Sunday – 682

Lefamulin Is Non-inferior to Moxifloxacin in Adults with Community-Acquired Bacterial Pneumonia (CABP): The Phase 3 Lefamulin Evaluation Against Pneumonia (LEAP 1) Study

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ABSTRACT

Background: Lefamulin is a novel pleuromutilin antibiotic (IV/oral) in development for treating CABP, a leading cause of infection and death. Lefamulin targets key CABP pathogens.

Methods: In a multi-center, randomized, double-blind, phase 3 study, CABP patients were randomized to lefamulin 150mg IV Q12 hr or moxifloxacin 400mg IV Q24 hr; Linezolid or placebo was added if MRSA was suspected. Patients with Patient Outcomes Research Team (PORT) Risk Class III (limit: 75%), IV, or V were eligible. After six IV doses, patients could switch to oral therapy if pre-specified criteria were met. The FDA endpoint was early clinical response (ECR) in the intent-to-treat (ITT) population. EMA co-primary endpoints were investigator assessment of clinical response (IACR) at test of cure in modified ITT (mITT) and clinically evaluable (CE) populations.

Results: 551 patients were randomized to lefamulin (*n*=276) or moxifloxacin (*n*=275). For the FDA endpoint, lefamulin was non-inferior (12.5% margin) to moxifloxacin (ECR 87.3% vs 90.2%, respectively; difference: 2.9% [95%CI: 8.5,2.8]). For the EMA primary endpoint, lefamulin was also non-inferior (10% margin) to moxifloxacin (IACR: mITT, 81.7% vs 84.2% respectively; difference 2.6 [8.9,3.9]; CE, 86.9% vs 89.4%; difference 2.5 [8.4,3.4]). Lefamulin was efficacious regardless of PORT class (ECR rates for PORT III, IV, and V were 89.3% [175/196], 82.9% [63/76], and 75% [3/4] in lefamulin, and 93% [187/201], 81.4% [57/70], and 100% [3/3] in moxifloxacin, respectively; IACR rates in the mITT population for PORT III, IV, and V were 84.0% [163/194], 76.0% [57/75], and 75.0% [3/4] in lefamulin, and 84.0% [168/200], 84.1% [58/69], and 100% [3/3] in moxifloxacin; IACR rates were similar for the CE population.

Conclusions: Lefamulin demonstrated non-inferiority for both the FDA and EMA efficacy endpoints vs moxifloxacin. Lefamulin demonstrates promise as a targeted monotherapy for the treatment of CABP in adults.

INTRODUCTION

- Community-acquired pneumonia (CAP) causes significant morbidity, mortality, and a substantial economic burden[1]
  - The estimated incidence of CAP ranges from 1.7 to 11.6 cases per 1000 person-years in Europe and ~10.6 cases per 1000 person-years in the United States[2,3]
  - CAP costs are ~€10.1 billion annually in Europe and over $17 billion annually in the United States[4,5]
  - *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most frequently isolated bacterial CAP pathogens[4]
- New therapies for community-acquired bacterial pneumonia (CABP) are needed because of the rise of antibacterial resistance, the intrinsic antimicrobial resistance of certain pathogens, and because current treatments have undesirable risks and side effects[6-8]
- Lefamulin is a novel semi-synthetic pleuromutilin antibiotic in development for the treatment of CABP. Lefamulin inhibits protein synthesis by binding selectively and specifically to the peptidyl transferase center of the 50S ribosomal subunit[9]
- Lefamulin shows potent *in vitro* activity against CABP-associated pathogens (*S. pneumoniae*, *H. influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella pneumophila*); its activity is unaffected by an organism's resistance to other major antibiotic classes[10-13]
- Lefamulin rapidly and predictably penetrates target sites including plasma and the epithelial lining fluid (ELF) of the lungs. Unbound lefamulin levels in ELF are 5.7-fold higher than in plasma, making it an ideal candidate for CABP therapy[14]
- The objective of the study was to describe the primary outcomes of the first phase 3 trial of lefamulin as monotherapy in adult patients with CABP

METHODS

Study Design

- LEAP1 was a prospective, multicenter, randomized, double-blind, double-dummy, noninferiority phase 3 study to evaluate adult patients with CABP conducted in 18 countries at 104 study sites **(Figure 1)**
- Patients were randomized to receive lefamulin 150 mg intravenously (IV) every 12 hours (q12h) or moxifloxacin 400 mg IV every 24 hours (q24h) for 7 days of therapy
  - If methicillin-resistant *S. aureus* (MRSA) was suspected at screening, linezolid (600 mg IV q12h) or placebo was added to moxifloxacin or lefamulin therapy, respectively; if MRSA was confirmed, treatment would continue for 10 days of total therapy, 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

METHODS (continued)

- Patients could be switched to oral therapy (lefamulin 600 mg q12h or moxifloxacin 400 mg q24h ± linezolid 600 mg q12h) after ≥6 IV doses of study drug (~3 days) if they met the following predefined criteria: were hemodynamically stable, had a normalizing temperature <38.0°C (<100.4°F) in the previous 24 hours, showed improvement by 1 severity category in ≥2 of 4 cardinal CABP symptoms, and could swallow oral medications

