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Randomized, Double-Blind, Multicenter Phase 2 Study Comparing the Efficacy and Safety of Oral Solithromycin (CEM-101) to Those of Oral Levofloxacin in the Treatment of Patients with Community-Acquired Bacterial Pneumonia

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Solithromycin, a new macrolide, and the first fluoroketolide in clinical development, with activity against macrolide-resistant bacteria, was tested in 132 patients with moderate to moderately severe community-acquired bacterial pneumonia (CABP) in a multicenter, double-blind, randomized phase 2 study. Patients were enrolled and randomized (1:1) to either 800 mg solithromycin orally (PO) on day 1, followed by 400 mg PO daily on days 2 to 5, or 750 mg levofloxacin PO daily on days 1 to 5. Efficacy outcome rates of clinical success at the test-of-cure visit 4 to 11 days after the last dose of study drug were comparable in the intent-to-treat (ITT) (84.6% for solithromycin versus 86.6% for levofloxacin) and microbiological-intent-to-treat (micro-ITT) (77.8% for solithromycin versus 71.4% for levofloxacin) populations. Early response success rates at day 3, defined as improvement in at least two cardinal symptoms of pneumonia, were also comparable (72.3% for solithromycin versus 71.6% for levofloxacin). More patients treated with levofloxacin than with solithromycin experienced treatment-emergent adverse events (TEAEs) during the study (45.6% versus 29.7%). The majority of TEAEs were mild or moderate gastrointestinal symptoms and included nausea (1.6% for solithromycin; 10.3% for levofloxacin), diarrhea (7.8% for solithromycin; 5.9% for levofloxacin), and vomiting (0% for solithromycin; 4.4% for levofloxacin). Six patients, all of whom received levofloxacin, discontinued the study drug due to an adverse event. Solithromycin demonstrated comparable efficacy and favorable safety relative to levofloxacin. These findings support a phase 3 study of solithromycin for the treatment of CABP. (This study has been registered at ClinicalTrials.gov under registration no. NCT01168713.)

Solithromycin is a new macrolide and the first fluoroketolide in clinical development. It is being developed in oral and intravenous (i.v.) formulations for the treatment of patients with community-acquired bacterial pneumonia (CABP). The emergence and spread of respiratory pathogens resistant to currently available antibiotic classes is a global public health concern. Development of new antibiotics to counter these trends is required.

Surveillance studies have documented a dramatic increase in rates of pneumococcal macrolide (i.e., erythromycin, clarithromycin, or azithromycin) resistance, from 17.8% in 1998 to 44.8% in 2011, in the United States, and globally, macrolide resistance was 37.2% in 2003 and 2004 (1, 2). In Asia, this problem has been even more pronounced: in a survey of 2,184 *Streptococcus pneumoniae* isolates collected across 11 countries from 2008 to 2009, 72.7% of the isolates were erythromycin resistant (with rates in individual countries ranging up to 96.4% [China]) (3). Macrolide resistance has been clearly associated with CABP treatment failures (4–7).

The activity of orally available β-lactam antibiotics commonly used in the treatment of mild-to-moderate CABP (e.g., amoxicillin, ampicillin, amoxicillin-clavulanate, and cefuroxime axetil) has also been eroded by increasing resistance (8). β-Lactam antibiotics also lack activity against the atypical pathogens *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae*. The Infectious Diseases Society of America and American Thoracic Society (IDSA-ATS) guidelines (9) for the treatment of CABP recommend use of a regimen that includes activity against *Legionella* for hospitalized patients, thus requiring either use of β-lactam–macrolide combinations or monotherapy with respiratory fluoroquinolones. *M. pneumoniae* has also been increasingly recognized as a significant pathogen in CABP, including among adults (10). Macrolide resistance in *M. pneumoniae* is also an emergent concern (11, 12) and has been associated with outbreaks of severe and prolonged pneumonia (13, 14).

Given these trends in pathogen resistance and the need for regimens for moderate to severe CABP that can be conveniently administered, respiratory fluoroquinolone use in CABP has increased significantly. However, fluoroquinolones are associated with a risk of tendonitis or tendon rupture, have been among the highest-risk classes of antibiotics associated with *Clostridium difficile* colitis (15–17), and are not therapeutic options for pediatric patients because of the potential risk of arthropathy.

Solithromycin has *in vitro* activity against the spectrum of bacteria isolated in CABP, including typical and atypical bacteria. It retains robust activity against macrolide-resistant

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pneumococci (18) and macrolide-resistant *M. pneumoniae* strains (14). Solithromycin was the most potent compound tested against *Mycoplasma* species and against *L. pneumophila* strains (14, 18). Solithromycin is active against most methicillin-susceptible *Staphylococcus aureus* (MSSA) strains (96%), and among methicillin-resistant *S. aureus* (MRSA) strains, those isolated from CABP (CA-MRSA) are susceptible, while MRSA strains with constitutive macrolide resistance are resistant (19, 20). Overall, 69% of 2,200 MRSA isolates collected in the United States and the European Union (EU) in a 2011 surveillance study were susceptible to solithromycin (21).

Macrolides were introduced into antibacterial therapeutics beginning with erythromycin in the early 1950s, which provided activity against *S. pneumoniae* and the atypical bacteria. The second-generation macrolides, clarithromycin and azithromycin, featured improved stability to acid degradation and improved pharmacokinetic (PK) profiles. The ketolides (third-generation macrolides) were subsequently developed to overcome developing macrolide resistance in Gram-positive and atypical respiratory tract pathogens (22). Telithromycin, approved for marketing in the United States in 2004, is the only member of the ketolide subclass to reach clinical use. Although clinical trials demonstrated the efficacy of telithromycin in the treatment of CABP (including against macrolide-resistant *S. pneumoniae*), its clinical use has been limited by safety concerns (23).

