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MAJOR ARTICLE

Efficacy and Safety of Intravenous-to-oral Lefamulin, a Pleuromutilin Antibiotic, for the Treatment of Community-acquired Bacterial Pneumonia: The Phase III Lefamulin Evaluation Against Pneumonia (LEAP 1) Trial

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Background. Lefamulin, a pleuromutilin antibiotic, is active against pathogens commonly causing community-acquired bacterial pneumonia (CABP). The Lefamulin Evaluation Against Pneumonia (LEAP 1) study was a global noninferiority trial to evaluate the efficacy and safety of lefamulin for the treatment of CABP.

Methods. In this double-blind study, adults with CABP of Pneumonia Outcomes Research Team risk class ≥III were randomized 1:1 to receive lefamulin at 150 mg intravenously (IV) every 12 hours or moxifloxacin at 400 mg IV every 24 hours. After 6 doses, patients could be switched to an oral study drug if prespecified improvement criteria were met. If methicillin-resistant *Staphylococcus aureus* was suspected, either linezolid or placebo was added to moxifloxacin or lefamulin, respectively. The US Food and Drug Administration primary endpoint was an early clinical response (ECR) 96 ± 24 hours after the first dose of the study drug in the intent-to-treat (ITT) population (noninferiority margin, 12.5%). The European Medicines Agency co-primary endpoints were an investigator assessment of clinical response (IACR) 5–10 days after the last dose of the study drug in the modified ITT (mITT) and clinically evaluable (CE) populations (noninferiority margin, 10%).

Results. There were 551 patients randomized (n = 276 lefamulin; n = 275 moxifloxacin). Lefamulin was noninferior to moxifloxacin for ECR (87.3% vs 90.2%, respectively; difference −2.9%, 95% confidence interval [CI] g −8.5 to 2.8) and IACR (mITT, 81.7% vs 84.2%, respectively; difference −2.6%, 95% CI −8.9 to 3.9; CE, 86.9% vs 89.4%, respectively; difference −2.5%, 95% CI −8.4 to 3.4). Rates of study drug discontinuation due to treatment-emergent adverse events were 2.9% for lefamulin and 4.4% for moxifloxacin.

Conclusions. Lefamulin was noninferior to moxifloxacin for the primary efficacy endpoints and was generally safe and well tolerated.

Clinical Trials Registration. NCT02559310.

Keywords. lefamulin; pleuromutilin; antibiotic; pneumonia; moxifloxacin.

Community-acquired bacterial pneumonia (CABP) produces significant morbidity and mortality. *Streptococcus pneumoniae* causes ~5% to 15% of all community-acquired pneumonias in the United States [1, 2], with higher rates in Europe [3, 4]. Other etiological bacterial pathogens are *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*, and atypical pathogens *Legionella pneumophila, Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae* [1, 5–7]. New therapies are needed because of resistance to existing antibiotics. *Streptococcus pneumoniae* has shown resistance to β-lactams, clindamycin, tetracyclines, and macrolides, with resistance rates up to 40% [8, 9]. Macrolide-resistant *M. pneumoniae* has also been observed [10]. Antimicrobial stewardship and safety concerns with current antibiotics also create a need for new therapies. For example, fluoroquinolones carry a black box warning for tendinitis and tendon rupture, peripheral neuropathy, central nervous system effects, and hypoglycemia [11, 12].

The novel, pleuromutilin antibiotic lefamulin inhibits the 50S ribosomal subunit at the peptidyl transferase center [13]. Lefamulin is active in vitro against the previously mentioned CABP pathogens, including methicillin-resistant *S. aureus* (MRSA) [14–18]; its activity is unaffected by resistance mechanisms to β-lactams, macrolides, fluoroquinolones, tetracyclines, and glycopeptides [15–19]. Lefamulin has a favorable pharmacokinetic and pharmacodynamic profile; the intravenous (IV)

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and oral dosing regimens used in the clinical trials achieve comparable drug exposures. The drug achieves rapid and predictable penetration into human tissues, with a mean 5.7-fold higher concentration in the pulmonary epithelial lining fluid, compared with plasma [20, 21].

The Lefamulin Evaluation Against Pneumonia (LEAP 1) study evaluated the efficacy and safety of IV-to-oral lefamulin monotherapy, as compared with moxifloxacin ± linezolid (hereafter referred to as "moxifloxacin") in adults with CABP.

METHODS

Study Design and Conduct

In this Phase III, multicenter, randomized, double-blind, double-dummy, active-controlled, parallel-group study (NCT02559310), participating centers obtained study approval from their institutional review boards/ethics committees; all patients provided written informed consent before any study procedure. The study was compliant with ethical principles aligned with the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws and regulations.

Study Population

Patients ≥18 years fulfilled the US Food and Drug Administration (FDA) entry criteria for CABP trials [22], including having radiographic findings suggestive of pneumonia, Pneumonia Outcomes Research Team (PORT) risk classes ≥III (Supplementary Methods 1), acute illness (≤7 days), and ≥3 CABP symptoms (dyspnea, new or increased cough, purulent sputum production, chest pain); ≥25% of patients enrolled were to be PORT class IV or V. Exclusion criteria included the receipt of prior antibiotics for the current illness; ≤25% of randomized patients could have received a single dose of a short-acting antibiotic. The Supplementary Methods 2 detail complete inclusion/exclusion criteria.

Randomization and Intervention

Patients were randomized 1:1 to receive lefamulin at 150 mg IV every 12 hours (q12h) or moxifloxacin at 400 mg IV every 24 hours (q24h). Moxifloxacin-treated patients received alternating doses of a placebo to maintain blinding. On or after 3 days (6 doses) of IV treatment, patients could be switched to oral lefamulin at 600 mg q12h or moxifloxacin at 400 mg q24h if predefined criteria were met (Supplementary Methods 3). If MRSA was suspected at screening, blinded linezolid at 600 mg IV q12h was added to moxifloxacin and a linezolid placebo was added to lefamulin (Supplementary Methods 4). If a baseline culture did not confirm MRSA, the linezolid/linezolid placebo was discontinued.

Treatment duration ranged from 5–10 days. In the initial protocol, patients with CABP due to MRSA or *L. pneumophila* and patients with *S. pneumoniae* with accompanying bacteremia received 10 days of active treatment. Otherwise, lefamulin-treated patients received 5 days of active therapy and moxifloxacin-treated patients received 7 days of active therapy. A protocol amendment changed the therapy duration to 7 days for both groups, except in patients with MRSA, who received 10 days of active therapy. The amendment was consistent with professional society guidelines and was implemented to simplify the study drug administration procedures.

