E1053

Safety and Tolerability of Lefamulin Versus Moxifloxacin in Adults With Community-Acquired Bacterial Pneumonia: Results of the Lefamulin Evaluation Against Pneumonia (LEAP) 1 and LEAP 2 Double-Blind Noninferiority Phase 3 Clinical Trials

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PURPOSE

- The clinical and economic burden of community-acquired pneumonia is substantial,[1-4] with annual costs estimated at €10.1 billion in Europe and more than $17 billion in the United States
- There is a growing need for new treatment options for community-acquired bacterial pneumonia (CABP) because of increasing rates of bacterial resistance and the undesirable risks and adverse effects associated with current treatments, including fluoroquinolone-associated disability (eg, tendon injury, aortic rupture, and glucose homeostasis imbalance)[1,5]
- Lefamulin (LEF), a first-in-class pleuromutilin antibiotic approved for intravenous (IV) and oral use in the treatment of adults with CABP,[6] inhibits protein synthesis by binding selectively and specifically to the peptidyl transferase center of the 50S ribosomal subunit[7,8]
- LEF has been evaluated in 2 phase 3 trials in adults with CABP
  - The Lefamulin Evaluation Against Pneumonia (LEAP) 1 study evaluated the efficacy and safety of LEF monotherapy, with an IV-to-oral switch option, compared with moxifloxacin (MOX) (± linezolid)[9]
  - The LEAP 2 study evaluated the efficacy and safety of oral LEF monotherapy compared with oral MOX monotherapy[10]
- We report overall safety and tolerability in pooled LEAP 1 and LEAP 2 analyses

METHODS

Study Design

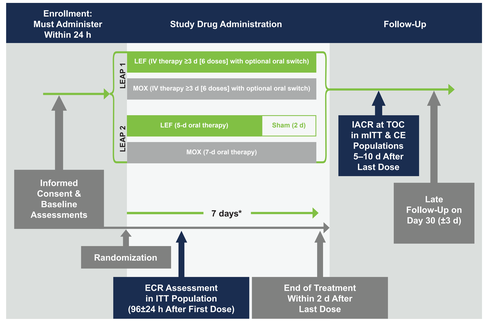
- Both studies were prospective, randomized, double-blind, double-dummy, phase 3 trials **(Figure 1)**[9,10]
- Patients in LEAP 1 and LEAP 2 were enrolled at 66 centers (18 countries) and 99 centers (19 countries), respectively
  - In LEAP 1, patients were randomized to receive LEF 150 mg IV every 12 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 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 ≥18 years old with CABP of Pneumonia Outcomes Research Team (PORT) risk class III–V or II–IV were eligible for LEAP 1 and LEAP 2, respectively
- Safety was assessed in all randomized patients who received any amount of study drug (safety analysis set)
- 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)
- Blood samples were collected for clinical laboratory assessments at baseline and throughout the study at predefined time points; blood samples were sent to a central laboratory for analysis
- For cardiac evaluations, triplicate 12-lead electrocardiograms were performed within a 5-minute interval at screening and on Days 1 and 3 for LEAP 1; in LEAP 2, patients were evaluated on Day 1 and on Day 4 (inpatients) or 96±24 h after first dose (outpatients)
- Clinically significant laboratory abnormalities were evaluated by the study investigator or a monitoring physician

METHODS (continued)

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.[9] 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

- 1289 patients randomized to LEF (*n*=646) and MOX (*n*=643) were included in the pooled intent-to-treat population
  - Patient demographics and disease characteristics were generally well balanced between treatment groups; please see Poster E1006 for full details on patient demographics and disease characteristics
  - Overall, patients in the pooled ITT population were predominantly male (55.6%) and white (79.3%), with a mean (SD) age of 58.7 (16.1) years; 70.8% of patients were PORT risk class III or higher
  - Within the pooled ITT population, 40.8% of patients had a history of smoking, 38.9% had a history of hypertension, 20.4% had baseline liver enzyme elevation, 13.0% had a history of diabetes mellitus, and 5.7% had a history of arrhythmia
- 1282 patients randomized to LEF (*n*=641) and MOX (*n*=641) were included in the pooled safety analysis set