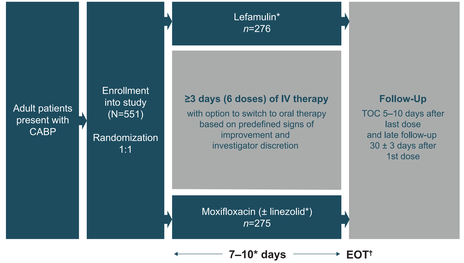
Patients

- Patients ≥18 years old with CABP (Pneumonia Outcomes Research Team [PORT] risk class III [limited to 75%], IV, or V) were eligible
- A single dose of short-acting antibiotic (as requiring >1 dose per day), within 24 hours of randomization, was allowed in up to 25% of the population
- Informed consent and approval of study procedures were provided in accordance with local regulations before enrollment

Assessments

- Screening occurred within 24 hours before the first dose of study drug
- Early clinical response (ECR), the US Food and Drug Administration (FDA) primary endpoint, was assessed in the intent-to-treat (ITT) population 72–120 hours after the first dose of study drug
  - ECR was achieved if (1) a patient showed improvement in ≥2 of 4 CABP signs or symptoms (dyspnea, cough, production of purulent sputum, chest pain), (2) had no worsening in any signs or symptoms, (3) was alive, and (4) did not receive nonstudy antibacterial therapy for CABP
  - Noninferiority of lefamulin for the FDA primary endpoint was concluded if the lower limit of the 2-sided 95% CI for the observed difference in ECR rates between treatment groups was greater than –12.5%
- Investigator assessment of clinical response (IACR), the European Medicines Agency (EMA) primary endpoint, 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 (patients who received any amount of study drug) and in the clinically evaluable (CE) population (patients that met pre-defined specified criteria related to adherence to the protocol)
  - IACR was classified as successful if the signs and symptoms of CABP resolved or improved such that no additional antibacterial therapy was administered for the treatment of CABP. IACR failure occurred if (1) the signs and symptoms of CABP did not resolve or improve, or worsened, such that nonstudy antibacterial therapy was administered for the treatment of CABP, (2) death occurred, or (3) an adverse event led to study drug discontinuation and institution of nonstudy antibacterial therapy for the treatment of CABP
  - Noninferiority of lefamulin for the EMA primary endpoints was concluded if the lower limit of the 2-sided 95% CI for the observed difference in IACR rates between the treatment groups was greater than –10% for both the mITT and CE populations

Figure 1. Study Design



FDA primary endpoint:
Early clinical response (ECR)
(assessed 72–120 hours after first dose)

EMA primary endpoint:
Investigator assessment of clinical response (IACR)
(assessed 5–10 days after last dose)

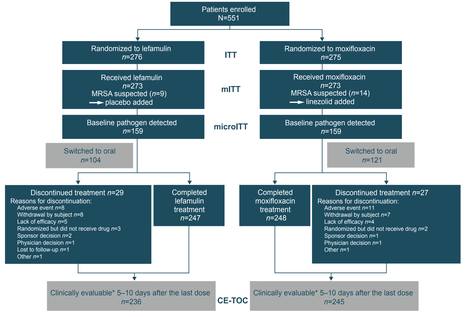
CABP=community-acquired bacterial pneumonia; CE-TOC=clinically evaluable at TOC; EMA=European Medicines Agency; EOT=end of treatment; FDA=US Food and Drug Administration; ITT=intent-to-treat; IV=intravenous; mITT=modified ITT; TOC=test of cure.
*If MRSA was suspected, linezolid or placebo was added to moxifloxacin or lefamulin therapy, respectively, for 10 days of total therapy.
†EOT assessment was within 2 days after the last dose of study drug.

RESULTS

Patients

- Of the 551 patients enrolled, 276 were randomized to receive lefamulin and 275 to receive moxifloxacin ± linezolid **(Figure 2)**
- Patient characteristics were similar between the 2 groups; however, there were more older patients in the lefamulin group **(Table 1)**
- *S. pneumoniae* was the most commonly isolated bacterium, being isolated from 59.7% (190/318) of patients with available microbiological data (the microbiological ITT [microITT] population), followed by *H. influenzae* (34.0% [108/318]), *M. pneumoniae* (12.3% [39/318]), *M. catarrhalis* (11.3% [36/318]), *L. pneumophila* (10.1% [32/318]), *C. pneumoniae* (9.4% [30/318]), and *S. aureus* (4.4% [14/318])
  - The distribution of baseline pathogens was similar between the treatment groups

Figure 2. Patient Disposition



CABP=community-acquired bacterial pneumonia; CE-TOC=clinically evaluable at TOC; EOT=end of treatment; IACR=investigator assessment of clinical response; ITT=intent-to-treat; mITT=modified ITT; MRSA=methicillin-resistant *Staphylococcus aureus*; TOC=test of cure.
*Met the criteria for CABP, received at least the prespecified minimal amount of the intended dose of study drug and duration of treatment, IACR not indeterminate, did not receive concomitant antibacterial therapy (other than adjunctive linezolid) potentially effective against CABP pathogens (except in the case of clinical failure), and had no other confounding factors that interfered with outcome assessment.