Study Evaluations and Endpoints

Patients were evaluated at the early clinical assessment, end of treatment, test of cure (TOC), and late follow-up visits. The FDA primary endpoint was the early clinical response (ECR) responder rate in the intent-to-treat (ITT) population at 96 ± 24 hours after the first study drug dose (Table 1). ECR responders showed improvement in ≥2 CABP signs/symptoms, had no worsening in any CABP sign/symptom, and had not received a concomitant, nonstudy antibiotic for CABP. The European Medicines Agency (EMA) co-primary endpoint was an investigator assessment of clinical response (IACR) at TOC (5–10 days after last study drug dose) in the modified ITT (mITT) and clinically evaluable (CE) populations (Table 1). IACR was classified as successful if CABP signs/symptoms resolved or improved such that no additional antibacterial therapy was administered for CABP. Additional endpoints included ECR and IACR by pathogen in the microbiological ITT (microITT; defined as patients with ≥1 baseline pathogen) and microITT-2 (defined as patients with ≥1 baseline pathogen identified by methodology other than polymerase chain reaction [PCR]) populations.

Safety assessments included treatment-emergent adverse events (TEAEs), clinical laboratory parameters, and vital signs. Triplicate 12-lead electrocardiograms were performed on Days 1 and 3.

Causative pathogens were identified by respiratory or blood sample cultures, quantitative real-time PCR, serology, or urine antigen testing, using a specimen collected within ±24 hours of the first study drug dose (Supplementary Methods 5). Strains were isolated at a local laboratory and confirmed at a central laboratory.

Statistical Analyses

The study was designed to have sufficient power for both the FDA and EMA primary analyses. Assuming IACR success rates of 80% and 85% in the mITT and CE populations [23], respectively, and an 80% clinical evaluability rate, 550 patients provided 80% power for the demonstration of noninferiority for IACR at TOC, using a 10% noninferiority margin and a 1-sided alpha of 0.025. Utilizing a 79% ECR responder rate in the ITT population [24] and a 1-sided alpha of 0.025, a sample size of 550 patients provided >90% power to establish the noninferiority of lefamulin, using a 12.5% margin. Margins of 12.5% for ECR and 10% for IACR were based on current FDA [22] and EMA guidance [25], respectively.

Table 1. Analysis Populations and Study Evaluation Time Points

Population	Definition
ITT	All randomized patients
Modified ITT	All randomized patients who received ≥1 dose of study drug; analyzed based on randomized treatment group
Microbiological ITT	All patients in the ITT analysis set who had ≥1 baseline pathogen detected
Microbiological ITT 2	All patients in the ITT analysis set who had ≥1 baseline pathogen detected by diagnostic means other than polymerase chain reaction
Clinically evaluable	Patient met the following predefined criteria: no indeterminate clinical response; completed ≥48 h of study drug (unless death occurred); no receipt of a nonstudy, systemic antibacterial with likely or documented activity against CABP pathogens; and no additional factor that might confound the assessment of efficacy
Safety analysis set	All randomized patients who received ≥1 dose of study drug; analyzed based on study drug received
Evaluation time point	
Early clinical assessment	96 ± 24 h after the first dose of study drug
Duration of study drug treatment[a]	Treatment duration = (date of last dose – date of first dose) + 1.
End of treatment	Within 2 d after the last dose of study drug
Test of cure	5–10 d after the last dose of study drug
Late follow-up	30 ± 3 d after the first dose of study drug

Abbreviations: CABP, community-acquired bacterial pneumonia, ITT, intent-to-treat.

[a]A single dose of the study drug on a calendar day counts as a full day of treatment. Therefore, the median is being driven by the number of patients who likely received only a single dose on Day 1 and a single dose on Day 8 to complete treatment.

A 2-sided 95% confidence interval (CI), calculated using a continuity-corrected Z-statistic for the difference in ECR responder rates in the ITT population, was used to test for the noninferiority of lefamulin versus moxifloxacin. Noninferiority was concluded if the lower limit of the 95% CI for treatment difference exceeded -12.5%. For IACR, a 2-sided 95% CI was used, calculated using the Miettinen and Nurminen method, with stratification for the randomization stratification factors (PORT risk class, region, and receipt of a single dose of a short-acting antibiotic). Noninferiority was concluded if the lower limit of the 95% CI for treatment difference exceeded -10% for both the mITT and CE populations. Given that the 2 primary endpoints were analyzed separately for the regulatory agencies, no adjustment for multiple comparisons was required. The 95% CIs for treatment differences for additional analyses were calculated using the same methodology as for ECR [22, 25].

RESULTS

Patients

This study enrolled 551 patients at 66 centers across 18 countries between February 2016 and May 2017 (Figure 1). Approximately 25% of patients were enrolled before the protocol amendment noted above. Demographics and baseline characteristics were generally well balanced between treatment groups (Table 2), with the noted exception that 47.8% and 39.3% of patients were aged ≥65 years in the lefamulin and moxifloxacin groups, respectively.

Table 1 describes the calculation of the study drug treatment duration; a single dose of a study drug on a calendar day counted as a full day of treatment. In the safety analysis set, the median (range) study drug treatment (IV and oral) duration was 7 (1–11) days for lefamulin and 7 (1–10) days for moxifloxacin. The median (range) IV therapy duration was 7 (1–11) days for lefamulin and 6 (1–10) days for moxifloxacin, and the median (range) oral therapy duration was 4 (1–7) and 4 (1–5) days, respectively. In lefamulin-treated patients, 38.1% (104/273) of patients switched from IV to oral therapy, compared with 44.3% (121/273) in moxifloxacin-treated patients.

The baseline pathogen distribution was similar between the treatment groups (Table 3). *Streptococcus pneumoniae* was the most commonly isolated pathogen. Most *H. influenzae* and *M. catarrhalis* isolates were detected by PCR, producing higher incidences in the microITT versus microITT-2 population. At baseline, MRSA was suspected in 23 patients (9 treated with lefamulin; 14 treated with moxifloxacin), but no case was confirmed. Both drugs were active in vitro against the most commonly isolated pathogens (Table 4).

Efficacy Outcomes

Clinical Response/Success: Early Clinical Response and Investigator Assessment of Clinical Response

Lefamulin demonstrated noninferiority to moxifloxacin for both the FDA primary endpoint of ECR (Figure 2A) and the EMA primary endpoint (Figure 2B) of IACR. Results were consistent under the original protocol and the revised protocol (Supplementary Figure 1).

Clinical Response/Success by Baseline Pathogen

In the microITT population (Table 5), lefamulin and moxifloxacin demonstrated similar ECR responder and IACR success rates across all baseline CABP pathogens. The microITT-2 population also showed similar responder/success rates across baseline pathogens, but had more variability than the microITT population, due to smaller sample sizes.

