P0449

Lefamulin Efficacy and Safety in Adults With Community-Acquired Bacterial Pneumonia: Pooled Analysis of the Lefamulin Evaluation Against Pneumonia (LEAP) 1 and LEAP 2 Trials by Age Group, Including in Patients Aged ≥85 Years

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PURPOSE

- Community-acquired bacterial pneumonia (CABP) is the most common cause of death due to infectious disease in US adults aged ≥65 years[1]
- Worldwide, the aging population is increasing,[2] and older patients with CABP are especially at risk with higher hospitalization and mortality rates than younger patients[1-3]
  – Those with advanced age are more vulnerable to having or developing CABP complications,[1,3,4] and treatment is often more difficult in these patients (eg, because of multimorbidity, immunosenescence, polypharmacy)[1-3]
- Increasing rates of bacterial resistance and the undesirable risks and adverse effects associated with current treatments (eg, fluoroquinolone-associated disability) are driving the need for new therapeutic options for CABP[5]
  – Moreover, some fluoroquinolone-associated adverse effects (eg, aortic tears/ruptures, hypoglycemia, tendon rupture) are observed more frequently in patients aged >60 years[6-9]
- The efficacy and safety of lefamulin (LEF), a pleuromutilin antibiotic approved for intravenous (IV) and oral use in adults with CABP, were shown in 2 noninferiority phase 3 trials, Lefamulin Evaluation Against Pneumonia (LEAP) 1 and LEAP 2[10-12]
- We report efficacy and safety outcomes by age groups (18–64, 65–74, 75–84, and ≥85 years) using pooled data from LEAP 1 and LEAP 2

