2386

Efficacy of Lefamulin Versus Moxifloxacin Against Common Pathogens in Adults With Community-Acquired Bacterial Pneumonia (CABP): Results From the Phase 3 Lefamulin Evaluation Against Pneumonia (LEAP 1) Study

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INTRODUCTION

- Increasing resistance to[1] and safety issues with[2] existing antibiotics create a need for novel therapies for patients with community-acquired bacterial pneumonia (CABP)
- The pleuromutilin antibiotic lefamulin inhibits protein synthesis by binding selectively and specifically to the peptidyl transferase center of the 50S ribosomal subunit[3]
  - Pleuromutilins bind to the ribosomal pocket within the A- and P-sites by forming 3 hydrogen bonds between the acetyl carbonyl on the C14 side chain
  - Lefamulin is unique in that its C14 extension, a nonplanar cyclohexane, forms a fourth hydrogen bond with the ribosome, which serves as a physical barrier to help maintain a tight binding pocket conformation
- Lefamulin has potent *in vitro* activity against *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*, as well as the atypical pathogens *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella pneumophila*; its activity is unaffected *in vitro* by an organism's resistance to other major antibiotic classes[4-7]
- Lefamulin demonstrates a mean 5.7-fold increase in concentration in the epithelial lining fluid of the lung relative to the plasma[8]
- The LEAP 1 study evaluated the efficacy and safety of lefamulin as monotherapy, with an intravenous (IV) to oral switch option, compared with moxifloxacin with or without linezolid in adults with CABP; we report efficacy outcomes by baseline pathogen from this study

METHODS

Study Design

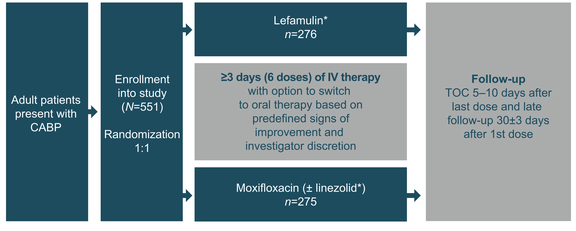
- LEAP 1 was a prospective, multicenter, randomized, double-blind, double-dummy, phase 3 study conducted in 18 countries **(Figure 1)**
- Patients were randomly assigned to receive lefamulin 150 mg IV every 12 hours (q12h) or moxifloxacin 400 mg IV every 24 hours (q24h; **Figure 1**)
  - Linezolid (600 mg IV or orally q12h) or matching placebo was added to moxifloxacin or lefamulin therapy, respectively, if methicillin-resistant *S. aureus* (MRSA) was suspected. If MRSA was confirmed, treatment continued for 10 days with the following modifications:
    - If MRSA was confirmed during the IV treatment period, patients on moxifloxacin plus linezolid discontinued moxifloxacin and instead received only linezolid. Patients randomized to receive lefamulin continued on lefamulin but discontinued linezolid placebo
    - If MRSA was confirmed during the oral treatment period, those on moxifloxacin plus linezolid discontinued moxifloxacin and continued to receive linezolid plus lefamulin placebo. Those randomized to lefamulin continued with this therapy and discontinued moxifloxacin placebo
    - If MRSA was suspected but cultures were negative, linezolid or matching placebo was discontinued, and the patient continued with moxifloxacin or lefamulin
- Patients could switch to oral therapy (lefamulin 600 mg q12h or moxifloxacin 400 mg q24h) after 6 IV doses of study drug (≥3 days) if predefined improvement criteria were met

Patients

- Patients ≥18 years of age with CABP of Pneumonia Outcomes Research Team (PORT) risk class III (limited to 75%), IV, or V were eligible
- A single dose of short-acting antibiotic within 24 hours before randomization was allowed in up to 25% of patients
- Informed consent and approval of study procedures were obtained in accordance with local regulations before enrollment

METHODS (continued)

Figure 1. Study Design



CABP=community-acquired bacterial pneumonia; EMA=European Medicines Agency; EOT=end of treatment; FDA=US Food and Drug Administration; IV=intravenous; TOC=test-of-cure visit.

*If methicillin-resistant *Staphylococcus aureus* (MRSA) was suspected, linezolid or placebo was added to moxifloxacin or lefamulin therapy, respectively; if MRSA was confirmed, treatment duration was 10 days. The original protocol indicated a 5-day lefamulin treatment period but was later adjusted to 7 days to reduce medication errors and limit the burden on study sites.

†EOT assessment was within 2 days after the last dose of study drug.