Baseline bacteremia occurred in 2.5% (7/276) of patients randomized to lefamulin (6 *S. pneumoniae*; 1 *S. aureus*) and 1.1% (3/275) randomized to moxifloxacin (2 *Escherichia coli*;

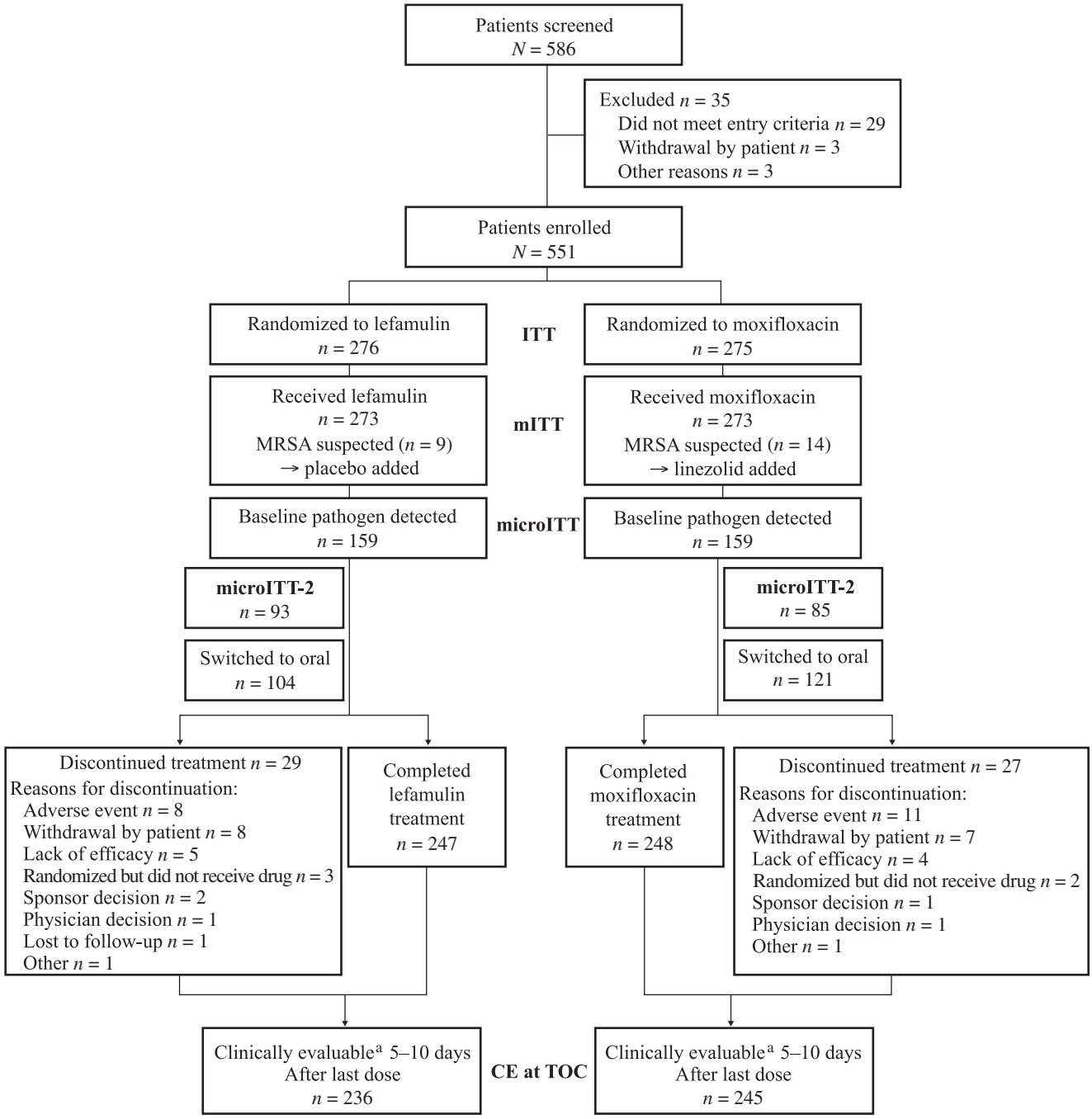

Figure 1. Patient disposition. See Table 1 for definitions of the patient populations. Abbreviations: CABP, community-acquired bacterial pneumonia; CE, clinically evaluable; IACR, investigator assessment of clinical response; ITT, intent-to-treat; microITT, microbiological ITT; microITT-2, microbiological ITT-2; mITT, modified ITT; MRSA, methicillin-resistant *Staphylococcus aureus*; TOC, test of cure. [a]Met the criteria for CABP, received at least the prespecified minimal amount of the intended dose of the study drug and minimum duration of treatment, IACR not indeterminate, did not receive a concomitant antibacterial therapy (other than adjunctive linezolid) that is potentially effective against CABP pathogens (except in the case of clinical failure), and had no other confounding factors that interfered with the outcome assessment.

1 *Burkholderia cepacia*). Among these, 4 of 7 lefamulin-treated patients and 2 of 3 moxifloxacin-treated patients were ECR responders. For IACR at TOC, 1 of 7 lefamulin recipients and 2 of 3 moxifloxacin recipients achieved treatment success. Of the 6 lefamulin-treated patients with pneumococcal bacteremia, 1 achieved treatment success, while 5 were treatment failures for IACR at TOC. Of the treatment failures, 1 patient died on Day 3, due to respiratory failure, while the other 4 patients had confounding factors: 2 had pleural empyema, requiring prolonged therapy beyond the study period; 1 discontinued on Day 3 due to bradycardia; and 1 had improved symptoms but persistent fever, for which the investigator continued antibiotic therapy beyond

Table 2. Baseline Characteristics (Intent-to-treat Population)

Characteristic	Lefamulin (n = 276)	Moxifloxacin ± Linezolid (n = 275)
Mean (SD) age, y	61.0 (16.3)	59.6 (14.9)
Age group, n (%)		
<65 y	144 (52.2)	167 (60.7)
65–74 y	74 (26.8)	66 (24.0)
≥75 y	58 (21.0)	42 (15.3)
Sex, n (%)		
Male	170 (61.6)	160 (58.2)
Mean (SD) BMI, kg/m^2	26.5 (6.0)	26.3 (6.3)
Race, n (%)		
White	239 (86.6)	239 (86.9)
Black	11 (4.0)	12 (4.4)
Asian	24 (8.7)	20 (7.3)
American Indian or Alaskan Native	0	1 (0.4)
Other	2 (0.7)	3 (1.1)
PORT risk class, n (%)		
II	0	1 (0.4)[a]
III	196 (71.0)	201 (73.1)
IV	76 (27.5)	70 (25.5)
V	4 (1.4)	3 (1.1)
Mean (SD) procalcitonin, µg/L	2.1 (7.8)	1.0 (2.4)
CURB-65 score, n (%)		
0	24 (8.7)	33 (12.0)
1	130 (47.1)	121 (44.0)
2	98 (35.5)	97 (35.3)
3	22 (8.0)	22 (8.0)
4	2 (0.7)	2 (0.7)
Met minor ATS severity criteria, n (%)[b]	54 (19.6)	48 (17.5)
Met SIRS criteria, n (%)[c]	268 (97.1)	267 (97.1)
Bacteremic, n (%)	7 (2.5)	3 (1.1)
Received prior systemic antibacterial medication within 72 h before randomization	69 (25.0)	71 (25.8)
1 dose of a short-acting antibacterial for CABP	66 (23.9)	66 (24.0)
>1 dose of a short-acting and/or ≥1 dose of a long-acting antibacterial for CABP	3 (1.1)	5 (1.8)
Renal status, n (%)		
Severe impairment (CrCl <30 mL/min)	3 (1.1)	3 (1.1)
Moderate impairment (CrCl 30–<60 mL/min)	61 (22.1)	62 (22.5)
Mild impairment (CrCl 60–<90 mL/min)	89 (32.2)	75 (27.3)
Normal function (CrCl ≥90 mL/min)	121 (43.8)	134 (48.7)
Patients randomized by region, n (%)		
Eastern Europe	218 (79.0)	217 (78.9)
Latin America	4 (1.4)	10 (3.6)
North America	2 (0.7)	1 (0.4)
Western Europe	17 (6.2)	14 (5.1)
Rest of world	35 (12.7)	33 (12.0)

CURB-65 criteria were defined as blood urea nitrogen >19 mg/dL, respiratory rate ≥30 breaths/min, blood pressure <90 mmHg systolic or ≤60 mmHg diastolic, and age ≥65 years.

