Efficacy in Adults With Moderate to Severe Community-Acquired Bacterial Pneumonia and Pneumonia Outcomes Research Team Risk Class III to V: Results of a Pooled Analysis of Lefamulin Evaluation Against Pneumonia (LEAP) 1 and LEAP 2 Study Outcomes

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INTRODUCTION & PURPOSE

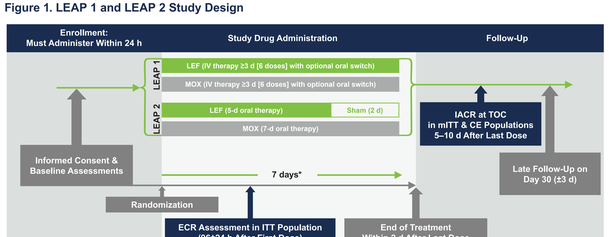
- Pneumonia, a leading cause of hospitalization in the United States, has prognoses ranging from rapid resolution to death, the likelihood of which can be estimated via the Pneumonia Outcomes Research Team (PORT) risk class[1-3]
  - Patients with PORT risk class I/II have predicted mortality rates of <1% and are generally managed as outpatients[1,2]
  - Patients with PORT risk class III have predicted mortality rates of approximately 3% and may be managed as inpatients or outpatients based on the judgment of the healthcare provider[2]
  - Patients with PORT risk class IV/V have higher predicted mortality rates (8%–31%) and are generally managed as inpatients[1,2]
- Lefamulin (LEF), a first-in-class pleuromutilin antibiotic approved for intravenous (IV) and oral use in adults with community-acquired bacterial pneumonia (CABP),[4] selectively inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit at the A- and P-sites in the peptidyl transferase center[5,6]
  - LEF demonstrated noninferiority to moxifloxacin (MOX) in the IV-to-oral switch Lefamulin Evaluation Against Pneumonia (LEAP) 1 phase 3 study[7] in patients with CABP and PORT risk class III-V and in the LEAP 2 oral-only phase 3 study[8] in patients with CABP and PORT risk class II-IV
  - Because LEF can be administered via the oral or IV route,[4] it is a good candidate for use in patients transitioning from inpatient to outpatient care and needing to switch from IV to oral antibiotics[9]
- We report results of pooled analyses of data from the LEAP 1 and LEAP 2 trials assessing efficacy and safety in patients with PORT risk class III and IV/V

METHODS

Study Design and Patients

- Both studies were prospective, randomized, double-blind, double-dummy, phase 3 trials **(Figure 1)**[7,8]
  - In LEAP 1, patients with PORT risk class III–V (25% required to have PORT risk class of IV or V) 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 (approximately 3 days) if predefined improvement criteria were met
  - In LEAP 2, patients with PORT risk class II–IV (50% required to have PORT risk class of III or IV) were randomized to receive oral LEF 600 mg q12h for 5 days or oral MOX 400 mg q24h for 7 days
- In both studies, randomization was stratified by PORT risk class
- Key study exclusion criteria in LEAP 1 and LEAP 2 included the following:
  - Evidence of significant hepatic disease (eg, known acute hepatitis, including active viral hepatitis; aspartate aminotransferase [AST] or alanine aminotransferase [ALT] >5× upper limit of normal [ULN]; total bilirubin >3× ULN [unless Gilbert's disease]; AST or ALT >3× ULN and total bilirubin >2× ULN; history of cirrhosis; manifestation of end-stage liver disease, including ascites and hepatic encephalopathy)
  - At risk for major cardiac events or dysfunction (eg, known QT prolongation or taking a medication with the potential for QT prolongation, clinically significant hypokalemia not treated before randomization, clinically unstable cardiac disease, complete left bundle branch block)
  - Have a life expectancy of ≤3 months because of any disease other than the current episode of CABP (eg, current or impending respiratory failure, acute heart failure, shock, acute coronary syndrome, unstable arrhythmia, hypertensive emergency, clinically relevant gastrointestinal bleeding, profound metabolic abnormality, acute cerebrovascular event)
  - Have known or suspected severe immunosuppression, defined as receipt of corticosteroid therapy (≥20 mg prednisone/day or equivalent for >4 weeks) within the previous 8 weeks; had solid organ or bone marrow transplantation within the previous 12 months; currently receiving cytotoxic chemotherapy; have or anticipated to have neutropenia (<500 neutrophils/mm^3) or thrombocytopenia (<50,000 platelets/mm^3); or have known HIV infection and a CD4 count <200/mm^3