Phase 1 studies have demonstrated that solithromycin is safe and well tolerated (24) and that it is differentiated from telithromycin chemically and by its biological activity. Telithromycin has a pyridine moiety in its aryl-alkyl side chain that is unique among macrolides. Pyridine analogs interact with nicotinic acetylcholine (nACh) receptors and telithromycin has been shown to inhibit the activity of nACh receptors. It has been hypothesized that certain adverse events (AEs) that have been observed with telithromycin, including visual disturbance, idiosyncratic liver injury, exacerbation of myasthenia gravis, and sudden loss of consciousness, may be attributable to inhibition of nACh receptors (25).

Solithromycin is being developed in both intravenous and oral formulations for the treatment of CABP, which should allow both oral therapy and i.v.-to-oral step-down therapy in appropriate patients. This paper reports the results of a phase 2, randomized, double-blind, multicenter study comparing the efficacy and safety of oral solithromycin to those of oral levofloxacin in the treatment of patients with CABP (NCT01168713).

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MATERIALS AND METHODS

This randomized, double-blind study compared 5-day dosing regimens of solithromycin and levofloxacin. Patients were enrolled from 30 centers in the United States (26) and Canada (4) from September 2010 through June 2011. The study design and conduct were consistent with the U.S. Food and Drug Administration (FDA) guidance at the time (26), and an exploratory analysis was also conducted using the criteria proposed by the Foundation for the NIH (FNIH) and discussed by the FDA Anti-Infective Drugs Advisory Committee on 3 November 2011 for future CABP trial design (submitted to Docket FDA-2009-D-0136 in August 2011; available at http://www.regulations.gov). All centers received approval to conduct the study from their institutional review boards (IRBs)/ethics committees (ECs), and informed consent forms were signed by all patients prior to any study procedures being performed. Patients were randomized to solithromycin or levofloxacin in a 1:1 ratio after the inclusion and exclusion criteria were verified. Randomization was stratified by age (<50 or ≥ 50 years) and pneumonia severity index (PORT) score. PORT severity scores were categorized as follows: II (51 to 70), III (71 to 90), IVa (91 to 98), or IVb (99 to 105).

Patient population. (i) Inclusion criteria. Male or female patients 18 years of age or older with a PORT risk class of II, III, or IV (pneumonia severity index score, >50 and ≤ 105) were enrolled. Patients had to have at least 3 of the following signs and symptoms: cough with production of purulent sputum or a change in the character of the sputum consistent with a bacterial infection, dyspnea or tachypnea, chest pain due to pneumonia, fever (within 24 h prior to randomization), rales, and/or evidence of pulmonary consolidation. The patient could not have received any prior systemic antibacterial therapy for the current CABP unless there was clinical evidence of treatment failure following at least 48 h of prior therapy and/or isolation of a resistant pathogen while on the prior therapy. The patients must have had a chest radiograph or computed tomography of the thorax within 48 h before the first dose of study drug showing the presence of a new lobar or multilobar infiltrate(s) consistent with acute bacterial pneumonia. In addition, the patients had to be suitable for oral therapy.

(ii) Exclusion criteria. Patients with PORT risk class I (≤ 50) or IV (>105) were excluded, as were patients with ventilator-associated pneumonia. Patients with known anatomical or pathological bronchial obstruction or a history of bronchiectasis or documented stage IV chronic obstructive pulmonary disease (COPD) were excluded. Additional exclusion criteria were other causes of noninfectious pneumonia that caused pulmonary infiltrates; a history of hospitalization within 90 days or residence in a long-term-care facility within 30 days prior to the onset of symptoms; any condition that could possibly affect drug absorption; a heart rate-corrected QT interval (QTc) of >450 ms; current use of drugs known to prolong the QT interval; intolerance of or hypersensitivity to fluoroquinolone or macrolide antibiotics; history of tendinopathy with fluoroquinolone use; known HIV, hepatitis B virus, or hepatitis C virus (HCV) infection; or known history of myasthenia gravis.

Antibacterial treatment and comparator. Levofloxacin, the comparator, is commonly used as oral monotherapy in the United States for the treatment of CABP. Patients received either solithromycin once daily (800 mg on day 1, followed by 400 mg on days 2 to 5) or levofloxacin once daily (750 mg on days 1 to 5). The solithromycin dosing regimen was based on the results of pharmacokinetic-pharmacodynamic (PD) modeling that used plasma and lung epithelial lining fluid (ELF) concentrations from phase 1 studies (27). This regimen resulted in probabilities of target attainment for stasis approaching 100% against *S. pneumoniae* pathogens with MICs of ≤ 1 μg/ml (28).

Study objective. The primary objective was to assess the clinical success rate based on investigator assessment at the test-of-cure (TOC) visit, 4 to 11 days after the last dose of study drug, in the intent-to-treat (ITT) and clinically evaluable (CE) populations. The secondary objectives were to assess the per-patient microbiological success rates in the microbiological ITT (micro-ITT) and microbiologically evaluable (ME) populations and to assess the safety and tolerability of both study drugs. In addition, a *post hoc* analysis of the early clinical response on day 3 consistent with the newly defined FDA and FNIH proposed primary endpoints of early clinical response was also performed.

Analysis populations. The ITT population consisted of all randomized patients. The CE population was the subset of the ITT population who adhered to the protocol and received ≥ 2 doses of the study drug during a 48-hour period if the patient was a clinical failure (unless the patient discontinued the study drug due to an AE or died) or ≥ 4 doses of the study drug if the patient was a clinical success. The safety population consisted of all randomized patients who received at least one capsule of the study drug. The micro-ITT population consisted of all patients in the

ITT population who received any amount of the study drug and who had a baseline bacterial pathogen known to cause CABP. The ME population was the subset of the CE population who had a baseline CABP pathogen. Baseline bacterial pathogens were identified by blood culture, by suitable respiratory specimen culture, by urinary antigen test, or by serologic response.

