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REVIEW

# Efficacy of Lefamulin for Community-Acquired Bacterial Pneumonia (CABP) Patients: Pooled Analysis of the Lefamulin Evaluation Against Pneumonia (LEAP) 1, LEAP 2 and LEAP China Trials

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**Purpose:** Lefamulin represents a newly developed pleuromutilin antibiotic utilized for treating Community-Acquired Bacterial Pneumonia (CABP). Two pivotal Phase 3 studies, the Lefamulin Evaluation Against Pneumonia (LEAP) 1 and LEAP 2 trials, along with the bridging LEAP China trial, each confirmed that Lefamulin has proven efficacy and is non-inferior to active control treatments. This study conducted a post-hoc pooled analysis of these trials to assess Lefamulin's overall efficacy and its effects on specific patient groups, particularly the elderly and those at high risk of drug resistance.

**Methods:** Trials compared lefamulin to moxifloxacin in adults with CABP. The primary outcome was early clinical response (ECR). Secondary outcomes included investigator assessment of clinical response (IACR), and these responses in subgroups, such as severe patients, elderly patients, and those with prior antibiotic treatment. The pooled analysis was conducted post hoc, using noninferiority margin of 10% and 95% confidence intervals.

**Results:** Lefamulin (n=728) can provide sustained high efficacy, which was noninferior to moxifloxacin (n=683). ECR and IACR success rates demonstrated similar elevation (≥ 84.0%). Comparable and elevated ECR and IACR rates across subgroup of PORT risk class III to V(84.1–88.6%) and subgroup of prior antibiotic treatment (81.8–85.6%) were observed. In the subgroup of age over 65 years old, higher ECR of lefamulin vs moxifloxacin in each ten years-stratification (65–74 years old: 87.2% vs 86.5%; 75–84 years old: 86.8 vs 85.4%; ≥85 years old: 88.5 vs 82.4%). The older the age over 65 years old, the more favorable lefamulin.

**Conclusion:** Lefamulin, non-inferior to moxifloxacin, showed high effectiveness in CABP patients, especially in patients over 65 years old, those with PORT III–V or prior antibiotic treatment.

**Keywords:** community-acquired bacterial pneumonia, efficacy, lefamulin, moxifloxacin

## Introduction

Community-acquired pneumonia (CAP), referring to pneumonia acquired outside of hospitals, ranks among the most prevalent infectious diseases and is linked to marked morbidity and mortality.[1,2] The incidence of CAP among adults can reach up to 14 per 1000 individuals,[3] with approximately 50% of patients requiring hospitalization and a mortality of approximately 0.7 per 1000 annually.[4,5] Numerous pathogens, exceeding 100 distinct types, have been identified as contributing factors to CAP, encompassing bacterial, viral and fungal agents.[6] Community-Acquired Bacterial Pneumonia (CABP) is the primary subtype of CAP, with *Streptococcus pneumoniae* (19%), *Mycoplasma pneumoniae* (15.5%), and *Klebsiella pneumoniae* (10.5%) being the major pathogens.[7] According to multiple domestic adult epidemiological surveys, *Mycoplasma pneumoniae* and *Streptococcus pneumoniae* are important pathogens causing CAP in Chinese adults.[8,9] Elderly

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patients face a higher mortality risk due to CAP, particularly those aged ≥60 years who often present with multiple comorbidities[10–12] Conditions such as chronic obstructive pulmonary disease, cardiovascular disease and cancer are known to further elevate this risk.[13–15] Managing sever CAP is particularly challenging and the Pneumonia Outcomes Research Team (PORT) score, also known as the pneumonia severity index (PSI), is recommended by the American Thoracic Society (ATS) to guide hospitalization decisions.[16,17]

Commonly used antimicrobial agents for treating CABP comprise macrolides (alone or combined with β-lactams), amoxicillin (alone or combined with a macrolide), fluoroquinolones and third-generation cephalosporins in combination with a macrolide.[18–22] Moxifloxacin is a broad-spectrum antibiotic with high bioavailability, which has become the first-line drug for CABP treatment,[23,24] However, the efficacy of treatment is influenced by a variety of factors, such antibiotic resistance, advanced age, severity of disease, and more. The bacterial resistance rates have been rising, making the treatment of CABP more complex.[25] In some areas of the United States, macrolide resistance in *Streptococcus pneumoniae* exceeds 40%.[26] Studies in certain regions of China have shown that *Streptococcus pneumoniae* exhibits macrolide resistance rates ranging from 63.2% to 75.4%.[27] Moxifloxacin-resistant have been observed in gram-negative pathogens associated with CABP, including *Klebsiella pneumoniae* (13%), *Escherichia coli* (25.5%), and *Pseudomonas aeruginosa* (45.6%), with particularly high rates in the latter.[28] These resistance problems often lead to failure of initial antibiotic therapy. Facing multiple challenges in treatment, new antimicrobials in CABP management are urgently needed.[6]

Lefamulin is a novel pleuromutilin antibiotic that received regulatory clearance from FDA, EMA, Health Canada and NMPA, for both oral and intravenous treatment of CAP.[29] Unlike moxifloxacin, which inhibits bacterial DNA gyrase to block DNA replication, Lefamulin selectively binds to the conserved regions of the bacterial 50S ribosomal subunit, inhibiting protein synthesis and showing no cross-resistance to other antibiotic class.[6,30–32] It demonstrates broad-spectrum activity against both typical and atypical CABP pathogens, including multidrug-resistant strains.[33] Its clinical efficacy was validated through two pivotal phase 3 studies. Lefamulin Evaluation Against Pneumonia (LEAP) 1 trial demonstrated that IV-to-oral switch Lefamulin was non-inferior to moxifloxacin in patients with PORT III–V CABP, while LEAP 2 trial showed that a 5-day oral Lefamulin regimen was similarly effective compared to a 7-day oral moxifloxacin regimen in PORT II–IV patients.[34,35] Adopting the same dosing regimen as the LEAP 1 trial, the LEAP China study assessed lefamulin's efficacy and safety relative to moxifloxacin in Chinese CABP patients categorized as PORT risk class II–IV and reached the same conclusion.[36]

