (–8.6 to 4.4)
CURB-65 score[a]			
0	74.4 (58/78)	72.8 (59/81)	+1.52 (–13.4 to 16.5)
1	80.2 (138/172)	84.2(139/165)	–4.01 (–12.7 to 4.7)
2	80.2 (105/131)	80.8 (101/125)	–0.65 (–11.1 to 9.8)
3	79.3 (23/29)	76.7 (23/30)	+2.64 (–21.9 to 27.2)
4	100.0 (1/1)	100.0 (1/1)	NA
Baseline symptom of CABP			
Cough	79.3 (344/434)	79.9 (342/428)	–0.6
Dyspnea	80.2 (333/415)	80.4 (332/413)	–0.2
Chest pain	80.2 (279/348)	82.7 (282/341)	–2.5
Difficulty with sputum production	80.4 (319/397)	80.9 (313/387)	–0.5
Blood specimen culture			
Bacteremia[b]	64.3 (9/14)	87.5 (7/8)	NA

Difference in clinical response rates (solithromycin minus moxifloxacin); CIs were calculated using an unadjusted continuity corrected Z-test.

Abbreviations: CABP, community-acquired bacterial pneumonia; CI, confidence interval; COPD, chronic obstructive pulmonary disease; NA, not applicable; PORT, Pneumonia Outcomes Research Team.

[a] CURB-65: 1 point each is assigned for the findings of confusion, blood urea nitrogen >19 mg/dL, respiratory rate >30 breaths/minute, systolic blood pressure <90 mm Hg or diastolic blood pressure ≤60 mm Hg, and age ≥65 years.

[b] Of the 5 patients in the solithromycin group considered nonresponders at early clinical response, 2 had *Streptococcus pneumoniae* bacteremia, 2 had *Staphylococcus aureus* bacteremia, and 1 had *Escherichia coli* bacteremia. The 1 moxifloxacin failure had *Pseudomonas aeruginosa* bacteremia.

renal failure acute, adrenal gland cancer) or a catastrophic event (cardiac arrest, myocardial infarction, aspiration, gastric hemorrhage, upper airway obstruction).

Increases of hepatic aminotransferases in both treatment arms were asymptomatic, not associated with bilirubin elevation (except 1 moxifloxacin recipient), and generally resolved with continued study drug administration or soon after EOT (Table 9). Increases in alanine aminotransferase (ALT) to >3 times the upper limit of normal (ULN) were observed in 9.1% of solithromycin recipients and 3.6% of moxifloxacin recipients. Increases in ALT to >5 times the ULN were observed in 3.1% of solithromycin recipients and 0.7% of moxifloxacin recipients. No increases >10 times the ULN were observed. The single patient who experienced a fatal SAE of sepsis in the moxifloxacin group met laboratory criteria for Hy's law on day 7. One 62-year-old man with cirrhosis in the solithromycin group had baseline laboratory values meeting criteria for Hy's law, and liver function tests continually improved during 7 days of therapy. No clinically meaningful differences between treatment groups were observed for other clinical chemistry and hematology parameters.

Overall, mean heart rate similarly decreased from baseline in each treatment group during the study. Mean QTcF values and mean changes from baseline were greater at all time points in the moxifloxacin group (day 4, +12.6 ms; EOT, +9.7 ms) than the solithromycin group (day 4, +7.1 ms; EOT, +6.5 ms). More moxifloxacin-treated patients experienced a QTcF change from baseline of >30 ms (25.4% vs 16.3%) and >60 ms (6.3% vs 4.1%).

DISCUSSION

Intravenous-to-oral solithromycin was noninferior to IV-to-oral moxifloxacin for treatment of CABP. Overall, 79.3% of solithromycin patients and 79.7% of moxifloxacin patients achieved ECR, with comparable response rates observed across subgroups. Solithromycin was noninferior to moxifloxacin for the secondary outcomes of ECR in the micro-ITT population (patients with an identified pathogen) and investigator-determined clinical success rates at SFU in the ITT population in the subgroup of patients with PORT class III/IV/V. With a minor modification of the CE-SFU population (exclusion of 5 patients with logistical study-drug interruption), solithromycin was also noninferior to moxifloxacin at SFU in this population.

The results and response rate for the primary endpoint were consistent with recent findings from the SOLITAIRE-Oral study [23], in which 78.2% of solithromycin patients and 77.9% of moxifloxacin patients achieved ECR.

Other predefined, symptom-based analyses at SFU (sustained ECR outcome, absence of patient-reported major symptoms of CABP) indicated that the therapeutic effect of solithromycin was maintained from ECR to SFU. Moreover, the solithromycin group had a higher percentage of patients with complete resolution of all CABP signs and symptoms than in the moxifloxacin group, both at EOT and at the SFU visit.