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 and symptoms, no worsening in any CABP sign or 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 and 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 *Legionella pneumophila* or methicillin-resistant *Staphylococcus aureus* [MRSA] or in patients with *Streptococcus 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.[7] If MRSA was suspected, linezolid or linezolid placebo was added to MOX or LEF therapy, respectively. A total of 14/275 (5.1%) patients randomized to MOX and 9/276 (3.3%) patients randomized to LEF received linezolid and linezolid placebo, respectively, because of suspected MRSA at baseline.

METHODS (continued)

Assessments

- Pooled efficacy analyses were evaluated using a 10% noninferiority margin
  - The primary efficacy endpoint for the US Food and Drug Administration (FDA) was early clinical response (ECR) at 96±24 hours after the first dose of study drug in the intent-to-treat (ITT) population (see **Figure 1** footnote for study population definitions)
  - The European Medicines Agency coprimary efficacy endpoints (FDA secondary endpoints) were investigator assessment of clinical response (IACR) at the test-of-cure assessment 5–10 days after the last dose of study drug in the modified ITT (mITT) and clinically evaluable populations
- Safety was assessed in all randomized and treated patients (safety analysis set); treatment-emergent adverse events (TEAEs) were monitored throughout each trial at all study visits and by patient reporting, as needed

RESULTS

Patients

- In the pooled ITT population, 1289 patients were randomized to LEF (*n*=646) or MOX (*n*=643)
  - Of these patients, approximately half (LEF, *n*=341 [52.8%]; MOX, *n*= 334 [51.9%]) were PORT risk class III and more than 18% (LEF, *n*=121 [18.7%]; MOX, *n*=117 [18.2%]) were PORT risk class IV/V (**Table 1**)
  - <1% of LEF (*n*=5; 0.8%) and MOX (*n*=5; 0.8%) patients were PORT risk class V
- As expected, patients with PORT risk class IV/V were older and more likely to have comorbidities than patients with PORT risk class III (**Table 1**)
  - 42% of patients with PORT risk class IV/V and 16% of patients with PORT risk class III were aged ≥75 years
  - Compared with patients with PORT risk class III, a greater percentage of patients with PORT risk class IV/V had comorbidities such as renal impairment, diabetes mellitus, and asthma or chronic obstructive pulmonary disease

Table 1. Demographics and Baseline Characteristics (Pooled ITT Population)

Parameter	Patients, *n* (%)			
	LEF*		MOX*	
	PORT III (*n*=341)	PORT IV/V (*n*=121)	PORT III (*n*=334)	PORT IV/V (*n*=117)
Age, *y*, mean (SD)	60.7 (15.3)	69.1 (14.2)	58.8 (14.3)	70.7 (12.6)
Male, *n* (%)	202 (59.2)	86 (71.1)	183 (54.8)	71 (60.7)
White, *n* (%)	277 (81.2)	92 (76.0)	277 (82.9)	96 (82.1)
BMI, kg/m^2, mean (SD)	26.4 (5.4)	26.6 (6.8)	26.3 (6.1)	27.3 (6.5)
Renal status,† *n* (%)				
Normal function	148 (43.4)	34 (28.1)	166 (49.7)	25 (21.4)
Mild impairment	129 (37.8)	30 (24.8)	104 (31.1)	36 (30.8)
Moderate impairment	61 (17.9)	51 (42.1)	63 (18.9)	51 (43.6)
Severe impairment	3 (0.9)	4 (3.3)	1 (0.3)	4 (3.4)
Met SIRS criteria,‡ *n* (%)	330 (96.8)	116 (95.9)	318 (95.2)	108 (92.3)
History of diabetes mellitus, *n* (%)	39 (11.4)	26 (21.5)	43 (12.9)	28 (23.9)
History of asthma or COPD, *n* (%)	60 (17.6)	33 (27.3)	51 (15.3)	37 (31.6)
Prior antibiotic use,§ *n* (%)	77 (22.6)	26 (21.5)	77 (23.1)	30 (25.6)
Smoking history, *n* (%)	157 (46.0)	58 (47.9)	133 (39.8)	42 (35.9)