Clinical efficacy evaluation. The investigator-assessed clinical outcome at end of treatment (EOT) and TOC. Co-primary efficacy outcome measures were rates of investigator-assessed clinical success at TOC in the ITT and CE populations. Patients were classified as a clinical success at TOC if they had complete or nearly complete resolution of disease-specific signs and symptoms present at enrollment; no new symptoms or complications attributable to CABP; and radiographic resolution, improvement, or stability and received at least 4 days of study drug. Secondary efficacy outcome measures were by patient microbiological response in the micro-ITT and ME populations at TOC. Early clinical response in the ITT population at day 3 was assessed programmatically through analysis of patient-reported symptoms and vital signs. To be considered a success at day 3 using the FNIH criteria, patients had to report improvement (on a scale ranging from absent through mild and moderate to severe) in at least two cardinal symptoms (cough, chest pain, shortness of breath, and sputum production) without worsening in any of these four symptoms. The numbers and percentages of patients determined to be an early clinical success at day 3 were tabulated by treatment group for patients in the ITT population.

Late follow-up. The late follow-up (LFU) visit was conducted as an office visit or by telephone contact or other interactive technology 30 to 35 days after the first dose of the study drug.

Microbiological assessment. All reasonable efforts to obtain a respiratory sample for culture and Gram stain were made before the first dose of the study drug. Subsequent respiratory samples for culture and Gram stain were obtained, if possible, at any point if clinically indicated or if the patient was considered a clinical failure. Microscopic examination of the Gram-stained respiratory secretions was done to exhibit <10 squamous epithelial cells (SECs) and >25 polymorphonuclear leukocytes (PMNs) per low-power field (lpf) at $\times 100$ magnification to be suitable for culture for bacterial pathogens. Blood cultures were obtained prior to the first dose of study drug and if positive were to be repeated until negative. Isolates identified at the local laboratories were to be shipped to the central microbiology laboratory (Eurofins Medinet, Chantilly, VA) for identification and susceptibility testing. All cultures that yielded a bacterial respiratory isolate were identified to genus and species levels. Urinary antigen tests for *S. pneumoniae* and *L. pneumophila* (BinaxNOW immunochromatographic assay; Alere, Waltham, MA) were performed at baseline, and serology tests for *M. pneumoniae* and *C. pneumoniae* (Immuno-Biological Laboratories [Minneapolis, MN] enzyme immunometric assay) were performed at baseline and TOC following the manufacturer's instructions. A high titer of IgM antibodies were considered indicative of infection. The following pathogens were used to determine the microbiological responses in the study: the typical bacterial pathogens *S. pneumoniae*, *Haemophilus influenzae*, *S. aureus*, *Klebsiella pneumoniae*, and *Moraxella catarrhalis* and the atypical bacterial pathogens *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila.* The causative pathogen was identified by isolation from a baseline specimen (either a respiratory specimen or blood) or by urinary antigen (*S. pneumoniae* and *L. pneumophila*) or serology (*C. pneumoniae* and *M. pneumoniae*).

Susceptibility criteria. *S. pneumoniae* and *S. aureus* were considered susceptible to solithromycin at MICs of ≤ 1 μg/ml, intermediate at an MIC of 2 μg/ml, and resistant at MICs of ≥ 4 μg/ml. *H. influenzae* and *Haemophilus parainfluenzae* were considered susceptible to solithromycin at MICs of ≤ 4 μg/ml, intermediate at an MIC of 8 μg/ml, and resistant at MICs of ≥ 16 μg/ml. As with other macrolides, including telithromycin, higher breakpoints were assigned to *Haemophilus* spp. The MIC cutoffs for susceptibility to levofloxacin were based on the Clinical and Laboratory Standards Institute (CLSI) document M100-S21.

Safety. All safety analyses were conducted in the safety population. Safety was assessed by analysis of the occurrence of AEs (coded using the Medical Dictionary for Regulatory Activities [MedDRA] version 13.0), as well as by adverse changes in laboratory evaluations (chemistry, hematology, coagulation, and urinalysis), electrocardiograph (ECG) parameters, vital signs, and physical examinations.

Clinical laboratory evaluations. Laboratory values were graded for selected chemistry and hematology parameter values, and changes from baseline at day 3, EOT, and TOC were recorded. A sparse sampling of blood samples was taken for plasma pharmacokinetic analysis of solithromycin.

Vital signs and ECG parameters. Measurements of vital signs, including heart rate, blood pressure, temperature, and respiratory rate, were recorded at baseline, on day 3, at EOT, and at TOC. Descriptive statistics for the RR interval, PR interval, QRS interval, QT interval, QT interval corrected with Bazett (QTcB), and QT interval corrected with Fridericia (QTcF), and the changes from baseline on day 3 and at EOT were summarized by treatment group.

Statistical methods. This phase 2 trial was not powered for inferential statistical analysis. With an overall sample size of 150 patients (75 per treatment group), and assuming an evaluability rate of 80%, approximately 60 patients were expected to be in each treatment group in the CE population. Assuming a 90% clinical success rate, the sample size of 60 patients would yield a 95% confidence interval (CI) around the clinical success rate of 74.49% to 96.24%. Two-sided exact 95% CIs were calculated for the point estimates of the proportion of patients with a clinical success and a microbiological success for solithromycin and levofloxacin using the Clopper-Pearson method.

Data-monitoring committee. An independent data-monitoring committee (DMC) reviewed safety data during the study. Two DMC meetings were held during the study (the first included the first 30 patients, and the second included 74 patients). The DMC recommended continued conduct of the trial following each review.