With rates of macrolide-resistant *S. pneumoniae* in the United States approaching 50%, new antimicrobial therapies are needed [5]. Of the infections due to macrolide-resistant *S. pneumoniae*, the ECR rate for solithromycin was 83% (10/12 patients) compared with 71% (10/14 patients) for moxifloxacin. For methicillin-sensitive *S. aureus*, the ECR rate for solithromycin and moxifloxacin was 70% (14/20) and 79% (11/14), respectively, with few patients (n = 3) with methicillin-resistant *S. aureus* isolated.

Macrolides as a class, particularly new macrolides such as solithromycin that overcome older macrolide resistance, are attractive

Table 6. Early Clinical Response and Investigator-assessed Clinical Success at Short-term Follow-up in the Microbiological Intent-to-Treat Population

	ECR, no./No. (%)		Clinical Success at SFU, no./No. (%)	
Pathogen	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)[a]	16/16 (100)
MRSA	1/1 (100)	2/2 (100)	0/1 (0)	2/2 (100)
MSSA	14/20 (70)	11/14 (79)	17/20 (85)	14/14 (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)
Atypical pathogens				
Mycoplasma pneumoniae	34/39 (87)	23/30 (77)	32/39 (82)	27/30 (90)
Macrolide-resistant	1/1 (100)	0	1/1 (100)	0
Legionella pneumophila	16/18 (89)	11/17 (67)	17/18 (90)	16/17 (94)

For patients with the same pathogen cultured from pleural fluid, bronchoalveolar lavage, blood, and/or sputum, a representative pathogen with the highest minimum inhibitory concentration (MIC) to study drug received was selected for analysis; thus, patients were counted only once for that pathogen. MICs from nasopharyngeal swabs were used if MICs from blood or another respiratory specimen were unavailable.

Abbreviations: ECR, early clinical response; MDRSP, multidrug-resistant *Streptococcus pneumoniae*; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; SFU, short-term follow-up.

[a] Of the 4 patients in the solithromycin group positive for *S. aureus* and considered to have failed treatment at SFU (assessment independent to ECR outcome), 3 patients had ECR: 1 patient had MRSA and a 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. The other patient with macrolide-resistant MSSA (solithromycin MIC = 0.12 µg/mL) also had coinfection with *Serratia marcescens*.

therapeutic options for CABP due to anti-inflammatory activity through decreased production of inflammatory cytokines [22, 26], and have been shown to decrease morbidity and mortality in retrospective studies [27, 28]. The importance of empiric treatment for atypical pathogens in adults with CABP is underscored by data from this trial. More than 30% of microbial diagnoses in each micro-ITT treatment arm were the "atypical" pathogens, *Legionella* species and *M. pneumoniae* (testing was not performed for *Chlamydophila pneumoniae*). *Mycoplasma pneumoniae* was the second most commonly identified etiologic agent, after *S. pneumoniae*, in this study. A high incidence of

Table 7. Infusion Site Events (Treatment-Emergent Adverse Event) in ≥2% of Patients in Either Treatment Group (Safety Population)

System Organ Class (Preferred Term)	Solithromycin (n = 432)	Moxifloxacin (n = 426)
Patients with at least 1 infusion site event[a]	135 (31.3)	23 (5.4)
General disorders and administration site conditions	128 (29.6)	32 (7.5)
Infusion site pain	45 (10.4)	6 (1.4)
Infusion site phlebitis	43 (10.0)	4 (0.9)
Infusion site erythema	19 (4.4)	2 (0.5)
Infusion site paresthesia	9 (2.1)	0
Infusion site thrombosis	9 (2.1)	7 (1.6)
Injury, poisoning, and procedural complications	31 (7.2)	3 (0.7)
Infusion-related reaction	28 (6.5)	1 (0.2)

Data are presented as No. (%). Patients reporting a particular adverse event (preferred term) more than once were counted only once by preferred term and system organ class.

[a] Preferred terms included catheter site pain, infusion site dermatitis, infusion site erythema, infusion site extravasation, infusion site hematoma, infusion site inflammation, infusion site irritation, infusion site edema, infusion site pain, infusion site paresthesia, infusion site phlebitis, infusion site pruritus, infusion site rash, infusion site reaction, infusion site thrombosis, infusion-related reaction, infusion site cellulitis.

Table 8. Treatment-Emergent Adverse Events (Excluding Infusion Site Events) in ≥2% of Patients in Either Treatment Group (Safety Population)

System Organ Class (Preferred Term)	Solithromycin (n = 432)	Moxifloxacin (n = 426)
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)
Dizziness	11 (2.5)	5 (1.2)
Metabolism and nutrition disorders	17 (3.9)	15 (3.5)
Hypokalemia	11 (2.5)	9 (2.1)
Psychiatric disorders	14 (3.2)	12 (2.8)
Insomnia	9 (2.1)	5 (1.2)
Vascular disorders	12 (2.8)	17 (4.0)
Hypertension	6 (1.4)	10 (2.3)

Data are presented as No. (%). Patients reporting a particular adverse event (preferred term) more than once were counted only once by preferred term and system organ class. Additionally, 2.5% of solithromycin recipients and 1.2% of moxifloxacin recipients had pneumonia reported as serious adverse events due to a requirement for hospitalization.