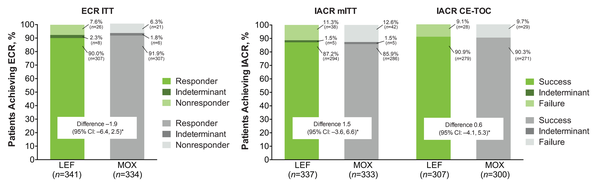
BMI=body mass index; COPD=chronic obstructive pulmonary disease; CrCl=creatinine clearance; ITT=intent to treat; LEAP=Lefamulin Evaluation Against Pneumonia; LEF=lefamulin; MOX=moxifloxacin; PORT=Pneumonia Outcomes Research Team; SIRS=systemic inflammatory response syndrome; WBC=white blood cell (count).
Data for PORT I/II patients not shown.
*In LEAP 1, 397 patients were PORT risk class III, 146 were PORT risk class IV, and 7 were PORT risk class V; in LEAP 2, 278 patients were PORT risk class III, 82 were PORT risk class IV, and 3 were PORT risk class V.
†National Kidney Foundation categories of renal impairment[10] based on baseline central laboratory serum creatinine. When baseline central laboratory serum creatinine was not available, local serum creatinine results were used. Renal impairment categories are: normal [CrCl ≥90 mL/min], mild [CrCl of 60 to <90 mL/min], moderate [CrCl of 30 to <60 mL/min], and severe [CrCl <30 mL/min].
‡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/mm^3, WBC >12,000 cells/mm^3, or immature polymorphonuclear neutrophils >10%.
§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.

Efficacy

- ECR and IACR response rates were similarly high between the LEF and MOX treatment groups across patient subgroups with PORT III (**Figure 2**) and PORT IV/V risk classes (**Figure 3**)
- ECR and IACR rates were numerically higher in patients with PORT risk class III vs PORT risk class IV/V
  - ECR was achieved in 90.0% (LEF) and 91.9% (MOX) of patients in the PORT risk class III group (**Figure 2**) and 83.5% (LEF) and 82.1% (MOX) of patients in the PORT risk class IV/V group (**Figure 3**)
  - IACR success (pooled mITT population) was achieved in 87.2% (LEF) and 85.9% (MOX) of patients in the PORT risk class III group (**Figure 2**) and 77.5% (LEF) and 82.8% (MOX) of patients in the PORT risk class IV/V group (**Figure 3**)

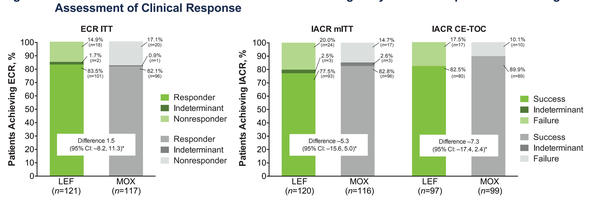
RESULTS (continued)

Figure 2. Pooled Patients With PORT Risk Class III Achieving Early Clinical Response and Investigator Assessment of Clinical Response



CE-TOC=clinically evaluable at test of cure; ECR=early clinical response; IACR=investigator assessment of clinical response; ITT=intent to treat; LEF=lefamulin; mITT=modified ITT; MOX=moxifloxacin; PORT=Pneumonia Outcomes Research Team.
*Weighted treatment difference and CI were computed using the method of Miettinen and Nurminen and adjusted for study, with the inverse variance of effect size as stratum weights.

Figure 3. Pooled Patients With PORT Risk Class IV/V Achieving Early Clinical Response and Investigator Assessment of Clinical Response



CE-TOC=clinically evaluable at test of cure; ECR=early clinical response; IACR=investigator assessment of clinical response; ITT=intent to treat; LEF=lefamulin; mITT=modified ITT; MOX=moxifloxacin; PORT=Pneumonia Outcomes Research Team.
*Weighted treatment difference and CI were computed using the method of Miettinen and Nurminen and adjusted for study, with the inverse variance of effect size as stratum weights.