RESULTS

Study population and disposition of patients. Patients were enrolled from 26 centers in the United States and 4 centers in Canada. A total of 132 patients were randomized and received at least 1 dose of the study drug. Sixty-five patients were randomized to solithromycin (64 received solithromycin), and 67 were randomized to levofloxacin (68 received levofloxacin). One patient randomized to solithromycin was erroneously dispensed levofloxacin. There were 85% and 87% clinically evaluable patients in the solithromycin and levofloxacin groups, respectively, with 10 solithromycin recipients and 9 levofloxacin recipients excluded (the majority [15 patients] for chest X rays not read as pneumonia; other reasons included PORT class I classification, receiving another antibacterial, receiving the wrong study treatment, and missing the EOT visit); 24% of the patients had a microbiological diagnosis of a presumptive CABP pathogen.

Demographic and selected baseline characteristics are presented in Table 1. Of the 132 patients, 67 (50.8%) were males and 109 (82.6%) were white, and the mean age was 55.6 years (range, 18 to 87 years). More females received solithromycin (56.9% versus 41.8%), and more patients with respiratory comorbidities (COPD and asthma) received solithromycin. The two treatment groups were otherwise comparable in demographic profiles and baseline characteristics.

Baseline signs and symptoms of CABP. Baseline assessments of clinical signs and symptoms of CABP for the ITT and CE populations are presented in Table 2 and were largely similar in the two treatment groups. However, more ITT patients in the solithromycin group had severe cough (43.1% versus 29.9%) and

TABLE 1 Demographic and baseline characteristics

Characteristic [statistic][a]	ITT population		CE population	
	Solithromycin 800/400 mg ($N = 65$)	Levofloxacin 750 mg ($N = 67$)	Solithromycin 800/400 mg ($N = 55$)	Levofloxacin 750 mg ($N = 58$)
Patients in each country [*n* (%)]				
United States	63 (96.9)	63 (94.0)	54 (98.2)	54 (93.1)
Canada	2 (3.1)	4 (6.0)	1 (1.8)	4 (6.9)
Age (yr)				
Mean ± SD	56.0 ± 13.0	55.2 ± 14.1	56.5 ± 13.2	54.8 ± 14.4
Range	25–87	18–79	25–87	18–79
≥65 [*n* (%)]	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)
American Indian or Alaskan Native	1 (1.5)	0 (0.0)	1 (1.8)	0 (0.0)
Native Hawaiian/other Pacific Islander	1 (1.5)	0 (0.0)	1 (1.8)	0 (0.0)
Other	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.7)
Ethnicity [*n* (%)]				
Non-Hispanic or Latino	54 (83.1)	56 (83.6)	46 (83.6)	48 (82.8)
Hispanic or Latino	11 (16.9)	11 (16.4)	9 (16.4)	10 (17.2)
Gender [*n* (%)]				
Male	28 (43.1)	39 (58.2)	25 (45.5)	34 (58.6)
Female	37 (56.9)	28 (41.8)	30 (54.5)	24 (41.4)
BMI[b] (kg/m^2)				
Mean ± SD	30.4 ± 7.5	28.6 ± 6.6	30.5 ± 7.3	27.9 ± 6.1
Range	14.1, 64.5	15.5, 52.6	14.1, 64.5	15.5, 46.2
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) (IVa + IVb)	4 (6.2)	2 (3.0)	4 (7.3)	1 (1.7)
IVa (91–98)	3 (4.6)	1 (1.5)	3 (5.5)	0 (0.0)
IVb (99–105)	1 (1.5)	1 (1.5)	1 (1.8)	1 (1.7)
Enrolled as a prior treatment failure [*n* (%)]	6 (9.2)	4 (6.0)	6 (10.9)	4 (6.9)

[a] *n*, number of patients with characteristic; *N*, number of patients in the specified population; %, 100 × (*n*/*N*).
[b] BMI, body mass index.

moderate or severe dyspnea (70.1% versus 56.7%) than in the levofloxacin group at baseline, and more patients in the levofloxacin group had moderate or severe chest pain due to pneumonia (64.2% versus 50.8%) than in the solithromycin group.

Chest radiographs. The majority of patients (99%) enrolled in the study were enrolled as outpatients. Baseline chest radiographs were initially interpreted by the investigator and subsequently reviewed and read by a radiologist. The majority of patients had a pulmonary infiltrate in 1 lobe (>60%). Fifteen (11.4%) patients were excluded from the CE population, as the radiologist's reading did not confirm the investigator's finding of an infiltrate consistent with pneumonia.

Medical history. In the ITT population, 60.0% of the patients in the solithromycin treatment group and 50.7% of patients in the levofloxacin group had a history of medical comorbidity (Table 3). The most common comorbidities were COPD, diabetes mellitus, and asthma. In both the ITT and CE populations, COPD and asthma were more frequent comorbidities in patients in the solithromycin group than in the levofloxacin group (COPD, 24.6% versus 16.4%, respectively, and asthma, 23.1% versus 16.4%, respectively).

Baseline microbiology. There were 32 patients (24.2%) with a microbiological diagnosis consistent with CABP. In the ITT population, baseline respiratory specimens were collected for 83.1% of patients in the solithromycin group and 85.1% of patients in the levofloxacin group. Baseline Gram stain results were available for 83.1% and 83.6% of patients in the solithromycin and levofloxacin groups, respectively. Sputum Gram stains showed <10 SECs/lpf for 48 (88.9%) and 50 (89.3%) patients in the solithromycin and levofloxacin groups, respectively, and >10 PMNs/lpf for 27 (50.0%) and 27 (48.2%) patients. Microbial isolates are presented here regardless of Gram stain results.

