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Efficacy and Safety of Lefamulin Versus Moxifloxacin for Atypical Respiratory Pathogens in Adults With Community-Acquired Bacterial Pneumonia: Pooled Results From the Lefamulin Evaluation Against Pneumonia (LEAP) 1 and LEAP 2 Double-Blind Noninferiority Phase 3 Clinical Trials

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PURPOSE

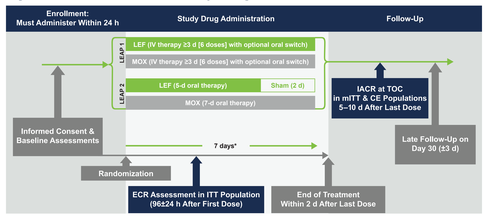
- Among adults with pneumonia, approximately 14% of infections are caused by the atypical pathogens *Mycoplasma pneumoniae, Chlamydophila pneumoniae,* and *Legionella pneumophila*[1]
  - Identification of atypical pathogens in the setting of pneumonia is difficult because of the lack of widely available, specific, validated microbiologic tests for their detection[2,3]
- Lefamulin (LEF), a first-in-class pleuromutilin approved for intravenous (IV) and oral use in adults with community-acquired bacterial pneumonia (CABP),[4] inhibits bacterial protein synthesis and has demonstrated potent in vitro activity against typical (eg, *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae*) and atypical CABP pathogens, including those resistant to other major antibiotic classes[5-7]
  - LEF has further shown accumulation within macrophages and in vitro activity against intracellular pathogens (eg, *C. pneumoniae*)[7,8]
- This investigation assessed the efficacy and tolerability of LEF vs moxifloxacin (MOX) in adults with CABP caused by atypical respiratory pathogens using data from pooled analyses of the Lefamulin Evaluation Against Pneumonia (LEAP) 1 and LEAP 2 phase 3 clinical trials[9,10]

METHODS

Study Design

- Both studies were global, prospective, randomized, double-blind, double-dummy, phase 3 trials **(Figure 1)**[9,10]
- In LEAP 1, patients were randomized to receive LEF 150 mg IV every 12 hours (q12h) for 5–7 days or MOX 400 mg IV every 24 hours (q24h) for 7 days
  - Patients could switch to oral therapy (LEF 600 mg q12h or MOX 400 mg q24h) after 6 IV doses of study drug (~3 days) if predefined improvement criteria were met
- In LEAP 2, patients were randomized to receive oral LEF 600 mg q12h for 5 days or oral MOX 400 mg q24h for 7 days

Figure 1. LEAP 1 and LEAP 2 Study Design



CABP=community-acquired bacterial pneumonia; CE=clinically evaluable (patients who met predefined specified criteria related to protocol adherence); ECR=early clinical response (patient assessed as responder if alive, showed improvement in ≥2 CABP signs/symptoms, no worsening in any CABP sign/symptom, and no receipt of a concomitant nonstudy antibiotic for the current CABP episode); IACR=investigator assessment of clinical response (patients assessed as success if alive, with signs/symptoms of CABP resolved or improved such that no additional antibacterial therapy was administered for CABP); ITT=intent to treat (all randomized patients); IV=intravenous; LEAP=Lefamulin Evaluation Against Pneumonia; LEF=lefamulin; mITT=modified ITT (all randomized patients who received any amount of study drug); MOX=moxifloxacin; TOC=test-of-cure visit.
*In LEAP 1, the original protocol indicated a LEF treatment period of 5 days (but 10 days in patients with CABP due to *L. pneumophila* or methicillin-resistant *Staphylococcus aureus* [MRSA] or in patients with *S. pneumoniae* and bacteremia); however, this was later adjusted to 7 days (except in cases of confirmed MRSA, which continued to receive 10 days of treatment) to reduce medication errors and limit the burden on study sites.[9]