Abbreviations: ATS, American Thoracic Society; BMI, body mass index; CABP, community-acquired bacterial pneumonia; CrCl, creatinine clearance; CURB-65, confusion of new onset; PORT, Pneumonia Outcomes Research Team; SD, standard deviation; SIRS, systemic, inflammatory response syndrome.

[a]There was 1 patient who was placed in PORT risk class III at randomization but was reclassified at PORT risk class II after randomization.

[b]Defined as the presence of ≥3 of the following 9 criteria at baseline: respiratory rate ≥30 breaths/min, oxygen saturation <90% or partial pressure of arterial oxygen <60 mmHg, blood urea nitrogen ≥20 mg/dL, white blood cell count <4000 cells/mm^3, confusion, multilobar infiltrates, platelet count <100 000 cells/mm^3, temperature <36°C, and systolic blood pressure <90 mmHg.

[c]Defined as ≥2 of the following 4 symptoms at baseline: temperature <36°C or >38°C, heart rate >90 beats/min, respiratory rate >20 breaths/min, white blood cell count <4000 cells/mm^3 or >12 000 cells/mm^3, and immature polymorphonuclear neutrophils >10%.

the study period. After the completion of 11 days of lefamulin, the patient with *S. aureus* infection improved, but received additional antibiotics for hemoptysis and was diagnosed with endobronchial diverticulitis; the patient was a responder based on ECR but an IACR failure based on the need for additional antibiotics. No patient with bacteremia had follow-up blood cultures.

Table 3. Baseline Pathogens

	Patients, n (%)			
	microITT		microITT-2	
Pathogen[a]	Lefamulin (n = 159)	Moxifloxacin ± Linezolid (n = 159)	Lefamulin (n = 93)	Moxifloxacin ± Linezolid (n = 85)
Gram-positive bacteria	97 (61.0)	100 (62.9)	47 (50.5)	47 (55.3)
Streptococcus pneumoniae[b]	93 (58.5)	97 (61.0)	42 (45.2)	44 (51.8)
Staphylococcus aureus	10 (6.3)	4 (2.5)	7 (7.5)	3 (3.5)
Streptococcus pyogenes	0	1 (0.6)	0	1 (1.2)
Gram-negative bacteria	74 (46.5)	66 (41.5)	21 (22.6)	16 (18.8)
Haemophilus influenzae	51 (32.1)	57 (35.8)	6 (6.5)	6 (7.1)
Moraxella catarrhalis	25 (15.7)	11 (6.9)	1 (1.1)	1 (1.2)
Acinetobacter baumannii	1 (0.6)	0	1 (1.1)	0
Acinetobacter calcoaceticus –A. baumannii complex	0	2 (1.3)	0	2 (2.4)
Acinetobacter junii	1 (0.6)	0	1 (1.1)	0
Acinetobacter lwoffii	2 (1.3)	0	2 (2.2)	0
Any *Acinetobacter* species	0	1 (0.6)	0	1 (1.2)
Burkholderia cepacia	0	1 (0.6)	0	1 (1.2)
Citrobacter koseri	1 (0.6)	0	1 (1.1)	0
Enterobacter aerogenes	1 (0.6)	1 (0.6)	1 (1.1)	1 (1.2)
Enterobacter cloacae	3 (1.9)	0	3 (3.2)	0
Escherichia coli	0	2 (1.3)	0	2 (2.4)
Haemophilus parainfluenzae	3 (1.9)	2 (1.3)	3 (3.2)	2 (2.4)
Klebsiella pneumoniae	3 (1.9)	2 (1.3)	3 (3.2)	2 (2.4)
Pseudomonas aeruginosa	1 (0.6)	0	1 (1.1)	0
Serratia marcescens	1 (0.6)	0	1 (1.1)	0
Atypical pathogens	45 (28.3)	46 (28.9)	37 (39.8)	35 (41.2)
Mycoplasma pneumoniae[c]	19 (11.9)	20 (12.6)	14 (15.1)	12 (14.1)
Legionella pneumophila[d]	18 (11.3)	14 (8.8)	17 (18.3)	14 (16.5)
Chlamydophila pneumoniae[d]	11 (6.9)	19 (11.9)	9 (9.7)	15 (17.6)

The microITT group consisted of all patients in the ITT analysis set who had ≥1 baseline pathogen detected. The microITT-2 group consisted of all patients in the ITT analysis set who had ≥1 baseline pathogen detected by diagnostic means other than polymerase chain reaction.

Abbreviations: ITT, intent-to-treat; microITT, microbiological ITT; microITT-2, microbiological ITT-2; PCR, polymerase chain reaction; RT-PCR, real-time PCR.

[a]A patient could have had >1 pathogen identified in ≥1 testing modality. Multiple isolates of the same species, from the same patient, identified by the same testing modality, were only counted once. Patients with >1 gram-positive, gram-negative, or atypical pathogen were only counted once in the overall tabulation of gram-positive bacteria, gram-negative bacteria, and atypical pathogens, respectively. Polymicrobial pathogens were identified in 121 (38.1%) and 33 (18.5%) patients included in the microITT and microITT-2 analysis sets, respectively. Monomicrobial atypical pathogens were identified in 50 (15.7%) patients included in the microITT analysis set and 54 (30.3%) patients included in the microITT-2 analysis set. Typical and atypical pathogen combinations were observed in 34 (10.7%) and 12 (6.7%) patients in the microITT and microITT-2 analysis sets, respectively.

[b]For *Streptococcus pneumoniae*, the urinary antigen test was used to identify pathogens in 14 (4.4%) and 35 (19.7%) patients in the microITT and microITT-2 analysis sets, respectively.

[c]In the microITT analysis set, *Mycoplasma pneumoniae* was identified by sputum RT-PCR in 8 (2.5%) patients; oropharyngeal swab PCR in 4 (1.3%) patients; both PCR methodologies in 1 (0.3%) patient; sputum RT-PCR plus serology in 3 (0.9%) patients; sputum RT-PCR, oropharyngeal swab PCR, and oropharyngeal swab culture in 1 (0.3%) patient; and sputum RT-PCR, serology, oropharyngeal swab PCR, and oropharyngeal swab culture in 5 (1.6%) patients. *M. pneumoniae* was identified by serology alone for the remaining 17 (5.3%) patients.