Despite these promising results, LEAP1 and LEAP2 included relatively limited Asian participants particularly from China. An overall analysis results of the three studies may be more representative of the population. Also, the efficacy of lefamulin in treatment-challenged populations and those at risk for resistance has not been fully elucidated. In particular, elderly individuals, those classified as PORT III–V, and patients with prior antibiotic exposure represent populations at elevated risk of treatment failure or harboring resistant pathogens. Thus, understanding the effectiveness of lefamulin in these specific subgroups is clinically important. To address these limitations, we conducted a pooled post hoc analysis of the LEAP trails (LEAP1, LEAP2 and LEAP China) to further evaluate the clinical efficacy of lefamulin overall and in three subgroups: patients aged 65 years or above, those classified as PORT risk class III to V, and individuals with a history of prior antibiotic use.

# Materials and Methods

## Characteristics of the Studies

All studies were muti-centers, double-blind, double-dummy, parallel-group trials assessing lefamulin relative to moxifloxacin in adults presenting with moderate-to-severe CABP. The designs of LEAP1 and LEAP2 trials (clinicaltrials.gov identifiers NCT02559310 and NCT02813694) have been reported previously (available at BMC Pulmonary Medicine and JAMA).[34,35] Whereas, the LEAP China trial (ClinicalTrials.gov Identifier: CTR20191226) has been reported as abstract in CHEST 2023. Methods for all three trials are summarized below.

Prior to research commencement, the participating institutions secured approval from respective ethical committees and review boards, while participants submitted signed consent documentation. The investigations observed principles

detailed in the Declaration of Helsinki, maintained Good Clinical Practice standards, and conformed to applicable regulatory requirements and regional legislation.

Detailed methodologies for LEAP 1 and LEAP 2 have been reported previously.[34,35] Briefly, randomization was performed in a 1:1 ratio for LEAP 1 and 2, and 2:1 for LEAP China, with stratification in all three studies based on PORT risk class (III vs IV/V for LEAP 1 and LEAP China; II vs III/IV for LEAP 2). In LEAP 1 and LEAP China, patients were administered IV lefamulin 150 mg every 12 hours (q12h) or moxifloxacin 400 mg every 24 hours (q24h). Starting on or after the third day (six doses) of IV therapy, participants could transition to oral lefamulin 600 mg q12h or moxifloxacin 400 mg q24h if specific criteria were fulfilled, with the total treatment course lasting 7 days (ie, 14 doses).

In the LEAP 2 study, subjects were administered oral lefamulin 600 mg q12h for 5 days or moxifloxacin 400 mg q24h for 7 days. Eligible subjects included adults with radiographic confirmation of pneumonia, classified as PORT risk class III–V (LEAP 1) or II–IV (LEAP 2 and LEAP China), exhibiting acute development of ≥ 3 (LEAP 1 and 2) or ≥ 2 (LEAP China) symptoms related to CABP (eg, dyspnea), ≥ 2 (LEAP 1 and 2) or ≥ 1 (LEAP China) altered vital signs (eg, tachycardia), and ≥ 1 further clinical presentation or laboratory marker of CABP (eg, hypoxemia). Exclusion parameters included prior receipt of more than one dose of a short-duration oral/intravenous CABP antibacterial agent (LEAP 1 and 2) or antimicrobial therapy beyond 24 h lacking adequate clinical improvement (LEAP China) within 72 h before randomization, together with potential for significant cardiovascular events or dysfunction, severe liver disease, or markedly impaired kidney function. Patients with comorbid conditions were not systematically excluded; those with diabetes mellitus, chronic obstructive pulmonary disease, or mild-to-moderate renal impairment were included and sufficiently represented across LEAP 1, LEAP 2, and LEAP China.

## Efficacy Endpoints

As previously described (2021), the principal effectiveness measure consisted of early clinical response (ECR) evaluation conducted 96 ± 24 h following initial medication administration in the intent-to-treat (ITT) group (encompassing all randomized subjects).[29] Participants qualified as ECR responders based on specific criteria: survival status, enhancement in ≥ 2 CABP symptoms, absence of CABP symptom worsening, and exclusion of alternative antibiotic treatments for CABP management. The assessment of ECR parameters occurred at designated study intervals, after therapy conclusion (EOT; evaluated within 2 days following final medication), and during subsequent monitoring (TOC; analyzed 5–10 days post-final medication administration) throughout all three clinical studies.

Secondary endpoints encompassed investigator assessment of clinical response (IACR) at TOC among the modified ITT (mITT) and clinically evaluable (CE) populations. The mITT cohort comprised all randomized subjects who had obtained at least one dose of study medication. The CE population encompassed participants with a definitive clinical outcome, ≥ 48 h of study treatment (unless death occurred before 48 h), no utilization of non-study antibacterial agents potentially active against CABP pathogens (except when administered for clinical failure), and the absence of other factors that could confound efficacy. The investigator's assessment categorized responses as effective when CABP manifestations resolved or showed sufficient improvement to discontinue antibiotics for the existing episode, or ineffective if additional antimicrobial agents became necessary or mortality occurred regardless of cause.

## Statistics

The proportions of individuals showing either ECR or IACR achievement were determined across distinct categories established by baseline patient characteristics.