METHODS

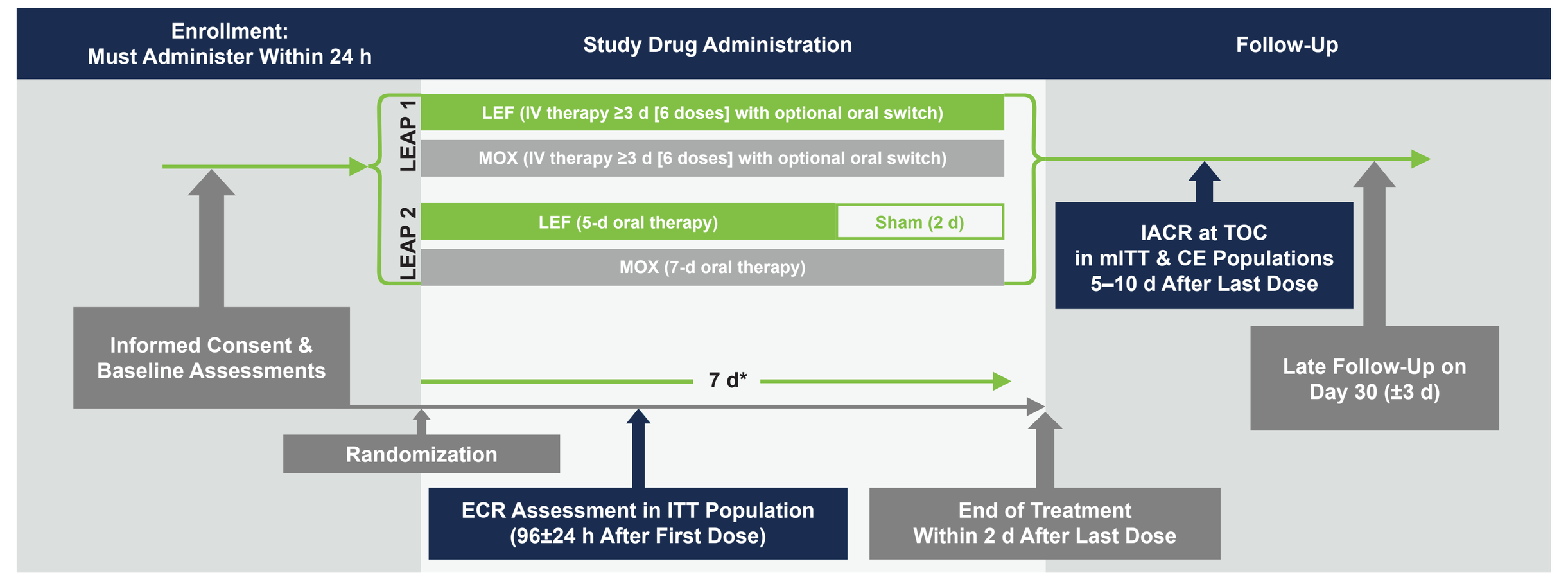
Study Design

- Both studies were prospective, randomized, double-blind, double-dummy, phase 3 trials **(Figure 1)**[11,12]
- In LEAP 1, patients were randomized to receive LEF 150 mg IV every 12 hours (q12h) for 5–7 days or moxifloxacin (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 were randomized to receive oral LEF 600 mg q12h for 5 days or oral MOX 400 mg q24h for 7 days

Patients and Assessments

- Patients aged ≥18 years with CABP of PORT risk class ≥III or 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 (see **Figure 1** footnote for study population definitions)
- 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 (mITT) and clinically evaluable (CE) populations
- Safety was assessed in all randomized patients who received any amount of study drug (safety population)
  – Treatment-emergent adverse events (TEAEs) were monitored throughout each trial at all study visits and by patient reporting, as needed
  – The investigator evaluated TEAEs for relationship to study drug (not related, possibly related, probably related, or definitely related)
- For this post hoc analysis, descriptive statistics were generated to characterize demographics, baseline characteristics, efficacy, and safety outcomes by age using pooled LEAP 1 and LEAP 2 data

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; MRSA=methicillin-resistant *Staphylococcus aureus*; TOC=test of cure visit.
*In LEAP 1, the original protocol indicated a LEF treatment period of 5 d (but 10 d in patients with CABP due to *Legionella pneumophila* or MRSA or in patients with *Streptococcus pneumoniae* and bacteremia); however, this was later adjusted to 7 d (except in cases of confirmed MRSA, which continued to receive 10 d of treatment) to reduce medication errors and limit the burden on study sites.[11] 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.

RESULTS

Patients

- The pooled ITT population included 1289 patients randomized to LEF (*n*=646) or MOX (*n*=643)
  – Patients were predominantly male (55.6%) and White (79.3%), with a mean (SD) age of 58.7 (16.1) years
- Overall, 772 patients (59.9%) were aged 18–64 years, 297 (23.0%) were aged 65–74 years, 177 (13.7%) were aged 75–84 years, and 43 (3.3%) were aged ≥85 years **(Table 1)**
  – Older patients (ie, those aged 75–84, ≥85 years) were more likely to have comorbidities (eg, moderate/severe renal impairment, hypertension, arrhythmia) vs younger patients (ie, those aged 18–64, 65–74 years)