Assessments

- Efficacy was assessed as early clinical response (ECR) and investigator assessment of clinical response (IACR)
  - ECR was assessed in the intent-to-treat (ITT) population 72–120 hours after the first dose of study drug
    - Responder: alive, improvement in ≥2 CABP signs and symptoms, no worsening in any CABP sign or symptom, and no receipt of a concomitant rescue nonstudy antibiotic for CABP
  - IACR was evaluated at the test-of-cure (TOC) assessment 5–10 days after the last dose of study drug in the modified ITT (mITT) population (ie, patients who received any amount of study drug) and in the clinically evaluable population (ie, patients who met predefined specified criteria related to adherence to the protocol)
    - Success: alive, with signs and symptoms of CABP resolved or improved such that no additional antibacterial therapy was administered for CABP
- Baseline pathogens were identified from specimens collected within ±24 hours of the first dose of study drug
  - The microbiological ITT (microITT) population included all patients with a baseline CABP pathogen detected by ≥1 of the following methods:
    - Culture: respiratory tract (ie, adequate sputum, pleural fluid, bronchoalveolar lavage) or blood
    - Urinary antigen test for *S. pneumoniae* and *L. pneumophila*
    - Serology (IgG titer increase at late follow-up vs baseline): ≥4-fold increase and titer ≥1:160 for *M. pneumoniae*; ≥4-fold increase for *C. pneumoniae*; ≥4-fold increase and titer ≥1:128 for *L. pneumophila*
    - Quantitative real-time polymerase chain reaction (RQ-PCR) from sputum: *S. pneumoniae*, *S. aureus*, *H. influenzae*, and *M. catarrhalis*
    - Qualitative real-time PCR from sputum: *L. pneumophila*, *M. pneumoniae*, and *C. pneumoniae*
    - RQ-PCR and culture from oropharyngeal swabs: *M. pneumoniae*
    - RQ-PCR (≥1 x 10^3 CFU/mL [amplified gene=*lytA*]) and culture from nasopharyngeal swabs: *S. pneumoniae*
  - The microITT-2 population included patients with a CABP pathogen detected by the methods listed above, excluding real-time PCR
- Confirmatory identification and susceptibility testing of isolates, Gram-staining of sputum, resistance gene determination, *S. pneumoniae* and *H. influenzae* serotyping, serology, and real-time PCR were performed by a central laboratory and by specialized laboratories (see Acknowledgments)

RESULTS

Patients and Baseline Characteristics

- 551 patients were randomized (*n*=276 lefamulin, *n*=275 moxifloxacin)
- The mean age was 60.3 years; most patients were male (59.9%) and white (86.8%)
- The most commonly identified baseline pathogens in the microITT and microITT-2 populations are shown in **Table 1**
- Lefamulin and moxifloxacin showed similar *in vitro* activity against the most commonly isolated CABP pathogens, including drug-resistant isolates **(Table 2)**

Table 1. Baseline Pathogens

Pathogen*	Patients, *n* (%)			
	Lefamulin		Moxifloxacin	
	microITT *n*=159	microITT-2 *n*=93	microITT *n*=159	microITT-2 *n*=85
Gram-positive bacteria	97 (61.0)	47 (50.5)	100 (62.9)	47 (55.3)
Streptococcus pneumoniae	93 (58.5)	42 (45.2)	97 (61.0)	44 (51.8)
Staphylococcus aureus	10 (6.3)	7 (7.5)	4 (2.5)	3 (3.5)
MSSA	7 (4.4)	7 (7.5)	3 (1.9)	3 (3.5)
Streptococcus pyogenes	0	0	1 (0.6)	1 (1.2)
Gram-negative bacteria	74 (46.5)	21 (22.6)	66 (41.5)	16 (18.8)
Haemophilus influenzae	51 (32.1)	6 (6.5)	57 (35.8)	6 (7.1)
Moraxella catarrhalis	25 (15.7)	1 (1.1)	11 (6.9)	1 (1.2)
All *Acinetobacter*	4 (2.5)	4 (4.3)	3 (1.9)	3 (3.5)
Burkholderia cepacia	0	0	1 (0.6)	1 (1.2)
Citrobacter koseri	1 (0.6)	1 (1.1)	0	0
All *Enterobacter*	4 (2.5)	4 (4.3)	1 (0.6)	1 (1.2)
Escherichia coli	0	0	2 (1.3)	2 (2.4)
Haemophilus parainfluenzae	3 (1.9)	3 (3.2)	2 (1.3)	2 (2.4)
Klebsiella pneumoniae	3 (1.9)	3 (3.2)	2 (1.3)	2 (2.4)
Pseudomonas aeruginosa	1 (0.6)	1 (1.1)	0	0
Serratia marcescens	1 (0.6)	1 (1.1)	0	0
Atypical pathogens†	45 (28.3)	37 (39.8)	46 (28.9)	35 (41.2)
Mycoplasma pneumoniae	19 (11.9)	14 (15.1)	20 (12.6)	12 (14.1)
Legionella pneumophila	18 (11.3)	17 (18.3)	14 (8.8)	14 (16.5)
Chlamydophila pneumoniae	11 (6.9)	9 (9.7)	19 (11.9)	15 (17.6)

microITT=microbiological intent to treat; microITT-2=microbiological intent to treat-2; MSSA=methicillin-susceptible *S. aureus*.