The ITT population served as the basis for ECR evaluation, whereas IACR success underwent analysis in both mITT and CE populations during the test of cure (TOC) visit. Two-sided 95% CIs for differences in ECR or IACR rates were computed for each subgroup.

Missing data were handled using complete-case analysis. The overall proportion of missing data was low and limited to the prior antibiotic use variable. No missing data were present in treatment allocation or primary efficacy endpoints.

A CONSORT-style diagram illustrating the derivation of pooled populations from LEAP 1, LEAP 2, and LEAP China, and the classification into ITT, mITT, and CE group, is provided in Figure 1.

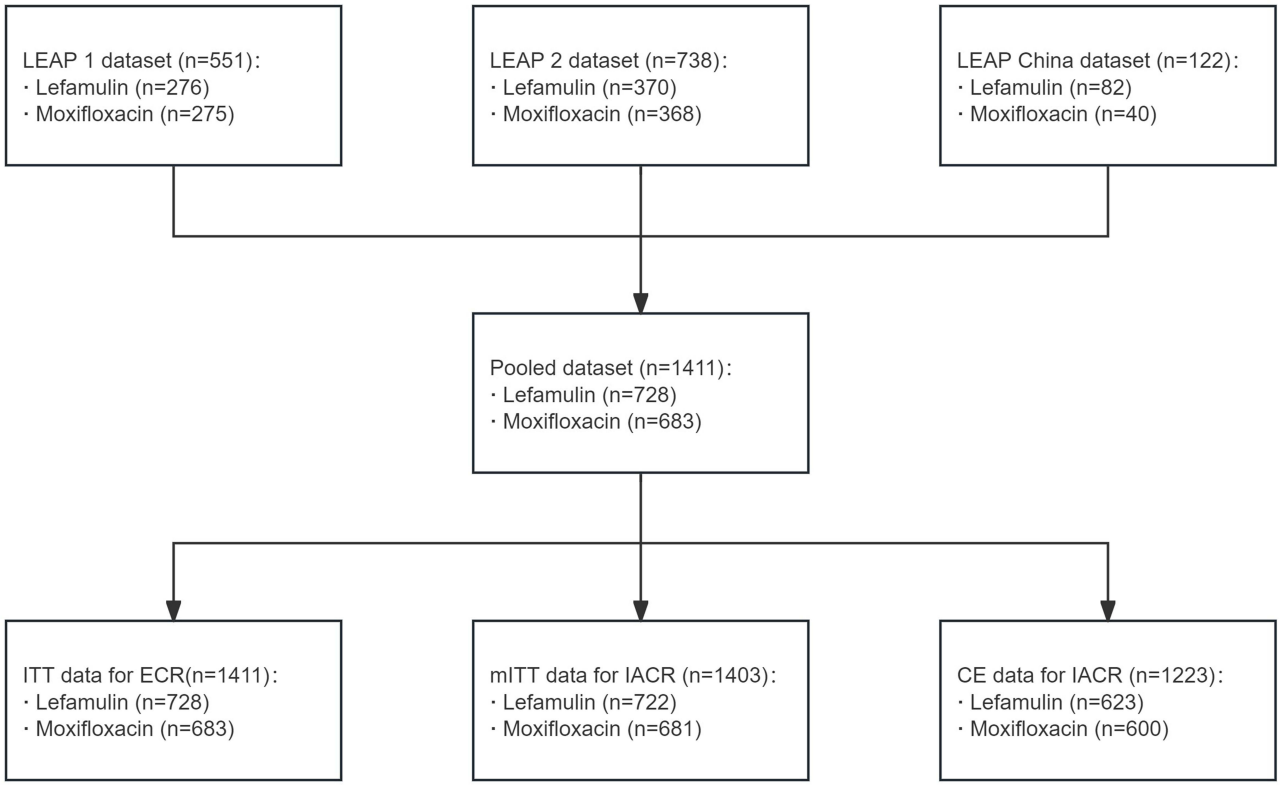


**Figure 1** Flow diagram of patient inclusion and data pooling from the LEAP 1, LEAP 2, and LEAP China studies. A total of 1411 adult patients with community-acquired bacterial pneumonia (CABP) were pooled across the three trials (Lefamulin, n=728; moxifloxacin, n=683). Based on study-specific criteria, patients were included in three analysis sets: the ITT population for early clinical response (ECR), the modified ITT (mITT) population for investigator assessment of clinical response (IACR), and the clinically evaluable (CE) population for IACR.

# Results

## Demographic and Pathogenic Characteristics at Baseline

The post-hoc investigation encompassed 1411 subjects (728 in the lefamulin group and 683 in the moxifloxacin group). The baseline characteristics of both groups were generally balanced and comparable, including the proportion of patients in different age groups and PORT risk classes (Table 1). A slightly higher proportion of male patients in the lefamulin group versus the moxifloxacin group (60.9% vs 54.3%). In terms of risk factors, the lefamulin and moxifloxacin groups had similar proportions of patients with age over 65 years old (40.8% vs 38.2%), PORT III–V (69.1% vs 69.3%) and Prior antibiotic treatment (27.3% vs 25.0%).

In terms of comorbidities, the lefamulin and moxifloxacin groups had similar proportions of patients with diabetes mellitus (13.2% vs 13.6%), asthma/COPD (16.2% vs 16.3%), hypertension (38.3% vs 38.5%), psychiatric disorders (2.5% vs 2.9%), and moderate-to-severe renal impairment (33.8% vs 31.2%). A higher percentage of patients in the lefamulin group experienced cardiac arrhythmias (6.9% vs 4.7%) and hepatobiliary disorders (8.0% vs 4.2%) versus those in the moxifloxacin group. However, the lefamulin group had a lower proportion of patients with heart failures (8.4% vs 11.3%).