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

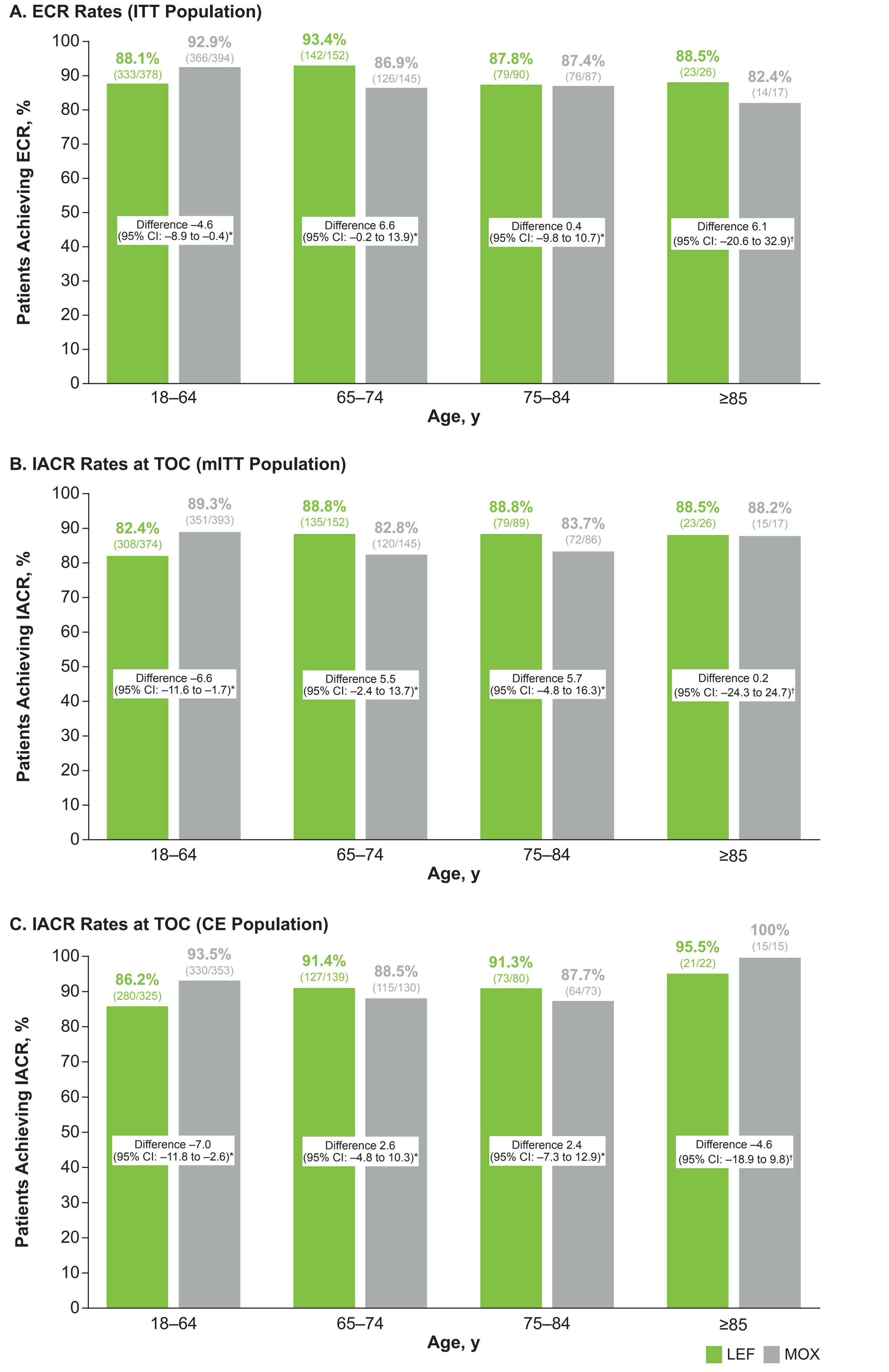
Parameters	Patient Age Group							
	18–64 y		65–74 y		75–84 y		≥85 y	
	LEF (*n*=378)	MOX (*n*=394)	LEF (*n*=152)	MOX (*n*=145)	LEF (*n*=90)	MOX (*n*=87)	LEF (*n*=26)	MOX (*n*=17)
Age, y, mean (SD)	48.2 (12.4)	48.9 (11.7)	68.9 (2.5)	68.9 (2.8)	78.8 (2.6)	78.5 (2.6)	87.7 (2.8)	88.1 (2.6)
Male, *n* (%)	219 (57.9)	209 (53.0)	93 (61.2)	80 (55.2)	51 (56.7)	42 (48.3)	14 (53.8)	9 (52.9)
White, *n* (%)	307 (81.2)	313 (79.4)	119 (78.3)	114 (78.6)	69 (76.7)	69 (79.3)	18 (69.2)	13 (76.5)
BMI, kg/m², mean (SD)	26.5 (5.9)	26.3 (6.4)	27.0 (5.9)	26.9 (5.6)	26.0 (5.5)	26.4 (5.2)	25.1 (4.9)	25.0 (4.5)
Renal status,* *n* (%)								
Normal function	265 (70.1)	279 (70.8)	42 (27.6)	30 (20.7)	4 (4.4)	3 (3.4)	0	0
Mild impairment	93 (24.6)	84 (21.3)	73 (48.0)	76 (52.4)	32 (35.6)	31 (35.6)	3 (11.5)	1 (5.9)
Moderate impairment	19 (5.0)	30 (7.6)	36 (23.7)	37 (25.5)	50 (55.6)	49 (56.3)	20 (76.9)	16 (94.1)
Severe impairment	0	1 (0.3)	1 (0.7)	2 (1.4)	3 (3.3)	3 (3.4)	3 (11.5)	0
Missing	1 (0.3)	0	0	0	1 (1.1)	1 (1.1)	0	0
Smoking history, *n* (%)	180 (47.6)	164 (41.6)	62 (40.8)	49 (33.8)	35 (38.9)	26 (29.9)	7 (26.9)	3 (17.6)
Hypertension history, *n* (%)	94 (24.9)	99 (25.1)	80 (52.6)	77 (53.1)	59 (65.6)	64 (73.6)	15 (57.7)	13 (76.5)