TABLE 2 Baseline assessments of clinical signs and symptoms of CABP

Sign/symptom present at baseline	ITT population		CE population	
	Solithromycin 800/400 mg ($N = 65$)	Levofloxacin 750 mg ($N = 67$)	Solithromycin 800/400 mg ($N = 55$)	Levofloxacin 750 mg ($N = 58$)
Patients with ≥3 signs/symptoms of CABP[a] [*n* (%)][b]	65 (100.0)	66 (98.5)	55 (100.0)	57 (98.3)
Fever[c] [*n* (%)]	26 (40.0)	30 (44.8)	21 (38.2)	27 (46.6)
Abnormal WBC[d] [*n* (%)]	185 (27.7)	21 (31.3)	15 (27.3)	19 (32.8)
Cough [*n* (%)]				
Mild	3 (4.6)	12 (17.9)	3 (5.5)	10 (17.2)
Moderate	33 (50.8)	35 (52.2)	27 (49.1)	28 (48.3)
Severe	28 (43.1)	20 (29.9)	24 (43.6)	20 (34.5)
Dyspnea [*n* (%)]				
Mild	16 (24.6)	20 (29.9)	11 (20.0)	17 (29.3)
Moderate	40 (61.5)	33 (49.3)	36 (65.5)	30 (51.7)
Severe	6 (9.2)	5 (7.5)	5 (9.1)	3 (5.2)
Chest pain due to pneumonia [*n* (%)]				
Mild	16 (24.6)	13 (19.4)	12 (21.8)	10 (17.2)
Moderate	19 (29.2)	27 (40.3)	16 (29.1)	23 (39.7)
Severe	14 (21.5)	16 (23.9)	12 (21.8)	16 (27.6)
Sputum production [*n* (%)]				
Mild	20 (30.8)	22 (32.8)	19 (34.5)	19 (32.8)
Moderate	25 (38.5)	30 (44.8)	20 (36.4)	24 (41.4)
Severe	14 (21.5)	10 (14.9)	11 (20.0)	10 (17.2)

[a] ≥3 of the following: cough with sputum production; dyspnea or tachypnea; chest pain due to pneumonia; fever; rales, rhonchi, dullness on percussion, bronchial breath sounds, wheezing, or egophony; abnormal white blood cell (WBC) count.
[b] *n*, number of patients with sign/symptom; *N*, number of patients with an assessment of the specified sign or symptom at baseline; %, 100 × (*n*/*N*).
[c] Temperature of >38°C (100.4°F), tympanic of >38.5°C (101.2°F), axillary of >38.1°C (100.6°F), or rectal/core of >39°C (102.2°F).
[d] WBC count of <3,000 cells/mm^3 or >11,000 cells/mm^3.

Among patients with a microbial isolate (the micro-ITT population), the most common baseline pathogen was *S. pneumoniae* (solithromycin, 7/18 [38.9%]; levofloxacin, 3/14 [21.4%]). *S. aureus* was identified in 1/18 (5.6%) patients in the solithromycin group and in 3/14 (21.4%) patients in the levofloxacin group. *H. influenzae* was identified in 3/18 (16.7%) patients in the solithromycin group and in 4/14 (28.6%) patients in the levofloxacin group.

***In vitro* susceptibilities of baseline pathogens isolated.** All baseline pathogens were susceptible to both study drugs, except for 2 isolates of *K. pneumoniae*, which were susceptible to levofloxacin and resistant to solithromycin. Three multidrug-resistant *S. pneumoniae* (MDRSP) strains (azithromycin MICs, >128 μg/ml [2 strains] and 16 μg/ml) were isolated from patients (one in the levofloxacin arm and 2 in the solithromycin arm). All 3 strains were susceptible to both solithromycin and levofloxacin. One of these azithromycin-resistant strains was also resistant to tetracycline, another was resistant to trimethoprim-sulfamethoxazole, and the third was resistant to both tetracycline and trimethoprim-sulfamethoxazole.

Prior and concomitant medications. Patients were not allowed to receive any prior systemic antibacterial therapy for the current CABP unless there was clinical evidence of treatment failure after receiving at least 48 h of a prior antibiotic. In the ITT population, 7 (10.8%) patients in the solithromycin group and 4 (6.0%) patients in the levofloxacin group received antibacterial

TABLE 3 Selected baseline comorbidities

Comorbidity	ITT population [*n* (%)][a]		CE population [*n* (%)]	
	Solithromycin 800/400 mg ($N = 65$)	Levofloxacin 750 mg ($N = 67$)	Solithromycin 800/400 mg ($N = 55$)	Levofloxacin 750 mg ($N = 58$)
Any	39 (60.0)	34 (50.7)	34 (61.8)	30 (51.7)
COPD (emphysema, chronic bronchitis)	16 (24.6)	11 (16.4)	14 (25.5)	9 (15.5)
Diabetes mellitus	15 (23.1)	15 (22.4)	13 (23.6)	14 (24.1)
Asthma (reactive airway disease)	15 (23.1)	11 (16.4)	14 (25.5)	10 (17.2)
Hepatitis C	3 (4.6)	1 (1.5)	3 (5.5)	1 (1.7)
Other chronic pulmonary disease	1 (1.5)	1 (1.5)	1 (1.8)	1 (1.7)

[a] *n*, number of patients with selected comorbidities; *N*, total number of patients in the population; %, 100 × (*n*/*N*).