Table 1. Patient Characteristics

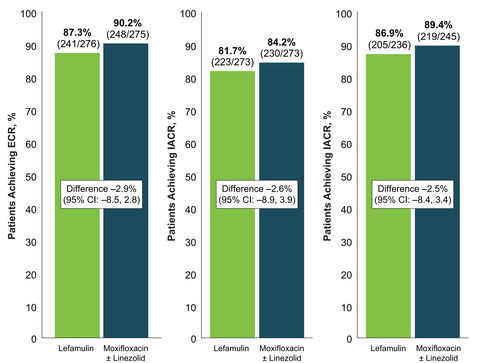
Characteristic	Lefamulin *n*=276	Moxifloxacin ± Linezolid *n*=275
Mean age, y	61.0	59.6
Patients, *n* (%)		
<65 y	144 (52.2)	167 (60.7)
65–74 y	74 (26.8)	66 (24.0)
≥75 y	58 (21.0)	42 (15.3)
Sex, *n* (%)		
Male	170 (61.6)	160 (58.2)
Mean BMI, kg/m^2	26.48	26.33
Race, *n* (%)		
White	239 (86.6)	239 (86.9)
Asian	24 (8.7)	20 (7.3)
Black	11 (4.0)	12 (4.4)
American Indian or Alaska Native	0	1 (0.4)
Other	2 (0.7)	3 (1.1)
PORT class, *n* (%)		
II	0	1 (0.4)
III	196 (71.0)	201 (73.1)
IV	76 (27.5)	70 (25.5)
V	4 (1.4)	3 (1.1)
Renal status, *n* (%)		
Severe impairment (CrCl <30 mL/min)	3 (1.1)	3 (1.1)
Moderate impairment (CrCl 30–<60 mL/min)	61 (22.1)	62 (22.5)
Mild impairment (CrCl 60–<90 mL/min)	89 (32.2)	75 (27.3)
Normal function (CrCl ≥90 mL/min)	121 (43.8)	134 (48.7)

BMI=body mass index; CrCl=creatinine clearance; PORT=Pneumonia Outcomes Research Team.

Early Clinical Response and Investigator Assessment of Clinical Response

- For the FDA primary endpoint, lefamulin was noninferior (12.5% margin) to moxifloxacin ± linezolid **(Figure 3A)**
- Lefamulin demonstrated noninferiority to moxifloxacin ± linezolid for the EMA primary endpoint (10% margin) in both mITT and CE-TOC populations **(Figure 3B & 3C)**

Figure 3. Responder Rates for the FDA Primary Endpoint (ECR) and the EMA Primary Endpoint (IACR) in the mITT and CE-TOC Populations



CE-TOC=clinically evaluable at test of cure; ECR=early clinical response; IACR=investigator assessment of clinical response; ITT=intent-to-treat; mITT=modified intent-to-treat.

Clinical Efficacy by PORT Classification

- Lefamulin demonstrated high ECR and IACR rates across the 3 PORT-defined severities of CABP **(Table 2)**

Table 2. Response by PORT Classification

PORT Class	ECR ITT			IACR mITT		
	Lefamulin *n*=276	Moxifloxacin ± Linezolid *n*=275	Treatment Difference (95% CI)	Lefamulin *n*=273	Moxifloxacin ± Linezolid *n*=273	Treatment Difference (95% CI)
II	0	1/1 (100%)	–	0	1/1 (100%)	–
III	175/196 (89.3%)	187/201 (93.0%)	–3.7 (–9.8, 2.3)	163/194 (84.0%)	168/200 (84.0%)	0.0 (–7.7, 7.8)
IV	63/76 (82.9%)	57/70 (81.4%)	1.5 (–12.3, 15.3)	57/75 (76.0%)	58/69 (84.1%)	–8.1 (–22.4, 6.3)
V	3/4 (75.0%)	3/3 (100%)	–25.0 (–96.6, 46.6)	3/4 (75.0%)	3/3 (100%)	–25.0 (–96.6, 46.6)

ECR=early clinical response; IACR=investigator assessment of clinical response; mITT=modified intent-to-treat; PORT=Pneumonia Outcomes Research Team.

Safety and Tolerability

- The safety and tolerability profile of lefamulin was generally comparable to that of moxifloxacin ± linezolid (please refer to the accompanying poster #683 for additional details on lefamulin's safety and tolerability in this study[15])

CONCLUSIONS

- In this phase 3 study in CABP, lefamulin demonstrated high response rates for ECR and IACR that were noninferior to the comparator, moxifloxacin (standard of care) ± linezolid
- Response rates were high across pneumonia severities as assessed by PORT scores
- Lefamulin shows promise as an empiric and targeted monotherapy with an IV to oral option for the treatment of CABP in adults

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