[d]In the microITT analysis set, sputum RT-PCR was used to identify *Legionella pneumophila* in 3 (0.9%) patients and *Chlamydophila pneumoniae* in 8 (2.5%) patients.

Clinical Response/Success by Subpopulations

Lefamulin and moxifloxacin demonstrated high ECR responder and IACR success rates across all CABP severities (Figure 3). Figure 4 shows results for other subpopulations. For patients aged <65 years and those meeting modified American Thoracic Society (ATS) severity criteria (baseline presence of ≥3 of the following: respiratory rate ≥30 breaths/min, oxygen saturation <90% or partial pressure of arterial oxygen <60 mmHg, blood urea nitrogen ≥20 mg/dL, white blood cell count <4000 cells/mm^3, confusion, multilobar infiltrates, platelet count <100 000 cells/mm^3, temperature <36°C, and systolic blood pressure <90 mmHg), the treatment differences favored moxifloxacin. Further analyses indicated that the lower response rate among patients <65 years was confounded by minor, not major, ATS severity criteria. When analyzed by the presence of minor ATS severity criteria, response rates among patients <65 years were lower among lefamulin-treated patients versus moxifloxacin-treated patients. However, for patients aged <65 years who did not meet minor ATS severity criteria, there was no difference between the treatment groups in efficacy (ECR or IACR; Supplementary Table 1). ATS variables associated with treatment group differences were not identifiable by logistic regression models (data on file).

Table 4. Minimum Inhibitory Concentrations for Key Pathogens (Microbiological Intent-to-treat Population)

Pathogen[a]	n	$MIC_{50/90}$, μg/mL[b]	
		Lefamulin	Moxifloxacin
Gram-positive bacteria			
Streptococcus pneumoniae	50	0.25/0.5	0.12/0.25
MDR	12	0.25/0.5	0.12/0.12
Macrolide-resistant[c]	12	0.25/0.5	0.12/0.12
Staphylococcus aureus	10	0.12/0.25	0.03/0.06
Gram-negative bacteria			
Haemophilus influenzae	11[d]	1/2	0.03/0.12
Moraxella catarrhalis	2	NE (0.12–0.12)	NE (0.06–0.06)
Atypical bacteria			
Mycoplasma pneumoniae	6	NE (≤0.001–≤0.001)	NE (0.12–0.12)

MDR isolates were defined as isolates displaying resistance phenotype to ≥2 of the following: oral penicillin, moxifloxacin, ceftriaxone, clindamycin, azithromycin or erythromycin, doxycycline, or trimethoprim/sulfamethoxazole. The microbiological intent-to-treat group consisted of all patients in the ITT analysis set who had ≥1 baseline pathogen detected. The microbiological intent-to-treat-2 group consisted of all patients in the ITT analysis set who had ≥1 baseline pathogen detected by diagnostic means other than polymerase chain reaction.

Abbreviations: ITT, intent-to-treat; MDR, multidrug-resistant; MIC_{50}, minimum inhibitory concentration required to inhibit 50% of isolates; MIC_{90}, minimum inhibitory concentration required to inhibit 90% of isolates; NE, not estimable due to small sample size.

[a]Pathogens were isolated from sputum, nasopharyngeal swabs, oropharyngeal swabs, blood, bronchoalveolar lavage, and/or pleural fluid via culture. A patient could have >1 pathogen. Multiple isolates of the same species and phenotype from the same patient were only counted once, using the isolate with the highest minimum inhibitor concentration.

[b]MIC_{50} and MIC_{90} values are only reported for pathogens with ≥10 isolates in the relevant group. For pathogen groups with <10 isolates, the range of the MIC values is provided in parentheses. Susceptibilities are based on Clinical and Laboratory Standards Institute breakpoints, 2017.

[c]Defined as resistant to azithromycin or erythromycin.

[d]Moxifloxacin was tested against n = 12.

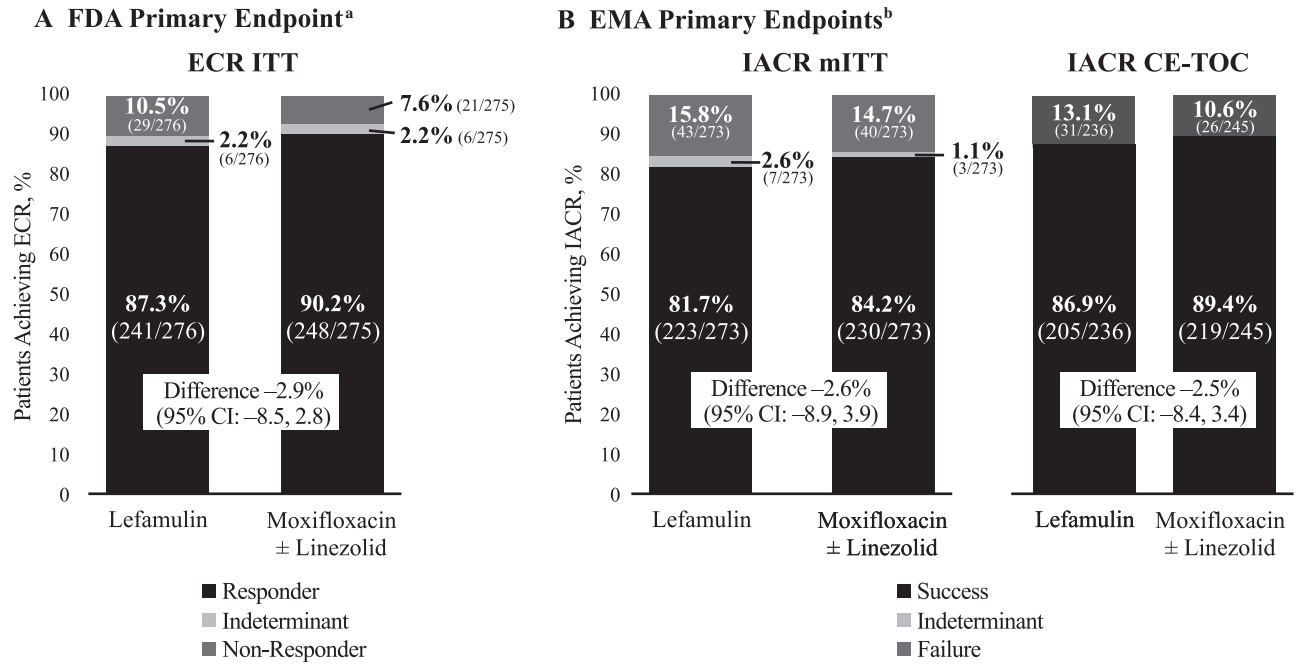

Figure 2. Lefamulin met the primary endpoints of noninferiority vs moxifloxacin: (*A*) FDA primary endpoint and (*B*) EMA primary endpoints. See Table 1 for definitions of the patient populations. Abbreviations: CE, clinically evaluable; CI, confidence interval; ECR, early clinical response; EMA, European Medicines Agency; FDA, Food and Drug Administration; IACR, investigator assessment of clinical response; ITT, intent-to-treat; mITT, modified ITT; TOC, test of cure. [a]Noninferiority of lefamulin for the FDA primary endpoint was concluded if the lower limit of the 2-sided 95% CI for the observed difference in ECR responder rates between treatment groups was greater than –12.5%. [b]Noninferiority of lefamulin for the EMA co-primary endpoints was concluded if the lower limit of the 2-sided 95% CI for the observed difference in IACR success rates between the treatment groups was greater than –10% for both the mITT and CE populations.