## Efficacy Outcomes

### Overall

Clinical response and success rates, as assessed by both ECR and IACR, were high and comparable between the two treatment groups (Table 2). In the ITT analysis set, the ECR rate was 86.0% with lefamulin and 88.9% with moxifloxacin (difference: −2.9% [95% CI, −6.5%, −0.7%]). Similarly, the IACR at the TOC was comparable between the groups, with 84.1% for lefamulin versus 86.2% for moxifloxacin (difference: −2.1% [95% CI, −6.0%, −1.7%]) in the mITT population. Among CE

**Table 1** Baseline Demographic Characteristics (ITT)

| | TOTAL (N=1411) | LEFAMULIN (N=728) | MOXIFLOXACIN (N=683) | P-Value |
|---|---|---|---|---|
| **Age** | | | | |
| Mean (SD) | 58.7 (15.7) | 59.0 (15.9) | 58.4 (15.4) | 0.367 |
| Median [Min, Max] | 61.0 [19.0, 97.0] | 61.0 [19.0, 97.0] | 60.0 [19.0, 93.0] | |
| **Age group, n (%)** | | | | |
| 18-64 y | 853 (60.5%) | 431 (59.2%) | 422 (61.8%) | 0.487 |
| 65–74 y | 335 (23.7%) | 180 (24.7%) | 155 (22.7%) | |
| 75–84 y | 180 (12.8%) | 91 (12.5%) | 89 (13.0%) | |
| ≧ 85 y | 43 (3.0%) | 26 (3.6%) | 17 (2.5%) | |
| **Sex, n (%)** | | | | |
| Female | 597 (42.3%) | 285 (39.1%) | 312 (45.7%) | 0.0152 |
| Male | 814 (57.7%) | 443 (60.9%) | 371 (54.3%) | |
| **Race, n (%)** | | | | |
| Non-Asian | 1143 (81.0%) | 573 (78.7%) | 570 (83.5%) | 0.0275 |
| Asian | 268 (19.0%) | 155 (21.3%) | 113 (16.5%) | |
| **Weight at Baseline, kg** | | | | |
| Mean (SD) | 74.0 (18.8) | 74.3 (18.7) | 73.7 (18.9) | 0.455 |
| Median [Min, Max] | 72.8 [26.5, 200] | 73.0 [31.0, 175] | 72.0 [26.5, 200] | |
| Missing | 1 (0.1%) | 1 (0.1%) | 0 (0%) | |
| **Height at Baseline, cm** | | | | |
| Mean (SD) | 168 (9.79) | 168 (9.62) | 167 (9.94) | 0.056 |
| Median [Min, Max] | 168 [130, 200] | 168 [133, 200] | 167 [130, 196] | |
| Missing | 1 (0.1%) | 1 (0.1%) | 0 (0%) | |
| **BMI, kg/m2** | | | | |
| Mean (SD) | 26.2 (5.84) | 26.2 (5.74) | 26.3 (5.95) | 0.707 |
| Median [Min, Max] | 25.7 [11.0, 63.9] | 25.7 [13.0, 56.8] | 25.7 [11.0, 63.9] | |
| Missing | 1 (0.1%) | 1 (0.1%) | 0 (0%) | |
| **PORT risk class, n (%)** | | | | |
| Class II | 435 (30.8%) | 225 (30.9%) | 210 (30.7%) | 0.963 |
| Class III | 719 (51.0%) | 367 (50.4%) | 352 (51.5%) | |
| Class IV | 246 (17.4%) | 130 (17.9%) | 116 (17.0%) | |
| Class V | 11 (0.8%) | 6 (0.8%) | 5 (0.7%) | |
| **CURB-65, n (%)** | | | | |
| 0 | 276 (19.6%) | 145 (19.9%) | 131 (19.2%) | 0.953 |
| 1 | 695 (49.3%) | 362 (49.7%) | 333 (48.8%) | |
| 2 | 361 (25.6%) | 181 (24.9%) | 180 (26.4%) | |
| 3 | 72 (5.1%) | 37 (5.1%) | 35 (5.1%) | |
| 4 | 7 (0.5%) | 3 (0.4%) | 4 (0.6%) | |
| **Renal status, n (%)** | | | | |
| Severe impairment (CrCl <30 mL/min) | 13 (0.9%) | 7 (1.0%) | 6 (0.9%) | 0.686 |
| Moderate impairment (CrCl 30–<60 mL/min) | 446 (31.6%) | 239 (32.8%) | 207 (30.3%) | |
| Mild impairment (CrCl 60–<90 mL/min) | 271 (19.2%) | 133 (18.3%) | 138 (20.2%) | |
| Normal function (CrCl ≥90 mL/min) | 677 (48.0%) | 346 (47.5%) | 331 (48.5%) | |
| Missing | 4 (0.3%) | 3 (0.4%) | 1 (0.1%) | |
| **Prior Antibiotics treatment, n (%)** | | | | |
| No | 995 (70.5%) | 498 (68.4%) | 497 (72.8%) | 0.244 |
| Yes | 370 (26.2%) | 199 (27.3%) | 171 (25.0%) | |
| Missing | 46 (3.3%) | 31 (4.3%) | 15 (2.2%) | |
| **Diabetes mellitus, n (%)** | | | | |
| No | 1222 (86.6%) | 632 (86.8%) | 590 (86.4%) | 0.874 |
| Yes | 189 (13.4%) | 96 (13.2%) | 93 (13.6%) | |

(*Continued*)


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**Table 1** (Continued).