Patients and Assessments

- Adults with CABP of Pneumonia Outcomes Research Team (PORT) risk class III–V and II–IV were eligible for LEAP 1 and LEAP 2, respectively
- In both studies, the primary efficacy endpoint for the US Food and Drug Administration (FDA) was early clinical response (ECR) at 96±24 hours after first dose of study drug in the intent-to-treat (ITT) population
- The European Medicines Agency coprimary endpoints (FDA secondary endpoints) were investigator assessment of clinical response (IACR) at the test-of-cure (TOC) assessment 5–10 days after the last dose of study drug in the modified ITT and clinically evaluable populations
- In both studies, baseline atypical pathogens were identified from specimens collected within 24 hours of the first dose of study drug and confirmed by central or specialized laboratories (see Acknowledgments).[11] Previously described diagnostic modalities varied by pathogen[9]:
  - *M. pneumoniae*: serology (IgG), real-time polymerase chain reaction (RT-PCR) of the community-acquired respiratory distress syndrome (CARDS) toxin gene in sputum, oropharyngeal culture, and RT-PCR of the *repMp1* gene from oropharyngeal specimens
  - *L. pneumophila*: serology, urine antigen testing, sputum culture, and sputum (RT-PCR) of the *ssrA* gene
  - *C. pneumoniae*: serology (IgG) and RT-PCR of the *argR* gene
- *M. pneumoniae* and *L. pneumophila* isolates were tested for LEF susceptibility by broth microdilution

METHODS (continued)

- Patients had to have baseline atypical pathogens to be included in the analyses described herein
  - Within this patient subgroup, efficacy analyses are presented for the microbiological intent-to-treat (microITT) population (randomized patients with ≥1 baseline CABP-causing pathogen), microITT-2 population (randomized patients with ≥1 baseline CABP-causing pathogen detected by a method other than PCR), and microbiologically evaluable (ME) population (met microITT and clinically evaluable population criteria)
  - Treatment-emergent adverse events (TEAEs) are presented for the microITT population

RESULTS

Patients and Baseline Characteristics

- The overall phase 3 ITT population included 1289 patients (LEF, *n*=646; MOX, *n*=643)
- Within the overall pooled microITT population (LEF, *n*=364; MOX, *n*=345), atypical pathogens were identified in 25.0% of patients treated with LEF (91/364) and 25.2% of patients treated with MOX (87/345)
  - Patient demographics and baseline characteristics in this subgroup were generally similar to those of the overall ITT population **(Table 1)**
- Of patients with *M. pneumoniae, L. pneumophila,* and *C. pneumoniae,* most (71.2% [52/73], 96.9% [63/65], and 79.3% [46/58], respectively) were identified by ≥1 standard diagnostic modality **(Figure 2)**
  - 80 patients (44.9%) had polymicrobial infections, of which coinfection with a gram-positive pathogen was the most common **(Figure 3)**
- All 17 cultured *M. pneumoniae* isolates were susceptible to LEF (minimum concentration required to inhibit 50%/90% of isolates was ≤0.001/≤0.001 µg/mL); the 2 cultured *L. pneumophila* isolates were inhibited by 0.5–1 µg/mL LEF

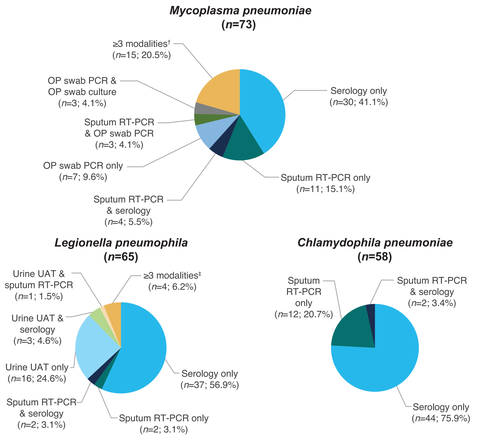
Table 1. Demographics and Baseline Characteristics