Safety and Tolerability

Rates of TEAEs, most of which were mild or moderate in severity, were similar between treatment groups (Table 6). The most common TEAEs in lefamulin recipients were hypokalemia, nausea, insomnia, and infusion site pain (each in 2.9% of patients). The most common TEAE in moxifloxacin recipients was diarrhea (7.7%). There was 1 case of angioedema

Table 5. Responder (Early Clinical Response) and Success (Investigator Assessment of Clinical Response) Rates by Baseline Pathogen

Baseline pathogen, rate[a] (n/N)	ECR				IACR at TOC			
	microITT		microITT-2		microITT		microITT-2	
	Lefamulin	Moxifloxacin ± Linezolid	Lefamulin	Moxifloxacin ± Linezolid	Lefamulin	Moxifloxacin ± Linezolid	Lefamulin	Moxifloxacin ± Linezolid
Streptococcus pneumoniae	88.2% (82/93)	93.8% (91/97)	85.7% (36/42)	88.6% (39/44)	84.9% (79/93)	87.6% (85/97)	81.0% (34/42)	86.4% (38/44)
MDR	… (6/6)	… (5/6)	… (6/6)	… (5/6)	… (6/6)	… (4/6)	… (6/6)	… (4/6)
Staphylococcus aureus[b]	100.0% (10/10)	… (4/4)	… (7/7)	… (3/3)	80.0% (8/10)	… (4/4)	… (6/7)	… (3/3)
Haemophilus influenzae	92.2% (47/51)	94.7% (54/57)	… (6/6)	… (5/6)	84.3% (43/51)	84.2% (48/57)	… (5/6)	… (6/6)
Moraxella catarrhalis	92.0% (23/25)	100.0% (11/11)	… (0/1)	… (1/1)	80.0% (20/25)	100.0% (11/11)	… (0/1)	… (1/1)
Mycoplasma pneumoniae	84.2% (16/19)	90.0% (18/20)	92.9% (13/14)	91.7% (11/12)	84.2% (16/19)	95.0% (19/20)	85.7% (12/14)	91.7% (11/12)
Legionella pneumophila	88.9% (16/18)	85.7% (12/14)	88.2% (15/17)	85.7% (12/14)	77.8% (14/18)	78.6% (11/14)	82.4% (14/17)	78.6% (11/14)
Chlamydophila pneumoniae	90.9% (10/11)	94.7% (18/19)	… (8/9)	93.3% (14/15)	72.7% (8/11)	68.4% (13/19)	… (7/9)	73.3% (11/15)

MDR isolates were defined as isolates displaying resistance phenotype to ≥2 of the following: oral penicillin, moxifloxacin, ceftriaxone, clindamycin, azithromycin or erythromycin, doxycycline, or trimethoprim/sulfamethoxazole. The microITT group consisted of all patients in the ITT analysis set who had ≥1 baseline pathogen detected. The microITT-2 group consisted of all patients in the ITT analysis set who had ≥1 baseline pathogen detected by diagnostic means other than polymerase chain reaction. Percentages are not included for numbers <10.

Abbreviations: ECR, early clinical response; IACR, investigator assessment of clinical response; ITT, intent-to-treat; MDR, multidrug-resistant; microITT, microbiological ITT; microITT-2, microbiological ITT-2; TOC, test of cure.

[a]MicroITT (lefamulin, n = 159; moxifloxacin ± linezolid, n = 159); microITT-2 (lefamulin, n = 93, moxifloxacin ± linezolid, n = 85); n/N = patients successfully treated/patients with a specific baseline pathogen.

[b]All *Staphylococcus aureus* isolates were susceptible to methicillin.

in the group of moxifloxacin-treated patients, but none in the lefamulin-treated patients.

Fewer gastrointestinal system organ class TEAEs were reported with lefamulin than moxifloxacin (6.6% vs 13.6%, respectively; 3.7% and 12.1%, respectively, during IV treatment and 7.7% and 5.8%, respectively, during oral treatment). The most common event overall was diarrhea (0.7% lefamulin; 7.7% moxifloxacin). No gastrointestinal TEAE led to a study drug discontinuation, and no *Clostridium difficile* infections were reported.

Infusion site reactions occurred in 7.7% of lefamulin recipients and 3.7% of moxifloxacin recipients. The most common event was infusion site pain (2.9% lefamulin; 0% moxifloxacin). Infusion site phlebitis was also more common with lefamulin than moxifloxacin (Table 6). There was 1 patient in each treatment group who discontinued the study drug because of an infusion site reaction (phlebitis for the patient in the lefamulin group and erythema for the patient in the moxifloxacin group).

Few patients experienced a hepatobiliary organ class TEAE (0.7% lefamulin; 1.5% moxifloxacin). No liver chemistry–associated TEAE resulted in study drug discontinuation. There was 1 moxifloxacin-treated patient who met the laboratory criteria for Hy's law on Day 3 [26], which was likely due to the patient's underlying cardiac disease. Liver chemistry test results were similar between treatment groups (Supplementary Table 2).

Overall incidences of cardiac disorders were comparable between treatment groups (2.9% lefamulin; 4.0% moxifloxacin). There were 8 patients (n = 3 lefamulin; n = 5 moxifloxacin) who had nonserious TEAEs of prolonged QT intervals; in 4 patients (n = 1 lefamulin; n = 3 moxifloxacin), the event led to study drug discontinuation. The overall mean (standard deviation) change from baseline in QT interval corrected according to Fridericia (QTcF) on Day 3 post-dose was 13.8 (19.8) millisecond for lefamulin and 16.4 (21.4) millisecond for moxifloxacin. No lefamulin-treated patient and 2 moxifloxacin-treated patients had a post-baseline increase of >60 millisecond that resulted in a value >480 millisecond; no patient in either group had a post-baseline increase of >60 millisecond that resulted in a value >500 millisecond.

The TEAEs leading to study drug discontinuations that affected >1 patient in either treatment group were infectious pleural effusion (n = 1 lefamulin; n = 2 moxifloxacin) and prolonged QT intervals (n = 1 lefamulin; n = 3 moxifloxacin). The serious TEAE of worsening pneumonia was reported in 5 patients (n = 4 lefamulin; n = 1 moxifloxacin). Treatment-related serious TEAEs were reported in 1.1% of lefamulin-treated patients (injection site reaction, increased liver function test, increased alanine aminotransferase) and 0.4% moxifloxacin-treated patients (angioedema). Only the case of angioedema resulted in study drug discontinuation. TEAEs resulted in 11 deaths (n = 6 lefamulin; n = 5 moxifloxacin) during the study (Table 6), none of which were considered by the investigator to be related to the study drug.