TABLE 4 Efficacy summary: clinical success at TOC

Population	Solithromycin 800/400 mg		Levofloxacin 750 mg	
	n/*N* (%)[a]	95% CI	*n*/*N* (%)	95% CI
Co-primary efficacy variable				
ITT	55/65 (84.6)	73.5–92.4	58/67 (86.6)	76.0–93.7
CE	46/55 (83.6)	71.2–92.2	54/58 (93.1)	83.3–98.1
Micro-ITT	14/18 (77.8)	52.4–93.6	10/14 (71.4)	41.9–91.6
ME	12/15 (80.0)	51.9–95.7	10/13 (76.9)	46.2–95.0
Day 3, ITT (according to Biomarkers Consortium criteria)	47/65 (72.3)	59.8–82.7	48/67 (71.6)	59.3–82.0

[a] *n*, number of patients with clinical success; *N*, number of patients in the specified population; %, 100 × (*n*/*N*).

medications within 30 days prior to the first dose of the study drug. Of these, 6 (9.2%) patients in the solithromycin group and 4 (6.0%) patients in the levofloxacin group were enrolled as prior treatment failures. Concomitant medications were defined as medications taken at any time from the first day of study drug administration through the last day of the study. Concomitant medications other than systemic antibacterials were taken by ≥10.0% of patients in either treatment group during the study, with acetaminophen being the most common concomitant medication. Patients were not allowed to receive another systemic antibacterial with likely or documented activity against CABP pathogens before the TOC assessment, unless the patient was a clinical failure.

Efficacy results: clinical response at TOC. In the ITT population, clinical success was observed in 55 (84.6%) patients randomized to receive solithromycin and 58 (86.6%) patients randomized to receive levofloxacin. In the CE population, clinical success was observed in 46 (83.6%) patients who received solithromycin and 54 (93.1%) patients who received levofloxacin.

Secondary outcomes included clinical response for the micro-ITT and ME populations. In the micro-ITT population, clinical success was observed for 14/18 (77.8%) patients randomized to receive solithromycin and for 10/14 (71.4%) patients randomized to receive levofloxacin. In the ME population, clinical success was observed for 12/15 (80.0%) patients who received solithromycin and for 10/13 (76.9%) patients who received levofloxacin. Clinical success rates at TOC by treatment group in the various analysis populations are shown in Table 4.

Early clinical response rates in the ITT population, from a *post hoc* analysis at day 3 by the FNIH criteria, were comparable in the solithromycin (72.3%) and levofloxacin (71.6%) treatment groups.

Clinical success rates among patients in the ITT population with baseline procalcitonin (PCT) levels of ≥0.2 ng/ml and ≥0.5 ng/ml were comparable in the solithromycin (88.0% and 93.3%, respectively) and levofloxacin (88.9% and 92.3%, respectively) treatment groups.

In summary, oral solithromycin showed efficacy comparable to that of levofloxacin in the treatment of CABP in this phase 2 study of 132 patients.

Clinical success at TOC by baseline pathogen. Clinical success rates at TOC by baseline pathogen for the micro-ITT and ME populations are presented in Table 5. Ten patients in the micro-ITT population had an *S. pneumoniae* infection at baseline: 7 (38.9%) in the solithromycin group and 3 (21.4%) in the levofloxacin group. *S. pneumoniae* was isolated at baseline from sputum cultures in 7 patients and blood cultures in 2 patients. Four patients had a detectable pneumococcal capsular antigen in urine. The overall number of patients with the diagnosis of pneumococcal infection is small, and thus, outcome rates shift significantly with minor adjustments.

TABLE 5 Clinical success at TOC by baseline pathogen

Pathogen	Micro-ITT population [*n* (%)][a]		ME population [*n* (%)]	
	Solithromycin 800/400 mg (*N* = 18)	Levofloxacin 750 mg (*N* = 14)	Solithromycin 800/400 mg (*N* = 15)	Levofloxacin 750 mg (*N* = 13)
Gram-positive aerobes				
S. aureus	1/1 (100.0)	3/3 (100.0)	1/1 (100.0)	3/3 (100.0)
S. pneumoniae	4/7 (57.1)	2/3 (66.7)	3/5 (60.0)	2/3 (66.7)
Streptococcus acidominimus	–[b]	0/1 (0.0)	–	0/1 (0.0)
Streptococcus pyogenes	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Streptococcus spp.	1/1 (100.0)	–	1/1 (100.0)	–
Gram-negative aerobes				
H. influenzae	2/3 (66.7)	3/4 (75.0)	1/2 (50.0)	3/4 (75.0)
H. parainfluenzae	1/1 (100.0)	–	1/1 (100.0)	–
Klebsiella oxytoca	1/1 (100.0)	–	1/1 (100.0)	–
K. pneumoniae	–	1/2 (50.0)	–	1/2 (50.0)
M. catarrhalis	1/1 (100.0)	0/1 (0.0)	1/1 (100.0)	–
Pseudomonas aeruginosa	–	1/1 (100.0)	–	1/1 (100.0)
Atypical pathogens				
C. pneumoniae	1/1 (100.0)	0/1 (0.0)	1/1 (100.0)	0/1 (0.0)
M. pneumoniae	1/1 (100.0)	–	1/1 (100.0)	–

[a] *n*, number of patients with clinical success; *N*, number of patients with the specified baseline pathogen; %, 100 × (*n*/*N*).
[b] –, pathogen not isolated.

For micro-ITT patients with *S. pneumoniae*, 4/7 (57.1%) in the solithromycin group had a response of clinical success at TOC. Of the 3 failures, one patient was considered a failure in this analysis due to a missed EOT visit. However, the patient was considered a success at TOC, and if included, 5/7 patients (71.4%) with *S. pneumoniae* in the solithromycin group can be considered to have had a response of clinical success.

In the levofloxacin group, 2/3 (66.7%) micro-ITT patients with *S. pneumoniae* infection had a response of clinical success at TOC. The 1 treatment failure was discovered to be HIV infected after randomization and had both *S. pneumoniae* and *H. influenzae* isolated at baseline from sputum. His symptoms recurred following completion of study drug dosing; therefore, he was considered a treatment failure at TOC.