Baseline liver enzyme elevation,† *n* (%)	77 (20.4)	88 (22.3)	24 (15.8)	38 (26.2)	13 (14.4)	15 (17.2)	5 (19.2)	3 (17.6)
Asthma/COPD, *n* (%)	52 (13.8)	53 (13.5)	35 (23.0)	34 (23.4)	29 (32.2)	21 (24.1)	3 (11.5)	5 (29.4)
Diabetes mellitus history, *n* (%)	42 (11.1)	35 (8.9)	17 (11.2)	30 (20.7)	15 (16.7)	20 (23.0)	6 (23.1)	3 (17.6)
Arrhythmia history, *n* (%)	13 (3.4)	4 (1.0)	16 (10.5)	9 (6.2)	10 (11.1)	16 (18.4)	4 (15.4)	1 (5.9)
Prior antibiotic use,‡ *n* (%)	91 (24.1)	80 (20.3)	29 (19.1)	36 (24.8)	20 (22.2)	27 (31.0)	7 (26.9)	2 (11.8)
PORT risk class,§ *n* (%)								
I/II	149 (39.4)	154 (39.1)	31 (20.4)	32 (22.1)	4 (4.4)	6 (6.9)	0	0
III	184 (48.7)	208 (52.8)	94 (61.8)	79 (54.5)	53 (58.9)	43 (49.4)	10 (38.5)	4 (23.5)
IV/V	45 (11.9)	32 (8.1)	27 (17.7)	34 (23.4)	33 (36.7)	38 (43.7)	16 (61.5)	13 (76.5)
CURB-65 score,‖ *n* (%)								
0–2	375 (99.2)	383 (97.2)	134 (88.2)	131 (90.3)	80 (88.9)	77 (88.5)	21 (80.8)	13 (76.5)
3–5	3 (0.8)	11 (2.8)	18 (11.8)	14 (9.7)	10 (11.1)	10 (11.5)	5 (19.2)	4 (23.5)
Minor ATS severity criteria,‖ *n* (%)	65 (17.2)	66 (16.8)	13 (8.6)	10 (6.9)	2 (2.2)	8 (9.2)	5 (19.2)	1 (5.9)
Modified ATS severity criteria,‖ *n* (%)	12 (3.2)	10 (2.5)	22 (14.5)	27 (18.6)	11 (12.2)	18 (20.7)	8 (30.8)	2 (11.8)
SIRS,‖ *n* (%)	363 (96.0)	371 (94.2)	148 (97.4)	139 (95.9)	84 (93.3)	83 (95.4)	26 (100.0)	16 (94.1)
Bacteremia, *n* (%)	7 (1.9)	7 (1.8)	1 (0.7)	3 (2.1)	4 (4.4)	2 (2.3)	1 (3.8)	0