Safety and Tolerability

Overview of TEAEs

- The overall rate of TEAEs was similar in the LEF (34.9%) and MOX (30.4%) treatment groups **(Table 1)**
  - TEAEs were primarily mild to moderate in severity; only 3.9% of TEAEs were severe
- Treatment-related TEAEs were reported in 15.4% and 10.6% of patients randomized to LEF and MOX, respectively **(Table 1)**
- The most frequently reported TEAEs were in the system organ class (SOC) of Gastrointestinal (GI) disorders (see section titled *Gastrointestinal Events*)

RESULTS (continued)

- Few TEAEs led to study drug discontinuation, with similar rates observed across treatment groups (LEF, 3.1%; MOX, 3.3%); 1.7% of patients treated with LEF (11/641) and 1.2% of patients treated with MOX (8/641) experienced TEAEs leading to death **(Table 1)**
- Serious TEAEs were recorded in 5.6% of patients treated with LEF (36/641) and 4.8% of patients treated with MOX (31/641) **(Table 1)**

Table 1. Overall Summary of TEAEs (Pooled Safety Analysis Set)

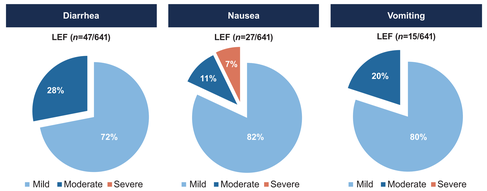
TEAEs*	Patients, *n* (%)	
	LEF (*n*=641)	MOX (*n*=641)
All TEAEs	224 (34.9)	195 (30.4)
Related TEAEs†	99 (15.4)	68 (10.6)
TEAEs by severity		
Mild	119 (18.6)	117 (18.3)
Moderate	78 (12.2)	55 (8.6)
Severe	27 (4.2)	23 (3.6)
Serious TEAEs	36 (5.6)	31 (4.8)
TEAEs leading to study drug discontinuation‡	20 (3.1)	21 (3.3)
TEAEs leading to death by study day 28§	8 (1.2)	7 (1.1)
TEAEs leading to death (over entire study duration)‖	11 (1.7)	8 (1.2)

AE=adverse event; LEF=lefamulin; MedDRA=Medical Dictionary for Regulatory Activities; MOX=moxifloxacin; TEAE=treatment-emergent AE.
*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.
†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." Patients with multiple events in each category were counted only once in that category.
‡A patient could have >1 TEAE leading to study drug discontinuation.
§Assessed in the intent-to-treat population (LEF, *n*=646; MOX, *n*=643)
‖Three 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; 1 patient died on study day 57 from endocarditis, which was first reported on study day 24; and 1 patient died on study day 271 from acute myeloid leukemia, which was first reported on study day 269. One 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.

Gastrointestinal Events

- The most common TEAEs were in the SOC of GI disorders (LEF, 13.1%; MOX, 10.1%)
  - Within this SOC, the most frequently reported individual TEAEs were diarrhea (LEF, 7.3%; MOX, 3.9%), nausea (LEF, 4.2%; MOX, 2.0%), and vomiting (LEF, 2.3%; MOX, 0.6%), each of which was more common in the LEF group
  - Differences between the 2 treatment groups were driven primarily by GI events associated with oral dosing in the LEAP 2 study
- Of the most frequently occurring GI TEAEs (ie, diarrhea, nausea, vomiting), most were mild to moderate in severity **(Figure 2)**
- No patients treated with LEF and 2 patients treated with MOX had a serious GI TEAE
- Few patients in each treatment group discontinued study drug due to GI TEAEs (LEF, 0.5%; MOX, 0.2%)
- One case of *Clostridium difficile* infection was reported in the LEF group of LEAP 2
  - The event occurred in a successfully treated patient who remained hospitalized, with onset approximately 1 week after completing 5 days of active LEF treatment
  - The event resolved after a course of oral vancomycin treatment

Figure 2. Most Common Gastrointestinal TEAEs (Pooled Safety Population)



LEF=lefamulin; TEAE=treatment-emergent adverse event.