| | TOTAL (N=1411) | LEFAMULIN (N=728) | MOXIFLOXACIN (N=683) | P-Value |
|---|---|---|---|---|
| **Asthma/COPD, n (%)** | | | | |
| No | 1182 (83.8%) | 610 (83.8%) | 572 (83.7%) | 1 |
| Yes | 229 (16.2%) | 118 (16.2%) | 111 (16.3%) | |
| **Hypertension, n (%)** | | | | |
| No | 869 (61.6%) | 449 (61.7%) | 420 (61.5%) | 0.988 |
| Yes | 542 (38.4%) | 279 (38.3%) | 263 (38.5%) | |
| **Heart failures, n (%)** | | | | |
| No | 1273 (90.2%) | 667 (91.6%) | 606 (88.7%) | 0.0819 |
| Yes | 138 (9.8%) | 61 (8.4%) | 77 (11.3%) | |
| **Cardiac arrhythmias, n (%)** | | | | |
| No | 1329 (94.2%) | 678 (93.1%) | 651 (95.3%) | 0.101 |
| Yes | 82 (5.8%) | 50 (6.9%) | 32 (4.7%) | |
| **Psychiatric disorders, n (%)** | | | | |
| No | 1373 (97.3%) | 710 (97.5%) | 663 (97.1%) | 0.716 |
| Yes | 38 (2.7%) | 18 (2.5%) | 20 (2.9%) | |
| **Hepatobiliary disorders, n (%)** | | | | |
| No | 1324 (93.8%) | 670 (92.0%) | 654 (95.8%) | 0.00522 |
| Yes | 87 (6.2%) | 58 (8.0%) | 29 (4.2%) | |

**Abbreviations**: BMI, body mass index; PORT, Pneumonia Outcomes Research Team; CURB-65, confusion of new onset; CrCl, creatine clearance; SD, standard deviation; COPD, chronic obstructive pulmonary disease.

**Table 2** ECR for the ITT Population and IACR at TOC in mITT and CE Populations

| | Lefamulin n (%) | Moxifloxacin n (%) | Between-Group Difference (95% CI), % |
|---|---|---|---|
| **ECR in ITT** | **N=728** | **N=683** | |
| Responder | 626 (86.0%) | 607 (88.9%) | −2.9% (−6.5%-0.7%) |
| Non-responder | 87 (12.0%) | 66 (9.7%) | |
| Indeterminate | 15 (2.0%) | 10 (1.4%) | |
| **IACR EOT in mITT** | **N=722** | **N=681** | |
| Success | 607 (84.1%) | 587 (86.2%) | −2.1% (−6.0%-1.7%) |
| Failure | 102 (14.1%) | 80 (11.7%) | – |
| Indeterminate | 13 (1.8%) | 14 (2.1%) | |
| **IACR TOC in CE** | **N=623** | **N=600** | |
| Success | 550 (88.3%) | 549 (91.5%) | −3.2% (−6.8%-0.3%) |
| Failure | 73 (11.7%) | 51 (8.5%) | |

**Abbreviations** ECR, early clinical response; IACR, investigator assessment of clinical response; TOC, Test of Cure; EOT, end of treatment.

patients, the success rate was 88.3% for lefamulin versus 91.5% for moxifloxacin (difference: −3.2% [95% CI, −6.8%, −0.3%]).

## Subgroup of PORT III-V

The subgroup analysis encompassed 976 participants (503 in the lefamulin group and 473 in the moxifloxacin group). The baseline characteristics of both groups were generally balanced and comparable, including the proportion of patients in different age groups and other risk classes. The ECR and IACR were high and comparable between the two subgroups

**Table 3** ECR for ITT Population and IACR at TOC in mITT and CE Populations in Individuals with PORT Risk Class III–V

| | Lefamulin n (%) | Moxifloxacin n (%) | Difference (95% CI) |
|---|---|---|---|
| **ECR in ITT** | **N=503** | **N=473** | |
| Responder | 431(85.7) | 417(88.2) | −2.5(−6.9,2.0) |
| Non-responder | 60(11.9) | 49(10.4) | 1.5(−2.6,5.7) |
| Indeterminate | 12(2.4) | 7(1.5) | 0.9(−1.0,2.8) |
| **IACR EOT in mITT** | **N=497** | **N=471** | |
| Success | 427(85.9) | 402(85.3) | 0.6(−4.1,5.2) |
| Indeterminate | 3(0.6) | 5(1.1) | −0.5(−1.8,0.9) |
| Failure | 67(13.5) | 64(13.6) | −0.1(−4.5,4.3) |
| **IACR TOC in mITT** | **N=497** | **N=471** | |
| Success | 418(84.1) | 396(84.1) | 0(−4.6,4.6) |
| Indeterminate | 10(2.0) | 8(1.7) | 0.3(−1.6,2.2) |
| Failure | 69(13.9) | 67(14.2) | −0.3(−4.9,4.2) |
| **IACR TOC in CE** | **N=431** | **N=414** | |
| Success | 382(88.6) | 371(89.6) | −1(−5.4,3.4) |
| Failure | 49(11.4) | 43(10.4) | 1(−3.4,5.4) |

**Abbreviations**: ECR, early clinical response; IACR, investigator assessment of clinical response; TOC, Test of Cure; EOT, end of treatment; CE, clinically evaluable.

of PORT III–V (Table 3). The ECR in ITT rate was 85.7% with lefamulin and 88.2% with moxifloxacin (difference: −2.5% [95% CI, −6.9%, 2.0%]). Similarly, the IACR at the TOC was 84.1% for two groups (difference: 0% [95% CI, −4.6%, 4.6%]) in the mITT population. Among CE patients, the success rate was 88.6% for lefamulin versus 89.6% for moxifloxacin (difference: −1% [95% CI, −5.4%, −3.4%]).