Rows shaded green indicate community-acquired bacterial pneumonia pathogens of interest.

*A patient could have had >1 pathogen identified. Patients with >1 Gram-positive, Gram-negative, or atypical pathogen are counted only once in the overall tabulation of Gram-positive bacteria, Gram-negative bacteria, and atypical pathogens, respectively.

†The most common testing modality was serology for identification of all atypical pathogens (microITT population: *n*=25 for *M. pneumoniae*, *n*=29 for *L. pneumophila*, and *n*=24 for *C. pneumoniae*; microITT-2 population: *n*=25 for *M. pneumoniae*, *n*=19 for *L. pneumophila*, and *n*=24 for *C. pneumoniae*).

Efficacy

- Lefamulin met the primary objective of noninferiority versus moxifloxacin (noninferiority margins were 12.5% for ECR and 10% for IACR)
- In the microITT population, ECR responder rates were 87.4% with lefamulin and 93.1% with moxifloxacin (treatment difference [95% CI]: –5.7 [–12.8, 1.5]) and IACR success rates at TOC were 79.9% and 85.5%, respectively (treatment difference [95% CI]: –5.7 [–14.1, 2.8])
- In the microITT-2 population, ECR responder rates were 90.3% with lefamulin and 90.6% with moxifloxacin (treatment difference [95% CI]: –0.3 [–10.0, 9.5]) and IACR success rates at TOC were 82.8% and 84.7%, respectively (treatment difference [95% CI]: –1.9 [–13.3, 9.2])
- In both the microITT and microITT-2 populations, lefamulin and moxifloxacin demonstrated similar ECR responder and IACR success rates across all baseline CABP pathogens **(Table 3)**
- The mean duration of combined IV and oral treatment was 7.2 days for lefamulin and 7.1 days for moxifloxacin

RESULTS (continued)

Table 2. Minimum Inhibitory Concentrations for Key Pathogens (microITT Population)

Pathogen*		MIC_{90}, µg/mL†	
	n	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
Penicillin-resistant	5	NA (0.25–0.5)	NA (0.06–0.25)
Macrolide-resistant	12	0.25/0.5	0.12/0.12
Staphylococcus aureus (MSSA)	10	0.12/0.25	0.03/0.06
Gram-negative bacteria			
Haemophilus influenzae	11‡	1/2	0.03/0.12
Moraxella catarrhalis	2	NA (0.12–0.12)	NA (0.06–0.06)
Haemophilus parainfluenzae	3	NA (0.5–>4)	NA (0.06–>2)
Atypical pathogens			
Mycoplasma pneumoniae	6	NA (≤0.001–≤0.001)	NA (0.12–0.12)

MDR=multidrug-resistant (ie, isolates displaying resistance phenotype to ≥2 drug classes); MIC=minimum inhibitory concentration; MIC_{50}=minimum concentration at which 50% of the isolates were inhibited; MIC_{90}=minimum concentration at which 90% of the isolates were inhibited; microITT=microbiological intent to treat; MSSA=methicillin-susceptible *S. aureus*; NA=not applicable because of small sample size.

*Pathogens were isolated from sputum, nasopharyngeal swab, oropharyngeal swab, blood, bronchoalveolar lavage, and/or pleural fluid via culture. A patient could have had >1 pathogen. Multiple isolates of the same species and phenotype from the same patient were counted only once, using the isolate with the highest MIC to study drug received.

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

‡12 isolates were tested for the moxifloxacin group.

Table 3. Responder (ECR) and Success (IACR) Rates by Baseline Pathogen

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

ECR=early clinical response; IACR=investigator assessment of clinical response; MDR=multidrug-resistant (ie, isolates displaying resistance phenotype to ≥2 drug classes); microITT=microbiological intent to treat; microITT-2=microbiological intent to treat-2; MSSA=methicillin-susceptible *S. aureus*; TOC=test-of-cure visit.

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

†Percentages are not included when *n*<10.

CONCLUSIONS

- In this global phase 3 study, lefamulin showed potent activity against common CABP pathogens, including drug-resistant strains and irrespective of whether pathogens were identified using classical detection methodologies (including culture, urinary antigen test, and serology) or real-time PCR in addition to these methods
- Lefamulin was efficacious against CABP caused by the atypical pathogens *M. pneumoniae*, *L. pneumophila*, and *C. pneumoniae*
- ECR responder and IACR success rates were high and similar between the lefamulin and moxifloxacin groups in patients with a pathogen (microITT and microITT-2 populations)
- Lefamulin demonstrates promise as a targeted monotherapy for treatment of CABP in adults

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