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ATS=American Thoracic Society; BMI=body mass index; COPD=chronic obstructive pulmonary disease; CrCl=creatinine clearance; ITT=intent to treat; LEF=lefamulin; MOX=moxifloxacin; PORT=Pneumonia Outcomes Research Team; SIRS=Systemic Inflammatory Response Syndrome; ULN=upper limit of normal.
*Renal impairment categories were defined as follows: 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 AST or ALT >ULN.
‡Patients received a single dose of short-acting systemic antibacterial medication within 72 h before randomization; randomization was stratified and capped such that no more than 25% of the total ITT population met these criteria.
§PORT risk class was calculated programmatically using data obtained at the site and reported in the electronic case report form and was not always consistent with the site-reported PORT risk class used for enrollment/stratification.
‖Refer to published manuscripts[11,12] for full details of criteria and definitions.

Early Clinical Response and Investigator Assessment of Clinical Response

- For all age groups, high and similar ECR rates (LEF ≥88%; MOX ≥82%; **Figure 2A**) were seen with each treatment, including in patients aged ≥85 years (LEF 88.5%; MOX 82.4%)
- IACR success rates at TOC were also high and similar across all age groups in the mITT (LEF ≥82%; MOX ≥83%; **Figure 2B**) and CE (LEF ≥86%; MOX ≥88%; **Figure 2C**) populations

Figure 2. Pooled Early Clinical Responder and Investigator Assessment of Clinical Response Success Rates



CE=clinically evaluable; ECR=early clinical response; IACR=investigator assessment of clinical response; ITT=intent to treat; LEF=lefamulin; mITT=modified ITT; MOX=moxifloxacin; TOC=test of cure.
*Computed using the method of Miettinen and Nurminen, adjusted for study, with the inverse variance of the effect size as the stratum weights.
†Absolute treatment difference (LEF minus MOX); CI computed using a continuity corrected Z-test.

Safety

- With both treatments, rates of serious TEAEs and TEAEs leading to death were somewhat lower in younger (3.4%–5.3% and 0.5%–2.6%, respectively) vs older (5.9%–12.4% and 0%–4.5%) patients **(Table 2)**
- Rates of study drug discontinuation due to TEAEs were similar for older (3.5%) and younger (3.0%) patients with LEF, whereas rates with MOX were higher in older (7.8%) vs younger (2.4%) patients
- The most common TEAEs were gastrointestinal, with generally similar rates across age groups for LEF (8.6%–15.0%) and MOX (5.9%–14.0%)

Table 2. Overall Summary of TEAEs (Safety Population)

TEAEs	Patient Age Group							
	18–64 y		65–74 y		75–84 y		≥85 y	
	LEF (*n*=374)	MOX (*n*=393)	LEF (*n*=152)	MOX (*n*=145)	LEF (*n*=89)	MOX (*n*=86)	LEF (*n*=26)	MOX (*n*=17)
All TEAEs*	143 (38.2)	115 (29.3)	34 (22.4)	46 (31.7)	36 (40.4)	30 (34.9)	11 (42.3)	4 (23.5)
Related TEAEs†	63 (16.8)	39 (9.9)	17 (11.2)	18 (12.4)	17 (19.1)	9 (10.5)	2 (7.7)	2 (11.8)
TEAEs by severity								
Mild	79 (21.1)	73 (18.6)	15 (9.9)	26 (17.9)	16 (18.0)	16 (18.6)	9 (34.6)	2 (11.8)
Moderate	53 (14.2)	32 (8.1)	13 (8.6)	16 (11.0)	12 (13.5)	7 (8.1)	0	0
Severe	11 (2.9)	10 (2.5)	6 (3.9)	4 (2.8)	8 (9.0)	7 (8.1)	2 (7.7)	2 (11.8)
Serious TEAEs	15 (4.0)	16 (4.1)	8 (5.3)	5 (3.4)	11 (12.4)	9 (10.5)	2 (7.7)	1 (5.9)
TEAEs leading to study drug discontinuation	12 (3.2)	8 (2.0)	4 (2.6)	5 (3.4)	4 (4.5)	6 (7.0)	0	2 (11.8)
TEAEs leading to death (by study Day 28)	2 (0.5)	2 (0.5)	3 (2.0)	2 (1.4)	3 (3.4)	3 (3.5)	0	0
TEAE leading to death (over entire study duration)	2 (0.5)	3 (0.8)	4 (2.6)	2 (1.4)	4 (4.5)	3 (3.5)	1 (3.8)	0