Abbreviation: TEAE, treatment-emergent adverse event.

Table 9. Mean Change from Baseline for Selected Laboratory Parameters (Safety Population)

	Mean Change from Baseline (SD)	
Parameter	Solithromycin (n = 432)	Moxifloxacin (n = 426)
ALT, U/L		
Day 4	16.0 (43.33)	5.1 (22.31)
EOT	18.4 (37.19)	6.7 (26.36)
SFU	3.0 (24.62)	1.2 (18.32)
AST, U/L		
Day 4	9.6 (46.26)	0.5 (20.44)
EOT	3.1 (26.14)	−1.8 (19.48)
SFU	−6.0 (22.79)	−4.7 (14.98)
ALP, U/L		
Day 4	5.6 (44.10)	−5.0 (23.26)
EOT	7.0 (54.83)	−6.0 (24.20)
SFU	1.8 (42.25)	−2.8 (26.00)
Total bilirubin, μmol/L		
Day 4	−1.77 (5.108)	−2.41 (5.185)
EOT	−2.02 (5.635)	−2.25 (5.912)
SFU	−1.77 (6.016)	−1.49 (5.731)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EOT, end of treatment; SD, standard deviation; SFU, short-term follow-up.

atypical pathogens was also observed in the recent SOLITAIRE-Oral trial [23].

Though patients were enrolled globally, the primary microbiology testing was done at 1 laboratory for consistency. A central microbiology laboratory was used to confirm pathogen identification, perform and read Gram stains, and perform all susceptibility testing. Additionally, all specialty microbiology testing, urine antigen testing, and serological testing were done by centralized laboratories.

The outcomes for gram-negative pathogens were comparable between solithromycin and moxifloxacin. For *Haemophilus influenzae*, 14 of 18 solithromycin patients (78%) had ECR compared with 17 of 20 moxifloxacin patients (85%). Outcomes for *Moraxella catarrhalis* were 100% in both groups (4 solithromycin and 3 moxifloxacin).

Solithromycin administered intravenously for up to 7 days with an optional oral switch was acceptably tolerated. The median duration of IV treatment was 3 days in each group, and similar percentages of patients in each treatment group remained on IV therapy for 7 days. Infusion site events led to the higher incidence of TEAEs overall in the solithromycin group, but other TEAEs were comparable between treatment groups (34.5% vs 32.9%). SAEs and deaths were balanced between treatment groups, with an observed 30-day mortality lower than predicted by PORT risk class [24] or recent studies in hospitalized patients (10%–12%) [29, 30], but consistent with other randomized clinical trials [31].

Local infusion site TEAEs are a well-known class effect of IV macrolides (eg, erythromycin and clarithromycin) and are not commonly observed with IV fluoroquinolones (eg, moxifloxacin and levofloxacin). In this study, local infusion site TEAEs were mostly mild and moderate in severity, though predictably more common in the solithromycin group. Some 2.3% of patients in the solithromycin group withdrew due to infusion site TEAEs, but despite these failures not due to efficacy, solithromycin still met all predefined efficacy noninferiority endpoints. These events are readily identifiable and addressable by clinicians, either by switching to oral administration or discontinuing the infusion.

Hepatic aminotransferase increases did occur, but were asymptomatic, unassociated with increased bilirubin (except for 1 moxifloxacin recipient who met Hy's law criteria), and resolved rapidly. While increases in ALT and aspartate aminotransferase (AST) were more common in the solithromycin recipients, these generally peaked on day 4 and were improving on day 7. Most patients with increased ALT and/or AST continued dosing, and these increases declined with continued dosing or soon after EOT. Mean heart rate decreased with therapy in both treatment arms at a nearly identical rate and extent; however, a lower percentage of solithromycin recipients experienced increases in QTcF.

Strengths of this study include its randomized, double-blind design, low rate of discontinuation, and high rate of microbiological diagnosis. Limitations of this study include the exclusion of immunocompromised patients and patients taking excluded medications (including medications that affect the QT interval), which limits the generalizability of these results, as well as the 30-day follow-up period, considering the longer-term mortality associated with CABP.

Solithromycin was noninferior to moxifloxacin in this registration trial (SOLITAIRE-IV). The potential for both IV and oral formulations with acceptable safety profiles and a targeted spectrum of activity against common respiratory pathogens suggests that solithromycin could be a useful monotherapy for adults with CABP. Clinical evaluation of IV and oral solithromycin in pediatric patients with CABP is ongoing.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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