Seven patients had *H. influenzae* isolated from sputum culture, 3 in the solithromycin group and 4 in the levofloxacin group. Two (66.7%) patients in the solithromycin group and 3 (75%) patients in the levofloxacin group had a response of clinical success. The treatment failure in the solithromycin group was a 58-year-old male with asthma and a low baseline PCT whose symptoms did not resolve during study drug treatment and worsened off treatment, requiring additional antibiotics. His underlying asthma likely contributed to the persistence of his symptoms. The patient with *H. influenzae* in the levofloxacin group who was a treatment failure was the patient with HIV infection.

Pharmacokinetic parameters in CABP patients. Sparse PK sampling was performed on a subset of patients, and these data were analyzed using a population PK model developed with data obtained from multiple phase 1 studies in healthy subjects (24). When phase 1 and phase 2 data were analyzed separately, the results of the analysis with the limited PK data from this phase 2 study showed no remarkable differences in parameter estimates by study phase, indicating that the population PK model for dose selection was appropriate (28).

Safety and tolerability. Sixty-four patients received solithromycin, and 68 received levofloxacin. A higher proportion of patients in the solithromycin group (96.9%) received 5 days of study drug than in the levofloxacin group (86.8%), as 6 patients in the levofloxacin group discontinued the study drug due to AEs. One levofloxacin-treated patient (0.8%) withdrew from the study due to fatal pulmonary embolism, and 6 (4.5%) levofloxacin-treated patients discontinued study drug dosing due to AEs. The treatment-related AEs are summarized in Table 6.

No patient receiving solithromycin died or discontinued study drug dosing due to an AE. Thirty-one (45.6%) patients who received levofloxacin reported at least 1 AE versus 19 (29.7%) patients who received solithromycin. The majority of AEs were mild or moderate in severity. The most frequently reported AEs were diarrhea (5.9% for levofloxacin; 7.8% for solithromycin), nausea (10.3% for levofloxacin; 1.6% for solithromycin), and vomiting (4.4% for levofloxacin; 0.0% for solithromycin). Most AEs considered by investigators to be treatment related were associated with gastrointestinal (GI) disorders and were reported in 10.3% and 7.8% of patients in the levofloxacin and solithromycin groups, respectively.

Two patients who received solithromycin and 6 patients who received levofloxacin experienced at least 1 nonfatal serious adverse event (SAE) during the study. None of the SAEs in the solithromycin group and 2 in the levofloxacin group (convulsions and hyponatremia, occurring in a single patient) were considered by the investigator to be related to the study drug.

TABLE 6 Summary of treatment-related AEs

System organ class preferred term[a]	Safety population [*n* (%)][b]	
	Solithromycin 800/400 mg (*N* = 64)	Levofloxacin 750 mg (*N* = 68)
Patients with at least 1 TEAE considered related to study drug	7 (10.9)	13 (19.1)
Cardiac disorders	0 (0.0)	2 (2.9)
Bradycardia	0 (0.0)	1 (1.5)
Palpitations	0 (0.0)	1 (1.5)
Gastrointestinal disorders	5 (7.8)	7 (10.3)
Abdominal discomfort	0 (0.0)	1 (1.5)
Constipation	0 (0.0)	1 (1.5)
Diarrhea	3 (4.7)	2 (2.9)
Flatulence	1 (1.6)	1 (1.5)
Nausea	1 (1.6)	3 (4.4)
Investigations	1 (1.6)	1 (1.5)
ALT increased	0 (0.0)	1 (1.5)
AST increased	0 (0.0)	1 (1.5)
Blood CPK increased	1 (1.6)	0 (0.0)
GGT increased	0 (0.0)	1 (1.5)
Metabolism and nutrition disorders	1 (1.6)	1 (1.5)
Hyponatremia	1 (1.6)	1 (1.5)
Nervous system disorders	0 (0.0)	3 (4.4)
Convulsions	0 (0.0)	1 (1.5)
Dysgeusia	0 (0.0)	1 (1.5)
Headache	0 (0.0)	1 (1.5)
Hypoaesthesia	0 (0.0)	1 (1.5)
Psychiatric disorders	0 (0.0)	1 (1.5)
Hallucination, visual	0 (0.0)	1 (1.5)
Insomnia	0 (0.0)	1 (1.5)
Nightmares	0 (0.0)	1 (1.5)

[a] CPK, creatine phosphokinase; GGT, gamma-glutamyltransferase.
[b] *n*, number of patients with selected comorbidities; *N*, total number of patients in the population; %, 100 × (*n*/*N*).

Six patients, all in the levofloxacin group, experienced at least 1 AE that resulted in discontinuation of the study drug, including pulmonary embolism, gastroenteritis, convulsions, hyponatremia, acute respiratory distress syndrome (ARDS), hypovolemic shock, insomnia, nightmares, and visual hallucinations. Among these patients, 1 experienced an SAE of unrelated pulmonary embolism that also led to withdrawal from the study (due to death).

No clinically meaningful differences between treatment groups were observed for clinical chemistry, hematology, or coagulation parameters. Three patients experienced a grade 3 alanine aminotransferase (ALT) elevation (3.0 to 8.0 times the upper limit of normal [ULN]): 2 levofloxacin patients and 1 solithromycin patient. The solithromycin patient had an underlying HCV infection and a grade 2 ALT elevation at baseline. Grade 3 aspartate transaminase (AST) elevations (3.0 to 8.0 times the ULN) were observed for 2 patients in the solithromycin group and 1 in the

levofloxacin group. In both patients, AST levels increased to a peak at <3-fold above baseline and returned to their approximate baseline levels in follow-up. No associated bilirubin elevation was observed. Grade 3 hyperbilirubinemia (2.0 to 3.0 times the ULN) was observed for 1 patient in the solithromycin group; the profile indicated that the indirect bilirubin elevation was likely attributable to Gilbert's syndrome.

No clinically significant mean changes from baseline or differences among treatment groups were observed for ECG parameters.