AE=adverse event; LEF=lefamulin; MedDRA=Medical Dictionary for Regulatory Activities; MOX=moxifloxacin; TEAE=treatment-emergent AE.
*A TEAE was defined as an AE that started or worsened at or during the time of or after the first study drug administration. An AE with an unknown start date or partial date was categorized as a TEAE. AEs were coded according to MedDRA version 20.0. Patients with multiple events in each category were counted only once in that category.
†Related TEAEs were defined as TEAEs that were considered "definitely," "probably," or "possibly" related to study drug by the investigator. If the TEAE relationship was missing, it was considered "related."

Table 3. TEAEs by Preferred Term in ≥2% of Patients (Safety Population)

TEAEs*	Patient Age Group							
	18–64 y		65–74 y		75–84 y		≥85 y	
	LEF (*n*=374)	MOX (*n*=393)	LEF (*n*=152)	MOX (*n*=145)	LEF (*n*=89)	MOX (*n*=86)	LEF (*n*=26)	MOX (*n*=17)
Diarrhea	33 (8.8)	18 (4.6)	9 (5.9)	3 (2.1)	5 (5.6)	4 (4.7)	0	0
Nausea	20 (5.3)	7 (1.8)	3 (2.0)	5 (3.4)	2 (2.2)	1 (1.2)	2 (7.7)	0
Vomiting	11 (2.9)	2 (0.5)	0	2 (1.4)	4 (4.5)	0	0	0
Headache	7 (1.9)	10 (2.5)	1 (0.7)	1 (0.7)	1 (1.1)	0	0	0
ALT increased	7 (1.9)	8 (2.0)	1 (0.7)	2 (1.4)	0	0	0	0
Hypokalemia	6 (1.6)	2 (0.5)	0	3 (2.1)	1 (1.1)	1 (1.2)	1 (3.8)	1 (5.9)
Insomnia	4 (1.1)	6 (1.5)	1 (0.7)	2 (1.4)	3 (3.4)	1 (1.2)	0	0
Pneumonia	4 (1.1)	1 (0.3)	3 (2.0)	1 (0.7)	1 (1.1)	0	1 (3.8)	0
COPD	4 (1.1)	1 (0.3)	2 (1.3)	2 (1.4)	2 (2.2)	0	0	0
Hypertension	3 (0.8)	5 (1.3)	1 (0.7)	4 (2.8)	3 (3.4)	2 (2.3)	0	0
Urinary tract infection	2 (0.5)	4 (1.0)	0	1 (0.7)	2 (2.2)	3 (3.5)	1 (3.8)	1 (5.9)
Oral candidiasis	2 (0.5)	1 (0.3)	0	0	0	2 (2.3)	0	0
Leukocyturia	0	2 (0.5)	0	0	1 (1.1)	2 (2.3)	0	0
Atrial fibrillation	0	1 (0.3)	1 (0.7)	1 (0.7)	2 (2.2)	2 (2.3)	0	0

AE=adverse event; ALT=alanine aminotransferase; COPD=chronic obstructive pulmonary disease; LEF=lefamulin; MedDRA=Medical Dictionary for Regulatory Activities; MOX=moxifloxacin; TEAE= treatment-emergent AE.
*A TEAE was defined as an AE that started or worsened at or during the time of or after the first study drug administration. An AE with an unknown start date or partial date was categorized as a TEAE. AEs were coded according to MedDRA version 20.0. Although a patient may have had ≥2 TEAEs, the patient is counted only once within a preferred term category.

CONCLUSIONS AND CLINICAL IMPLICATIONS

- LEF demonstrated high ECR and IACR success rates across all age groups, including among patients aged ≥85 years
- LEF demonstrated similar safety and tolerability across all age groups
- LEF provides a safe and effective empiric monotherapy alternative to fluoroquinolones for the treatment of CABP in patients with advanced age and comorbidities

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