### Subgroup of Patients ≧65 Years of Age

The subgroup analysis encompassed 558 participants (297 in the lefamulin group and 261 in the moxifloxacin group). The baseline characteristics of both groups were generally balanced and comparable. In patients aged 65–74, 75–84, and ≥85 years, the ECR in ITT population (Figure 2a), IACR in mITT population (Figure 2b) and IACR in CE population (Figure 2c) were comparable between the two subgroups. Numerically higher ECR of lefamulin vs moxifloxacin in each ten years-stratification (65–74 years old: 87.2% vs 86.5%; 75–84 years old: 86.8 vs 85.4%; ≥85 years old: 88.5 vs 82.4%). Interestingly, we found a trend of favoring lefamulin: the older the age over 65 years old, the more favorable lefamulin.

### Subgroup of Prior Antibiotic Treatment

The subgroup analysis encompassed 370 participants (199 in the lefamulin group and 171 in the moxifloxacin group). The baseline characteristics of both groups were generally balanced and comparable, including the proportion of patients in different age groups and PORT risk classes.

The ECR and IACR were high and comparable between the two subgroups of Prior antibiotic treatment (Table 4). The ECR in ITT rate was 83.4% with lefamulin and 83.6% with moxifloxacin (difference: −0.2% [95% CI, −8.0%, 7.6%]). Similarly, the IACR at the TOC was 81.8% in Lefamulin which was a little higher than 79.9% in moxifloxacin (difference: 1.9% [95% CI, −6.7%, 10.6%]) in the mITT population. Among CE patients, the corresponding rate was 85.6% for lefamulin versus 88.1% for moxifloxacin (difference: −2.5% [95% CI, −10.8%, 5.9%]).

## Discussion

Lefamulin, a novel pleuromutilin antibiotic authorized for both IV and oral administration in adults with CABP, exhibited noninferiority to moxifloxacin in the LEAP 1 IV-to-oral transition study and the LEAP 2 oral-only study.[34,35] Combined data analysis from these pivotal CABP clinical trials (LEAP 1/2) indicated that lefamulin potentially serves as an

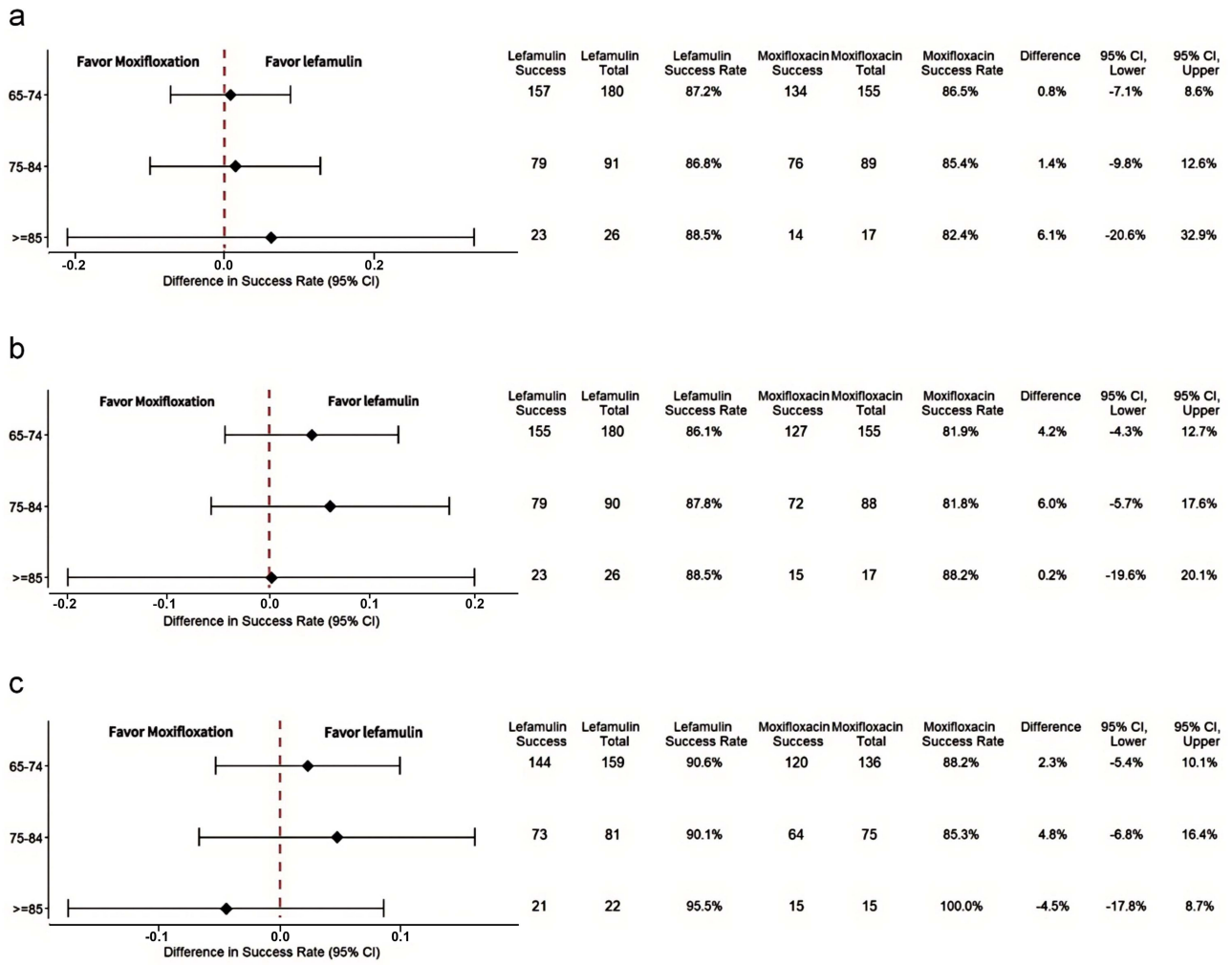


**Figure 2** Clinical response to lefamulin versus moxifloxacin across three elderly subgroups: 65–74, 75–84, and ≥85 years old. (**a**) Early clinical response (ECR) in the intent-to-treat (ITT) population; (**b**) Investigator-assessed clinical response (IACR) in the modified ITT (mITT) population; (**c**) IACR in clinically evaluable (CE) population. Lefamulin and moxifloxacin success rates are shown as percentage, with the risk difference and corresponding 95% confidence intervals (CIs) calculated for each age group.