DISCUSSION

This is the first clinical efficacy study with solithromycin, a new macrolide antibiotic and the first fluoroketolide in clinical development. It was tested as monotherapy in patients with moderate to moderately severe CABP using an 800-mg loading dose and 400-mg maintenance dose regimen administered orally for a total of 5 days.

In this randomized, double-blind phase 2 study, solithromycin demonstrated efficacy comparable to that of levofloxacin in adult patients with PORT II to IV CABP. The co-primary efficacy endpoints of clinical success rates in the ITT and CE populations at TOC were comparable for the solithromycin and the levofloxacin treatment groups, as were clinical and by-patient microbiological success rates in the solithromycin and levofloxacin treatment groups for the micro-ITT and ME populations. Clinical success at TOC in the ITT population was observed for 84.6% and 86.6% of patients in the solithromycin and levofloxacin groups, respectively. In the CE population, clinical success was observed for 83.6% and 93.1% of patients, respectively. Secondary efficacy endpoints related clinical success at TOC in the micro-ITT and ME populations.

S. pneumoniae was the most commonly isolated pathogen. All isolates of *S. pneumoniae* were susceptible to solithromycin, as has been noted in global surveillance studies (29), whereas 3 isolates were resistant to azithromycin. By-patient microbiological success at TOC in the micro-ITT population was observed for 77.8% and 71.4% of patients in the solithromycin and levofloxacin groups, respectively. In the ME population, by-patient microbiological success at TOC was observed for 80.0% and 76.9% of patients, respectively.

The safety profile of solithromycin compared favorably with that of levofloxacin administered at 750 mg once a day (QD) for 5 days. Patients receiving solithromycin experienced fewer treatment-emergent adverse events (TEAEs) overall, fewer SAEs, fewer study-drug related AEs, and fewer GI-related AEs than patients receiving levofloxacin. Compared with the levofloxacin arm, the solithromycin arm had fewer drug discontinuations due to AEs (0 versus 6 subjects), fewer SAEs (2 versus 7 subjects), and lower percentages of subjects with TEAEs (30% versus 46%) and GI-related AEs (14% versus 26%). No bitter aftertaste was reported with solithromycin, a concern with some macrolides.

Mean changes from baseline and shift analyses in laboratory parameters throughout the study were not considered clinically meaningful in either treatment group.

There were no treatment-limiting AEs or laboratory abnormalities in solithromycin recipients and no liver safety or QT signals of concern. The ketolide telithromycin was reported to cause liver damage in rare instances and has been associated with unusual adverse events, including visual disturbance, exacerbation of myasthenia gravis, and sudden loss of consciousness. There has been no evidence of these adverse events being associated with solithromycin use in the clinical trials to date (approximately 500 subjects). This could potentially be explained by the lack of a pyridine moiety in solithromycin, which has been hypothesized as being a cause of the unusual side effects observed with telithromycin use due to the known interaction of pyridine analogs with nACh receptors (25). The older macrolides and telithromycin have been noted to have a QT effect. While a definitive QT study is planned, no clinically significant prolongation of the QT interval has been observed in association with solithromycin to date.

In recent years, emergence of resistance to older macrolides and other pathogens has begun to limit therapeutic options for CABP, resulting in the need for newer agents that are active against resistant strains (30–34). Solithromycin is being developed in i.v. and oral formulations for the treatment of patients with CABP. Solithromycin has excellent pulmonary penetration, with high ELF and alveolar macrophage concentrations (27); these concentrations are well above the MICs for likely respiratory pathogens, including those resistant to currently available macrolides.

Macrolides combined with an appropriate β-lactam agent are recommended as empirical coverage for hospitalized patients with CABP who have more severe disease or are suspected to have *L. pneumophila* infection. Solithromycin has activity *in vitro* against *L. pneumophila*, including when bacteria are residing within macrophages (35, 36).

Azithromycin or another macrolide could not be used as a comparator in this study because of the high percentage of resistant pneumococci and because macrolides are not indicated for use as monotherapy to treat moderate to moderately severe CABP. Solithromycin was therefore compared to a fluoroquinolone antibiotic, levofloxacin.

Recent changes proposed by the FDA for CABP studies require evaluation of an early clinical response on day 3. Although fluoroquinolones are rapidly bactericidal, solithromycin had comparable efficacy on day 3, despite the fact that macrolides are generally bacteriostatic or slowly bactericidal relative to a fluoroquinolone, with early success for 47 (72.3%) and 48 (71.6%) patients in the solithromycin and levofloxacin groups, respectively.

This study had a low microbial isolation rate of (24.2%), which may be related to the fact that the majority of patients in the study were outpatients. *S. pneumoniae* was the most commonly identified pathogen in both treatment groups. *H. influenzae* was the second most common organism isolated, and solithromycin had efficacy comparable to that of levofloxacin against both of these pathogens. By comparison, in the inpatient phase 3 ceftaroline trials, the microbial isolation rate of CABP pathogens was 27% for typical pathogens only (atypical pathogens were excluded from the analyses) (37). Sputum samples from outpatient centers must be refrigerated and sent to central laboratories for culture. It is known that pneumococci may not survive refrigeration because of autolysin activation (38). In the phase 3 study, a significant effort will be made to collect adequate sputum specimens and to encourage rapid transport to laboratories for isolation of CABP pathogens. PCR- based diagnostics, as well as mycoplasma and legionella culture, will be used to complement standard diagnostic methods for the micro-ITT population.

In conclusion, in this phase 2 study, solithromycin administered as an oral loading dose regimen for 5 days showed efficacy comparable to that of levofloxacin in the treatment of CABP, with a favorable safety and tolerability profile. These results support

advancing solithromycin to evaluation as monotherapy in phase 3 oral studies in moderate to moderately severe CABP.

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