Parameter	All Patients (Pooled ITT Population) LEF (*n*=646)	All Patients (Pooled ITT Population) MOX (*n*=643)	Patients With Atypical Pathogens (Pooled microITT Population) LEF (*n*=91)	Patients With Atypical Pathogens (Pooled microITT Population) MOX (*n*=87)
Age, y,* mean (SD)	58.9 (16.5)	58.5 (15.7)	54.7 (17.8)	55.6 (17.5)
Male, *n* (%)	377 (58.4)	340 (52.9)	53 (58.2)	49 (56.3)
White, *n* (%)	513 (79.4)	509 (79.2)	84 (92.3)	74 (85.1)
PORT risk class, *n* (%)				
I/II†	184 (28.5)	192 (29.9)	26 (28.6)	21 (24.1)
III	341 (52.8)	334 (51.9)	49 (53.8)	44 (50.6)
IV/V†	121 (18.7)	117 (18.2)	16 (17.6)	22 (25.3)
Met minor ATS severity criteria,‡ *n* (%)	85 (13.2)	85 (13.2)	15 (16.5)	9 (10.3)
Met modified ATS severity criteria,§ *n* (%)	53 (8.2)	57 (8.9)	8 (8.8)	7 (8.0)
Met SIRS criteria,‖ *n* (%)	621 (96.1)	609 (94.7)	89 (97.8)	82 (94.3)
CURB-65 score,¶ *n* (%)				
0–2	610 (94.4)	604 (93.9)	87 (95.6)	80 (92.0)
3–5	36 (5.6)	39 (6.1)	4 (4.4)	7 (8.0)
Multilobar pneumonia, *n* (%)	170 (26.3)	177 (27.5)	20 (22.0)	17 (19.5)
Bacteremic, *n* (%)	13 (2.0)	12 (1.9)	0	1 (1.1)
Prior antibiotic use,# *n* (%)	147 (22.8)	145 (22.6)	28 (30.8)	23 (26.4)
Baseline pathogen,# *n* (%)				
Streptococcus pneumoniae	216 (33.4)	223 (34.7)	24 (26.4)	29 (33.3)
Staphylococcus aureus	23 (3.6)	10 (1.6)	5 (5.5)	1 (1.1)
Haemophilus influenzae	107 (16.6)	105 (16.3)	8 (8.8)	13 (14.9)
Moraxella catarrhalis	46 (7.1)	22 (3.4)	7 (7.7)	1 (1.1)
Mycoplasma pneumoniae	39 (6.0)	34 (5.3)	39 (42.9)	34 (39.1)
Legionella pneumophila	34 (5.3)	31 (4.8)	34 (37.4)	31 (35.6)
Chlamydophila pneumoniae	27 (4.2)	31 (4.8)	27 (29.7)	31 (35.6)

ATS=American Thoracic Society; BUN=blood urea nitrogen; eCRF=electronic case report form; ITT=intent to treat; LEF=lefamulin; microITT=microbiological ITT; MOX=moxifloxacin; PORT=Pneumonia Outcomes Research Team; SD=standard deviation; SIRS=systemic inflammatory response syndrome; WBC=white blood cell (count).
*Median (range) age, y: all patients, 61 (19–97) LEF vs 60 (19–93) MOX; patients with atypical pathogens, 59 (19–89) LEF vs 56 (19–92) MOX.
†PORT risk class I/II and IV/V for all patients; PORT risk class II and IV for patients with atypical pathogens. PORT risk class was calculated programmatically using data obtained at the site and reported in the eCRF and was not always consistent with the site-reported PORT risk class used for enrollment/stratification.
‡Defined as presence of ≥3 of the following 9 criteria at baseline: respiratory rate ≥30 breaths/min, O_2 saturation <90% or PaO_2 <60 mm Hg, BUN ≥20 mg/dL, WBC <4000 cells/mm³, confusion, multilobar infiltrates, platelets <100,000 cells/mm³, temperature <36°C, or systolic blood pressure <90 mm Hg.[12]
§Defined as presence of ≥3 of the following 6 criteria at baseline: respiratory rate ≥30 breaths/min, SpO_2/FiO_2 <274 where $SpO_2/FiO_2 = 64+0.84\ (PaO_2/FiO_2)$, BUN ≥20 mg/dL, confusion, age ≥65 years, or multilobar infiltrates.[13]
‖Defined as having ≥2 of the following 4 criteria at baseline: temperature <36°C or >38°C; heart rate >90 bpm; respiratory rate >20 breaths/min; and WBC <4000 cells/mm³, WBC >12,000 cells/mm³, or immature polymorphonuclear neutrophils >10%.
¶Defined as confusion of new onset, BUN >19 mg/dL, respiratory rate ≥30 breaths/min, systolic blood pressure <90 mm Hg or diastolic blood pressure ≤60 mm Hg, and age ≥65 years.
#Patients received a single dose of short-acting systemic antibacterial medication within 72 hours before randomization; randomization was stratified and capped such that no more than 25% of the total ITT population met these criteria.
**A patient could have had >1 pathogen identified. Multiple isolates of the same species from the same patient were counted only once.