effective IV/oral single-agent alternative to existing fluoroquinolone or macrolide treatments for empirical CABP therapy, particularly in patients facing elevated risk due to advanced age or underlying health conditions. The research explored lefamulin's therapeutic efficacy across the general population and specific subgroups presenting various CABP-

**Table 4** ECR for ITT Population and IACR at TOC in mITT and CE Populations in Patients with Prior Antibiotic Treatment

| | Lefamulin n (%) | Moxifloxacin n (%) | |
|---|---|---|---|
| **ECR in ITT** | **N=199** | **N=171** | |
| Responder | 166 (83.4) | 143 (83.6) | −0.2 (−8.0, 7.6) |
| Non-responder | 28 (14.1) | 23 (13.5) | |
| Indeterminate | 5 (2.5) | 5 (2.9) | |
| **IACR TOC in mITT** | **N=198** | **N=169** | |
| Success | 162 (81.8) | 135 (79.9) | 1.9 (−6.7, 10.6) |
| Failure | 31 (15.7) | 27 (16.0) | |
| Indeterminate | 5 (2.5) | 7 (4.1) | |

(*Continued*)

**Table 4** (Continued).

| | Lefamulin n (%) | Moxifloxacin n (%) | |
|---|---|---|---|
| **IACR TOC in CE** | **N=160** | **N=134** | |
| Success | 137 (85.6) | 118 (88.1) | −2.5 (−10.8, 5.9) |
| Failure | 23 (14.4) | 16 (11.9) | |

related comorbidities. However, these investigations notably lacked data from Chinese populations. Subsequently, a post-hoc evaluation incorporating information from three randomized controlled studies (LEAP 1, LEAP 2, and LEAP China) assessed the comparative effectiveness between lefamulin and moxifloxacin in CABP treatment. Both lefamulin and moxifloxacin demonstrated rapid onset of action, good and comparable efficacy, as evidenced by high and similar rates of ECR and IACR at the TOC.

Nowadays, the treatment of CABP faces many challenges. Age is a risk factor for CAP patients, affecting the length of hospitalization and mortality. Younger patients usually respond better to treatment and antibiotic resistance is less common. In contrast, due to comorbidities and weakened immune function, older patients respond more poorly to treatment, have longer hospitalizations and higher mortality.[37] Different age groups have different considerations for treatment options. For example, elderly patients need to choose those with a wider antibacterial spectrum, lower drug resistance, and better safety.

Elderly patients (≥ 65 years old) in China often develop CAP due to advanced age, multiple underlying diseases, and host immune damage (account for 28.7% of CAP patients nationwide[38]), which has become one of the main diseases among the elderly in China, especially reaching its peak in the elderly population aged 80 and above.[39] The mortality of elderly CAP patients is high (5.7%), and it is age significantly related. Elderly patients over 65 years old are up to 11.9%.[40] This serious situation will become more severe with the aging of the population in China (13.50% of the population is ≥ 65 years old, an increase of 4.63% over the last survey[39]). So, it is urgent to pay attention to the treatment of CABP in the elderly in China, especially patients over 65 years old. In the previous studies we have published,[16,34] we have never been stratified by age, but we are pleased to see new findings in this study. From our study, we found a trend that the older age over 65 years old, the more favorable of lefamulin, which will be great evidence-based support for the clinical application of this drug in the elderly population. Although older patients often have underlying medical conditions, such as renal insufficiency, liver disease, diabetes, etc., the results of this study show that for the elderly population, lefamulin has achieved a higher IACR success rate and ECR response rate, and has a tendency to increase the success rate of treatment with older age, which was similar to the results of LEAP1.[35] This approach serves as a viable therapeutic alternative for these individuals.[29]

PORT risk assessment tool with better quality of evidence is recommended by ATS to facilitate the decision of hospitalization,[17,26] PORT risk class, also known as PSI, has underwent extensive validation and review[17,41] in heterogeneous patient populations with proven rigorousness in identifying risk and predicting mortality in patients diagnosed with CAP. Patients in class III were recommended of brief inpatient observation or outpatients based on the judgement of physician, patients in class IV–V should be treated as inpatients.[42] Based on the original derivation studies, predicted mortality for patients in PORT risk class I–II, III, IV, and V was 0.3%, 0.9%, and 9.3%, and 27%, respectively.[42] Later, these results were calibrated with observed mortality in many studies and the mortality for high-risk classes IV and V were similar (8.9% and 28.2%, respectively).[17] These consistent results demonstrated that higher PORT risk classes (III–V) are robust indicators of higher mortality, henceforth, patients categorized in high PORT risk class (III–V) should be paid attention when examining the effectiveness and safety of CAP treatments. In this pooled analysis from 2 pivotal CABP trials and 1 China trial, lefamulin, non-inferior to moxifloxacin, showed high effectiveness in individuals with CABP in PORT risk class III–V, ECR rates were 85.7% (lefamulin) and 88.2% (moxifloxacin) and ICAR rates were 84.1%–88.6% (lefamulin) and 84.1%–89.6% (moxifloxacin). Both ECR and IACR maintained high regardless of the pathogen detected or the presence of drug-resistant strains or polymicrobial infection. Even though PORT III–V is a

relatively severe population with a relatively low cure rate, but lefamulin still showed a high response rate in this study, which was non-inferior to moxifloxacin.