PORT Risk Class	No. of Patients Successfully Treated/Total No. (%) Lefamulin	Moxifloxacin ± Linezoid	Between-Group Difference (95% CI), %
ECR (ITT population)			
Class II	0/0	1/1 (100.0)	NE
Class III	175/196 (89.3)	187/201 (93.0)	–3.7 (–9.8, 2.3)
Class IV	63/76 (82.9)	57/70 (81.4)	1.5 (–12.3, 15.3)
Class V	3/4 (75.0)	3/3 (100.0)	NE
IACR (mITT population)			
Class II	0/0	1/1 (100.0)	NE
Class III	163/194 (84.0)	168/200 (84.0)	0.0 (–7.7, 7.8)
Class IV	57/75 (76.0)	58/69 (84.1)	–8.1 (–22.4, 6.3)
Class V	3/4 (75.0)	3/3 (100.0)	NE

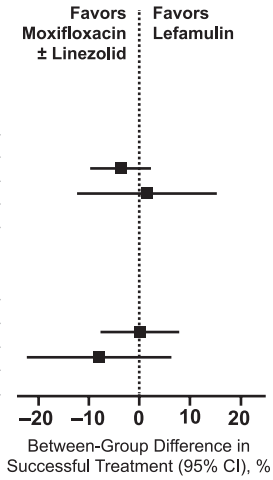

Figure 3. Responder (ECR) and success (IACR) rates by PORT risk class. Abbreviations: CI, confidence interval; ECR, early clinical response; IACR, investigator assessment of clinical response; ITT, intent-to-treat; mITT, modified ITT; NE, not evaluable due to n < 10; PORT, Pneumonia Outcomes Research Team.

DISCUSSION

This study demonstrated that efficacy of lefamulin, the first pleuromutilin for IV and oral use in humans, was noninferior to that of moxifloxacin in adults with CABP. Noninferiority was achieved for both ECR and IACR. Outcome rates were high with both agents, with observed ECR responder rates of 87.3% (lefamulin) and 90.2% (moxifloxacin) and IACR success rates of 81.7–86.9% (lefamulin) and 84.2–89.4% (moxifloxacin). Lefamulin and moxifloxacin were generally safe and well tolerated.

Lefamulin monotherapy achieved high response rates for CABP caused by *S. pneumoniae*, *S. aureus, H. influenzae*, and *M. catarrhalis*. Lefamulin also demonstrated efficacy against CABP caused by atypical pathogens *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila*. These data are consistent with previous in vitro studies demonstrating lefamulin activity against typical and atypical CABP pathogens, with its activity unaffected by resistance to other antibiotic classes [14, 16, 18]. In this study, an atypical pathogen was detected in ~17% (91/551) of all patients, consistent with published epidemiologic data [7, 27].

Lefamulin- and moxifloxacin-treated patients reported similar TEAE rates; most were mild or moderate in severity. Gastrointestinal events and infusion site reactions, the most frequent TEAEs, were rarely treatment-limiting. Gastrointestinal events more commonly began during oral versus IV treatment with lefamulin (7.7% vs 3.7%, respectively), but more commonly began during IV versus oral treatment with moxifloxacin (12.1% vs 5.8%, respectively). *Clostridium difficile* infection was not reported. Hepatic aminotransferase increases were infrequent, transient, and of similar incidences in both treatment groups. The mean QTcF prolongation from baseline with IV lefamulin was numerically less than that with IV moxifloxacin; outlier QTcF values were observed only in the moxifloxacin group. The mortality rate was comparable to those reported in other randomized, controlled trials in patients with similar CABP severity indicators (ie, PORT risk class, CURB-65 [confusion of new onset, defined as blood urea nitrogen >19 mg/dL, respiratory rate ≥30 breaths/min, blood pressure <90 mmHg systolic or ≤60 mmHg diastolic, and age ≥65 years], and systemic, inflammatory response syndrome [SIRS] criteria) [28, 29].

The strengths of this study include the exclusion of patients with milder CABP forms and the limitation on prior antibiotic use. In addition, diagnostic tests yielded a high pathogen-detection rate. The selection of moxifloxacin as an active control ensured assay sensitivity and allowed for a clinically relevant noninferiority comparison. Possible limitations include the low number of PORT risk class V patients and the few patients enrolled from North America, Western Europe, and Latin America. Planned sensitivity analyses by geographic region could not be performed.

Subpopulation analyses suggested that moxifloxacin appeared to be more efficacious than lefamulin in patients aged <65 years. A similar result was observed in patients meeting the minor ATS severity criteria [6]. The clinical significance of the ATS severity criteria findings is unknown and may reflect the effect of chance on the small ATS subpopulation, given that (1) treatment differences in efficacy were not observed across other severity indices (ie, PORT, CURB-65, SIRS criteria), (2) logistic regression models did not identify ATS variables that could explain treatment group differences, (3) there was an imbalance in study drug discontinuations before ECR assessments, for reasons apparently unrelated to efficacy (eg, withdrawal from study for adverse events or personal reasons, n = 7 lefamulin and n = 1 moxifloxacin), and (4) preliminary pharmacokinetic analyses from this study indicate no difference in lefamulin exposure in younger versus older patients.