Safety

- LEF and MOX had generally similar safety profiles in patients with PORT III and PORT IV/V risk classes (**Table 2**), although overall TEAE and serious TEAE rates were higher in patients with PORT risk class IV/V (44.9%; 11.9%) vs PORT risk class III (29.1%; 3.9%)
- Mortality rates were low, but rates in patients with PORT risk class IV/V (LEF, 4.2%; MOX, 5.2%) were higher than those in patients with PORT risk class III (LEF, 1.5%; MOX, 0.6%)
- The most common TEAEs were generally similar with LEF and MOX treatment in patients with PORT III and IV/V risk classes (**Table 3**)

Table 2. Overall Summary of TEAEs in Patients With PORT Risk Class III and IV/V (Safety Analysis Set)

TEAE	Patients, *n* (%)			
	LEF		MOX	
	PORT III (*n*=337)	PORT IV/V (*n*=120)	PORT III (*n*=333)	PORT IV/V (*n*=116)
Any TEAE	97 (28.8)	55 (45.8)	98 (29.4)	51 (44.0)
Mild	56 (16.6)	24 (20.0)	62 (18.6)	26 (22.4)
Moderate	32 (9.5)	18 (15.0)	26 (7.8)	14 (12.1)
Severe	9 (2.7)	13 (10.8)	10 (3.0)	11 (9.5)
Serious TEAE	12 (3.6)	15 (12.5)	14 (4.2)	13 (11.2)
TEAE leading to study drug discontinuation	8 (2.4)	9 (7.5)	8 (2.4)	8 (6.9)
TEAE leading to death by study Day 28	3 (0.9)	5 (4.2)	2 (0.6)	5 (4.3)
TEAE leading to death (over entire study duration)	5 (1.5)*	5 (4.2)	2 (0.6)	6 (5.2)†

LEF=lefamulin; MOX=moxifloxacin; PORT=Pneumonia Outcomes Research Team; TEAE=treatment-emergent adverse event.
*2 patients in the LEF group had a TEAE leading to death after study Day 28: 1 patient died on study Day 32 from sepsis, which was first reported on study Day 31; the second patient died on study Day 57 from endocarditis, which was first reported on study Day 24.
†1 patient in the MOX group had a TEAE leading to death on study Day 48 due to testicular seminoma, which was first reported on study Day 21.

Table 3. TEAEs Occurring in >2% of Patients With PORT Risk Class III or IV/V in Either Treatment Group (Safety Analysis Set)

TEAE	Patients, *n* (%)			
	LEF		MOX	
	PORT III (*n*=337)	PORT IV/V (*n*=120)	PORT III (*n*=333)	PORT IV/V (*n*=116)
Diarrhea	14 (4.2)	5 (4.2)	18 (5.4)	7 (6.0)
Nausea	8 (2.4)	7 (5.8)	5 (1.5)	4 (3.4)
Headache	4 (1.2)	2 (1.7)	7 (2.1)	1 (0.9)
Hypokalemia	5 (1.5)	3 (2.5)	3 (0.9)	4 (3.4)
Insomnia	5 (1.5)	3 (2.5)	5 (1.5)	1 (0.9)
Hypertension	0	3 (2.5)	6 (1.8)	3 (2.6)
Urinary tract infection	1 (0.3)	3 (2.5)	2 (0.6)	4 (3.4)
Vomiting	5 (1.5)	3 (2.5)	1 (0.3)	1 (0.9)
Infusion site pain	8 (2.4)	0	0	0

LEF=lefamulin; MOX=moxifloxacin; PORT=Pneumonia Outcomes Research Team; TEAE=treatment-emergent adverse event.

CONCLUSIONS

- LEF demonstrated high and similar rates in efficacy outcomes in both the LEAP 1 and LEAP 2 phase 3 trials in adults with CABP compared with MOX
  - Similarly, among patients with PORT III and PORT IV/V risk classes, effective ECR and sustained success rates with LEF were high and similar to those with MOX
- LEF and MOX had similar safety profiles and were well tolerated, with higher TEAE and serious TEAE rates seen in patients with PORT IV/V vs PORT III risk classes, consistent with the older and sicker demographic of PORT IV/V patients
  - The favorable safety profile observed in patients with PORT risk class III suggests that these patients may be candidates for outpatient treatment, in accordance with Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) consensus guidelines[9]
- LEF is a promising new IV-to-oral empiric monotherapy for patients with CABP and PORT risk class II–V

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