CAP is a common infectious disease, and many patients present with a history of antibiotic use. Guidelines have recommended that the treatment of CAP depends on the severity, age, and underlying medical conditions determine the use of initial anti-infective drugs after establishing the clinical diagnosis of CAP and arranging appropriate etiological examination and specimen sampling.[21,24] Prior antibiotic treatment inevitably affects the efficacy of subsequent treatments, which we should pay more attention to. In this study, lefamulin (n=199) can provide sustained high efficacy in patients with Prior Antibiotic Treatment and this efficacy was noninferior to moxifloxacin (n=171). ECR rates were 83.4% (lefamulin) and 83.6% (moxifloxacin) and IACR rates were 81.8–85.6% (lefamulin) and 79.9–88.1% (moxifloxacin). Lefamulin, non-inferior to moxifloxacin, showed high effectiveness in CABP patients with Prior Antibiotic Treatment, lefamulin showed a good success rate in CABP patients with prior antibiotic treatment.

Other approved agents for CABP, such as omadacycline, have shown comparable efficacy to lefamulin in clinical trials. Data from an indirect comparison further support the comparable efficacy of lefamulin, with higher response rate observed in certain subgroups, including elderly patients ≥65 years and those with Haemophilus influenzae.[43]

Chinese data involved and multi-dimensional analysis from age, severity, prior antibiotic treatment are the strength of this article, the Asian population was preferred in the LEAP 1 and LEAP 2 trials, and the LEAP China population was included in the analysis, which further improved demographically representativeness, all which provides evidence-based evidence from more perspectives for clinical applications.

In addition to demonstrating noninferior efficacy to moxifloxacin, lefamulin showed a generally well-tolerated safety profile across the LEAP 1, LEAP 2 and LEAP China studies. The overall incidence of treatment-emergent adverse events (TEAEs) was similar in both groups, primarily due to mild-to-moderate gastrointestinal events such as diarrhea, nausea, and vomiting, but these rarely led to drug discontinuation.[34–36] Of note, QTc interval prolongation was observed in both treatment groups. However, the mean change from baseline was slightly lower with lefamulin compared to moxifloxacin, and no associated cardiac arrhythmias were reported, suggesting lefamulin may offer a safety advantage in patients at risk for fluoroquinolone-associated cardiac adverse effects.[34–36]

There are also some limitations. First, although the analysis combined data from three randomized controlled trials, difference in study design such as the 2:1 randomization ratio used in LEAP China may have introduced potential bias. Second, due to the limited sample size, there was no microbiological analysis of the population according to geographical differences, which reduced the generality of the study. Also, the observed trend in the ≥85-year subgroup requires cautious interpretation given the limited sample size (n=43), and further studies are needed to validate these findings. Third, long-term follow-up data including 30-day mortality, hospital readmission, and relapse rates were not collected, which limits the ability to assess sustained clinical outcomes. Fourth, analysis of multiple subgroups may result in insufficient or unstable data within each subgroup, potentially compromising the reliability of the results. Furthermore, there is no relevant data on whether these patients are first CABP infection or reinfection, for the elderly, immunocompromised patients, multiple comorbidities, CABP recurrence may still exist, so for the drug selection of such patients, and the efficacy of lefamulin, which deserves further exploration. Also, this analysis only focuses on efficiency, and the safety outcomes should be further evaluated in the future. Finally, the current absence of real-world evidence studies highlights the need for further research to confirm the applicability of these findings in routine clinical settings.

## Conclusions

In this pooled analysis from 2 pivotal CABP trials and 1 China bridging trial, lefamulin, non-inferior to moxifloxacin, showed high effectiveness in CABP patients, achieving rapid clinical response. Subgroup analyses indicate that lefamulin may represent a viable empiric monotherapy option for both hospitalized and ambulatory CABP patients, encompassing those with advanced age, greater disease severity, prior antibiotic exposure, or multiple comorbidities. These findings suggest that lefamulin offers an effective alternative for patients at elevated risk of treatment failure and adverse drug reactions, including elderly individuals and those with prior antibiotic use. Moreover, given the increasing resistance to macrolides, tolerability issues associated with certain antibiotic classes (eg, fluoroquinolones, beta-lactams), and potential failure of alternative regimens, lefamulin could serve as a critical IV/oral empiric choice moving forward.[16]

## Abbreviations

CAP, Community-acquired pneumonia; CABP, Community-Acquired Bacterial Pneumonia; LEAP, Lefamulin Evaluation Against Pneumonia; ECR, Early clinical response; IACR, Investigator assessment of clinical response; IPD, Invasive pneumococcal disease; PORT, Pneumonia Outcomes Research Team; ATS, American Thoracic Society; PSI, Pneumonia severity index; CE, Clinically evaluable.

## Data Sharing Statement

The data supporting the conclusions of this study are proprietary to the sponsor and cannot be disclosed publicly due to confidentiality constraints.

## Ethics Approval and Consent to Participate

As noted in the Characteristics of the studies section, centers participating in the LEAP 1, LEAP 2, and LEAP China trials obtained approval from appropriate ethics committees or institutional review boards, and written informed consent was provided by all patients. This manuscript presents a secondary analysis derived from the three completed clinical trials, with informed consent secured from the original study investigators.

## Trial Registration

ClinicalTrials.gov LEAP 1 (NCT02559310; Registration Date: 09/2015), LEAP 2 (NCT02813694; Registration Date: 08/2016) and LEAP China (CTR20191226;Registration Date:12/2019).

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## Disclosure

The authors have no potential conflicts of interest to disclose.

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