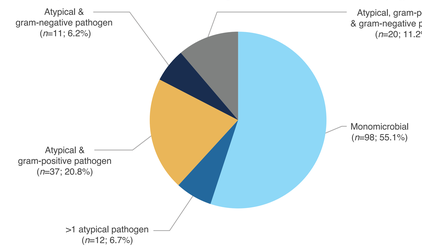
RESULTS (continued)

Figure 2. Diagnostic Modalities for Patients With Atypical Pathogens at Baseline* (Pooled microITT Population [Combined Treatment Groups])



microITT=microbiological intent to treat; *n*=number of patients with the respective baseline pathogen; OP=oropharyngeal; PCR=polymerase chain reaction; RT-PCR=real-time PCR; UAT=urine antigen testing.
*A patient could have had >1 pathogen identified. Multiple isolates of the same species from the same patient identified by the same testing modality were counted only once. Patients were counted only once for each pathogen based on the unique diagnostic modality or combination of diagnostic modalities by which the pathogen was identified. RT-PCR was performed on OP samples; if RT-PCR was positive for *M. pneumoniae*, OP samples were used for isolation of *M. pneumoniae* and for subsequent susceptibility testing. On some occasions, RT-PCR and culture were performed in parallel. Inclusion of *L. pneumophila* as a baseline pathogen from sputum culture did not require an adequate Gram stain. Culture of *C. pneumoniae* by the local laboratories was allowed per protocol, but it was not cultured by any of the laboratories.
†Includes sputum RT-PCR, serology, and OP swab PCR; sputum RT-PCR, OP swab PCR, and OP swab culture; serology, OP swab PCR, and OP swab culture; and sputum RT-PCR, serology, OP swab PCR, and OP swab culture.
‡Includes urine UAT, sputum RT-PCR, and serology; and sputum culture, urine UAT, sputum RT-PCR, and serology.

Figure 3. Pathogen Distribution for Patients With Atypical Pathogens at Baseline* (Pooled microITT Population [Combined Treatment Groups])

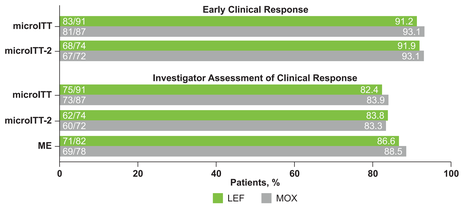


microITT=microbiological intent to treat; *n*=number of patients with the respective baseline pathogen.
*A patient could have had >1 pathogen identified.

Efficacy

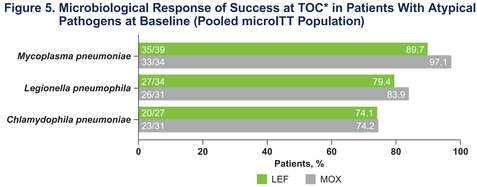
- ECR and IACR rates in patients with baseline atypical pathogens were high, similar between treatment groups **(Figure 4)**, and consistent with results observed in the overall pooled populations
- Microbiological response of success/presumed success at TOC (defined as either microbiologic eradication or, if follow-up cultures were not indicated and not performed, clinical success at TOC) in the microITT population was similar between treatment groups for each atypical pathogen **(Figure 5)**; findings in the microITT-2 and ME populations were consistent

Figure 4. Early Clinical Response and Investigator Assessment of Clinical Response at TOC by Analysis Population in Patients With Atypical Pathogens at Baseline



LEF=lefamulin; ME=microbiologically evaluable; microITT=microbiological intent to treat; MOX=moxifloxacin; TOC=test-of-cure visit.