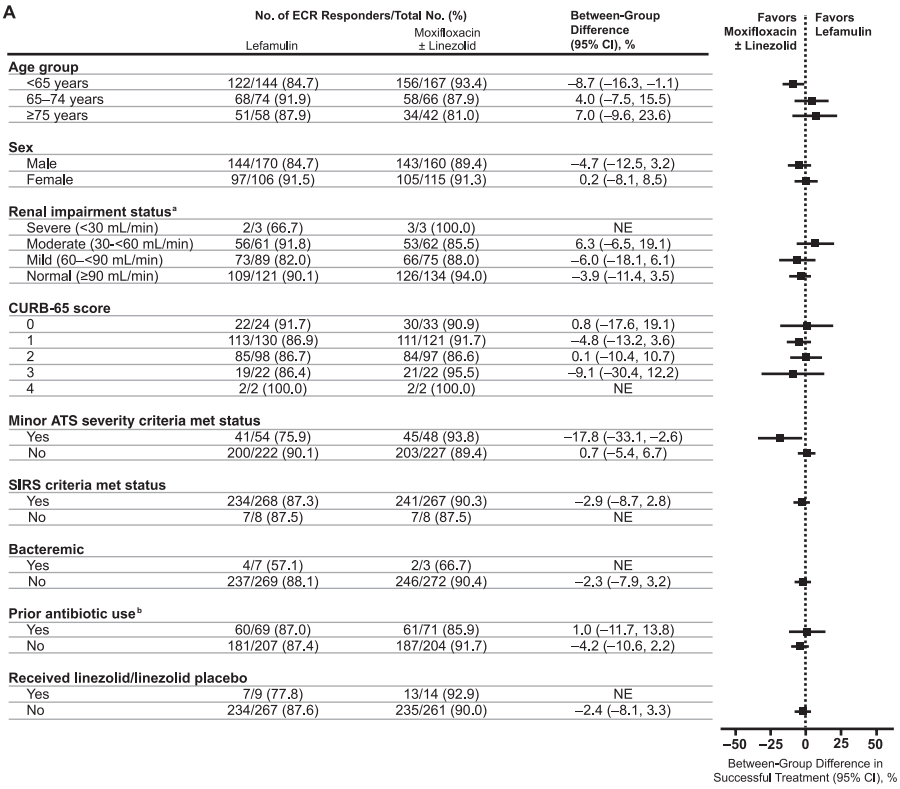

Figure 4. Outcome by subpopulation: (*A*) ECR in ITT population and (*B*) IACR in mITT population. Minor ATS severity criteria were defined as the presence of ≥3 of the following at baseline: respiratory rate ≥30 breaths/min, oxygen saturation <90% or partial pressure of arterial oxygen <60 mmHg, blood urea nitrogen ≥20 mg/dL, white blood cell count <4000 cells/mm^3, confusion, multilobar infiltrates, platelet count <100 000 cells/mm^3, temperature <36°C, and systolic blood pressure <90 mmHg. CURB-65 criteria were defined as blood urea nitrogen >19 mg/dL, respiratory rate ≥30 breaths/min, blood pressure <90 mmHg systolic or ≤60 mmHg diastolic, and age ≥65 years. Abbreviations: ATS, American Thoracic Society; CI, confidence interval; CURB-65, confusion of new onset; ECR, early clinical response; IACR, investigator assessment of clinical response; ITT, intent-to-treat; mITT, modified ITT; NE, not evaluable due to n < 10; SIRS, systemic inflammatory response syndrome. [a]National Kidney Foundation categories of renal impairment were determined by Cockcroft-Gault (30) using baseline central laboratory serum creatinine. [b]Prior antibiotic use within 72 hours before randomization, as reported on the case report form.

Table 6. Overview of Treatment-emergent Adverse Events (Safety Analysis Set)

	Patients, n (%)	
	Lefamulin (n = 273)	Moxifloxacin ± Linezolid (n = 273)
All TEAEs[a,b]	104 (38.1)	103 (37.7)
Mild	56 (20.5)	62 (22.7)
Moderate	34 (12.5)	28 (10.3)
Severe	14 (5.1)	13 (4.8)
TEAEs occurring in >2% of patients in either group		
Hypokalemia	8 (2.9)	6 (2.2)
Nausea	8 (2.9)	6 (2.2)
Insomnia	8 (2.9)	5 (1.8)
Infusion site pain	8 (2.9)	0
Infusion site phlebitis	6 (2.2)	3 (1.1)
ALT increase	5 (1.8)	6 (2.2)
Hypertension	2 (0.7)	6 (2.2)
Diarrhea	2 (0.7)	21 (7.7)
Treatment-related TEAEs	41 (15.0)	39 (14.3)
Mild	28 (10.3)	30 (11.0)
Moderate	9 (3.3)	6 (2.2)
Severe	4 (1.5)	3 (1.1)
Serious TEAEs	19 (7.0)	13 (4.8)
Treatment-related serious TEAEs[c]	3 (1.1)	1 (0.4)
TEAE leading to death[d]	6 (2.2)	5 (1.8)
TEAE leading to discontinuation of study drug[e]	8 (2.9)	12 (4.4)
TEAE leading to withdrawal from study[f]	5 (1.8)	11 (4.0)

Abbreviations: ALT, alanine aminotransferase; QTcF, QT interval corrected according to Fridericia; TEAE, treatment-emergent adverse event.

[a]A TEAE is defined as an adverse event that starts or worsens with or after the first dose of the study drug.

[b]Per protocol, sites were instructed to report nonserious adverse events through the test-of-cure visit and serious adverse events through late follow-up.

[c]Lefamulin (elevated liver function test, injection site reaction, and ALT increase); moxifloxacin (angioedema).

[d]Lefamulin (ventricular arrhythmia, sepsis, congestive heart failure, myocardial infarction, pneumonia, and chronic obstructive pulmonary disease); moxifloxacin (cerebrovascular accident, testicular seminoma, hematemesis/hemorrhagic shock, cardiac arrest, and death due to natural causes).

[e]Lefamulin (pulmonary tuberculosis, congestive heart failure, pleural empyema, infusion site phlebitis, prolonged QTcF interval, bradycardia, pneumonia, and chronic obstructive pulmonary disease); moxifloxacin (n = 3 prolonged QTcF interval, n = 2 pleural empyema, and n = 1 each for acute respiratory failure/pneumonia, hemorrhagic shock, infusion site erythema, atrial fibrillation/arterial hypertension/pulmonary embolism, confusion, angioedema, and acute cystitis).

[f]Lefamulin (congestive heart failure, myocardial infarction, pneumonia, chronic obstructive pulmonary disease, and pleuritis); moxifloxacin (n = 2 prolonged QTcF interval and n = 1 each for pneumonia, hematemesis/hemorrhagic shock, infusion site erythema, pulmonary embolism, cardiac arrest, death due to natural causes, angioedema, atrial tachycardia/atrial fibrillation/prolonged QTcF interval, and acute cystitis).

An early protocol amendment changed active lefamulin treatment duration from 5 to 7 days; most patients enrolled in the lefamulin group received the longer treatment duration. This protocol change was undertaken for logistical reasons and not as a result of any interim analysis of efficacy or safety data. An analysis of clinical response rates by protocol version demonstrated comparable findings.

In conclusion, lefamulin treatment was noninferior to moxifloxacin, and both treatments were generally safe and well tolerated. Lefamulin is the first systemic antibacterial of a new antibiotic class with favorable clinical data in the treatment of CABP in >15 years. Lefamulin is an IV and oral empiric monotherapy that provides targeted antimicrobial activity against the most prevalent CABP pathogens, providing clinicians a potential CABP treatment option that aligns with the principles of antimicrobial stewardship [6].

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. T. M. F. has served as a consultant for Motif BioSciences, Merck, Nabriva Therapeutics, Paratek, GlaxoSmithKline, Melinta, and Shionogi. L. G., C. S., S. P. G., J. S., E. S., S. P., W. W. W., and L. B. G. are employees of Nabriva Therapeutics or were employees when the study was performed. A. D. and G. H. T. served as consultants for Nabriva Therapeutics during the design and execution of the study. G. H. T. is currently a member of the Board of Directors of Nabriva Therapeutics and has received personal fees and/or other support from Actelion, Adynxx, AN2 Therapeutics, Calixa Therapeutics, Meiji-Seika, Nabriva Therapeutics, Recida Therapeutics, Tripex, and Zavante Therapeutics, outside the submitted work. A. D. has also served as a consultant for Contrafect, Tetraphase, Paratek, Cempra, Achaogen, Zavante, UTILITY, Iterum, AntibioTx, and Wockhardt. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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