Hepatobiliary Events

- The incidence of TEAEs in the SOC of hepatobiliary disorders was 0.9% in both the LEF and MOX treatment groups
- Similarly, a low incidence of liver enzyme elevation was observed in each treatment group, with few patients experiencing an elevation of alanine aminotransferase or aspartate aminotransferase >10× upper limit of normal (ULN) **(Table 2)**
- No clinically meaningful patterns were identified in liver chemistry laboratory parameters
  - No patients in the LEF group and 1 patient in the MOX group met the laboratory criteria for Hy's Law (ie, any postbaseline alanine aminotransferase or aspartate aminotransferase value >3× ULN, any postbaseline total bilirubin value >2× ULN, and any postbaseline alkaline phosphatase value ≤2× ULN)

Table 2. Maximum Postbaseline Elevation in Liver Enzymes (Pooled Safety Population)

Laboratory Measurement*	Patients, *n* (%)	
	LEF (*n*=641)	MOX (*n*=641)
ALT		
>3× ULN†	34 (5.5)	34 (5.4)
>5× ULN	13 (2.1)	8 (1.3)
>10× ULN	2 (0.3)	0
AST		
>3× ULN†	23 (3.7)	15 (2.4)
>5× ULN	8 (1.3)	7 (1.1)
>10× ULN	2 (0.3)	0
ALP		
>2× ULN‡	19 (3.0)	11 (1.7)
Total bilirubin		
>1.5× ULN†	6 (1.0)	6 (1.0)
>2× ULN	2 (0.3)	2 (0.3)

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; LEF=lefamulin; MOX=moxifloxacin; ULN=upper limit of normal.
*Baseline was defined as the last assessment before the first dose of study drug. Table includes both local and central laboratory results. If central laboratory baseline values were not available, then local laboratory baseline values were used.
†LEF (*n*=623) and MOX (*n*=628).
‡LEF (*n*=625) and MOX (*n*=629).

Cardiac Events

- The incidence of TEAEs in the SOC of cardiac disorders was 2.5% in the LEF group and 3.1% in the MOX group
- After dosing, the mean QT interval corrected according to Fridericia increased from baseline in both treatment groups, although the magnitude of change was numerically smaller for LEF than for MOX **(Table 3)**
  - No associated cardiac arrhythmias of concern were observed

Table 3. Postbaseline QTcF Changes (Pooled Safety Population)

QTcF	LEF (*n*=641)	MOX (*n*=641)
Patients with both baseline* and postbaseline values	636	638
Any postbaseline increase, *n* (%)	554 (87.1)	563 (88.2)
Any postbaseline increase >30 ms, *n* (%)	114 (17.9)	142 (22.3)
Any postbaseline increase >60 ms, *n* (%)	11 (1.7)	16 (2.5)
Any postbaseline value >480 ms, *n* (%)	20 (3.1)	21 (3.3)
Any postbaseline value >500 ms, *n* (%)	2 (0.3)	6 (0.9)
Maximum change from baseline, ms, mean (SD)	16.9 (16.9)	19.3 (17.7)

LEF=lefamulin; MOX=moxifloxacin; QTcF=QT interval corrected according to Fridericia.
*Baseline was defined as the last assessment before the first dose of study drug.

Other Findings From LEAP 1 and LEAP 2 Pooled Analyses

- Please refer to Poster E1006 for efficacy results and Poster E1142 for efficacy and safety results in patients with atypical respiratory pathogens

CONCLUSIONS AND CLINICAL IMPLICATIONS

- Pooled data from these 2 pivotal phase 3 trials of adults with CABP generally showed similar safety and tolerability for LEF, a first-in-class IV and oral pleuromutilin, and MOX, a standard of care fluoroquinolone
- These results suggest a favorable benefit-to-risk profile for LEF for the management of inpatients and outpatients presenting with CABP
- LEF provides a well-tolerated new IV and oral monotherapy option for the empiric treatment of adults with CABP

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