Figure 5. Microbiological Response of Success at TOC* in Patients With Atypical Pathogens at Baseline (Pooled microITT Population)



EOT=end of treatment; IACR=investigator assessment of clinical response; LEF=lefamulin; microITT=microbiological intent to treat; MOX=moxifloxacin; TOC=test-of-cure visit.
*Microbiological response of success at TOC was defined as either microbiologic eradication (absence of the baseline causative pathogen from repeat cultures obtained between EOT and TOC) or presumed eradication (the IACR at TOC was success and culture was not repeated at TOC).

Safety

- TEAE rates among patients with atypical pathogens at baseline were 34.1% (31/91) and 32.2% (28/87) in the LEF and MOX groups, respectively **(Table 2)**
  - Most TEAEs were mild or moderate in severity and rarely led to study drug discontinuation
  - Results in patients with atypical pathogens at baseline were consistent with those observed in the overall pooled safety population
- Among patients with atypical pathogens at baseline, TEAE system organ classes that occurred in >5% of patients were gastrointestinal disorders and infections and infestations
  - The most common gastrointestinal disorder TEAEs were diarrhea and nausea (LEF, 3.3% [*n*=3]; MOX, 2.3% [*n*=2] for each), and the most common infection and infestation TEAE was urinary tract infection (LEF, 1.1% [*n*=1]; MOX, 1.1% [*n*=1])

Table 2. Overall Summary of TEAEs

Patients, *n* (%)	All Patients (Pooled Safety Population) LEF (*n*=641)	All Patients (Pooled Safety Population) MOX (*n*=641)	Patients With Atypical Pathogens (Pooled microITT Population) LEF (*n*=91)	Patients With Atypical Pathogens (Pooled microITT Population) MOX (*n*=87)
Any TEAE	224 (34.9)	195 (30.4)	31 (34.1)	28 (32.2)
Mild	119 (18.6)	117 (18.3)	16 (17.6)	16 (18.4)
Moderate	78 (12.2)	55 (8.6)	12 (13.2)	7 (8.0)
Severe	27 (4.2)	23 (3.6)	3 (3.3)	5 (5.7)
Related TEAE	99 (15.4)	68 (10.6)	8 (8.8)	7 (8.0)
Serious TEAE	36 (5.6)	31 (4.8)	6 (6.6)	5 (5.7)
Related serious TEAE	3 (0.5)	2 (0.3)	0	0
TEAE leading to death	11 (1.7)	8 (1.2)	1 (1.1)	0
28-d all-cause mortality – deceased at Day 28*	8 (1.2)	7 (1.1)	0	0
TEAE leading to study drug discontinuation	20 (3.1)	21 (3.3)	0	4 (4.6)

ITT=intent to treat; LEF=lefamulin; microITT=microbiological ITT; MOX=moxifloxacin; TEAE=treatment-emergent adverse event.
*Assessed in the ITT population (LEF, *n*=646; MOX, *n*=643).

CONCLUSIONS AND CLINICAL IMPLICATIONS

- Baseline clinical characteristics of patients with atypical pathogens were similar to those of the general patient population with CABP.[14] As with the general patient population, the majority of patients had CABP with a PORT risk class of III, for which outpatient therapy may be appropriate[12,15]
- Therapy with LEF led to high efficacy rates (ECR, IACR, and microbiological) in patients with CABP due to atypical pathogens, including when given as short-course (5-day) oral therapy
- The safety profile of LEF in patients with atypical pathogens was similar to that of the overall safety profile of LEF
- LEF may provide a new empiric IV and oral monotherapy alternative to fluoroquinolones and macrolides in patients with CABP caused by atypical pathogens

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Acknowledgments & Disclosures

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