Efficacy and Symptom Resolution by Visit in Adults With Community-Acquired Bacterial Pneumonia Treated With Lefamulin or Moxifloxacin: Pooled Analysis of Lefamulin Evaluation Against Pneumonia (LEAP) 1 and LEAP 2 Study Results

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INTRODUCTION & PURPOSE

Preliminary results with lefamulin appear promising. Early mortality and hospitalization are leading causes of hospitalizations and subsequent deaths in the United States.1

Although lefamulin has been shown to be efficacious in prior randomized controlled trials (RCTs),2–4 no head-to-head comparisons have been made with one of the most frequently used community-acquired bacterial pneumonia (CABP) treatments, moxifloxacin (MOX) therapy.3,5

Lefamulin (LEF) is a tail-in-class penem with a novel mechanism of action that may offer advantages over other classes of antibacterial agents.6

Previous studies1,2 showed no difference in the success rates between LEF and MOX for patients with community-acquired bacterial pneumonia (CABP). A meta-analysis7 of these studies found that LEF demonstrated noninferiority to MOX in CABP. In one of the studies included in the pooled analysis, LEF had superior bacterial eradication rates compared to a glycylcycline in CABP.8

METHODS

Study Design

This was a pooled analysis of the LEAP 1 and LEAP 2 trials. Both were randomized, double-blind, double-dummy, active-controlled phase 3 studies of 2013–2016. All patients were ≥18 years old and received intravenous (IV) or intramuscular (IM) LEF or IV MOX for up to 5 days. The randomized treatment period was 3 days, followed by the IV or IM route to oral therapy for 1 to 2 days. The control arm for LEF was placebo, and the control arm for MOX was another antibiotic. The LEF LEAP 1 and LEAP 2 studies were not blinded, whereas LEAP 2 was blinded to the IV-to-oral switch.

Study Inclusion Criteria

• Pneumonia according to the American Thoracic Society definition (1993),10

• White blood cells (WBC) ≤10,000 cells/mm3 or ≥15% immature neutrophils

• Clinical signs and symptoms of CABP, which were defined as temperature ≥38°C or ≤35°C, cough, sputum production, and at least one additional clinical sign or laboratory finding of CABP: hypoxemia, auscultatory/percussion findings consistent with consolidation, leukocytosis/leukopenia, arterial hypotension, or altered mental status

• Baseline and study visits were conducted using hospital electronic medical records, and visits were confirmed by site monitoring personnel.

Study Exclusion Criteria

• Non-CABP pneumonia

• SIRS,11 or in patients with other clinical signs and symptoms, hypoxemia, auscultatory/percussion findings consistent with consolidation, leukocytosis/leukopenia, arterial hypotension, or altered mental status

• History of allergy to lefamulin, MOX, or components of LEF

• Patients were <18 years old

• Other antibacterial therapy within 72 hours before randomization

• Cytopenia

• Infections due to multiresistant or other multiply resistant organisms

• Known or suspected HIV infection

• Immunocompromised states

• History of malignancy

• Chronic kidney disease stage 5 requiring dialysis

• Uncontrolled hypertension

• Known or suspected alcohol abuse or drug addiction

• Other medical or psychiatric conditions requiring chronic medication

• Other concomitant medication

• Severe cardiovascular disease

• Severe gastrointestinal disease

• Other serious medical conditions

• Pregnant or nursing women

• Patients who had received lefamulin or moxifloxacin or both before randomization

Patients and Assessments

All patients were randomized to receive LEF 600 mg q24h or MOX 400–800 mg q12h for 6 IV doses of study drug. LEF was administered every 24 hours (q24h) for 3 days or MOX 400 mg IV q12h for 5–7 days or MOX 800 mg q12h for 3 days or MOX 400 mg IM q24h for 3 days. After 6 IV doses of study drug, patients received a single dose of short-acting systemic antibacterial medication within 72 hours before randomization. Randomization was stratified by site-reported PORT risk class used for enrollment/stratification.

The PORT risk class was calculated programmatically using data obtained at the site and reported in the eCRF and was not always consistent with the site-reported class. Therefore, for the purposes of the pooled analysis, the site-reported PORT risk class was used. In the case of missing site-reported PORT risk class data, the PORT risk class was estimated via nearest neighbor matching using site-based demographic variables.

Patients were assessed as success if alive, with signs and symptoms of CABP resolved or improved such that no additional antibacterial therapy was needed. This occurred during at least one treatment period (TOC, ≤14 days) and subsequent evaluation (S3, ≤90 days) of CABP clinical signs and symptoms, white blood cell (WBC) count (≥10,000 cells/mm3 or ≤4500 cells/mm3 or ≥15% immature neutrophils).12

Efficacy assessments were based on the intent-to-treat (ITT) population, including all randomized patients who were exposed to study drug. Efficacy analyses were performed at the TOC and late follow-up (LFU; days 27–34). The success rates at TOC, as well as at EOT (end of treatment) and LFU, in the mITT and CE populations were high (>83%) and similar to LEF and MOX efficacy rates observed in other LEAP studies.9

In the pooled analysis, ECR criteria were applied to each study visit through LFU in the ITT population. Efficacy was assessed at least once during treatment (TOC) and at least once during follow-up (TOC+LFU; days 27–34).

In the LEAP 2 study, a local procedure was used for S3 follow-up (days 27–34). A study visit during the open-label period (days 27–34) was considered a late follow-up visit (LFU) if the patient had not had any late follow-up visits (LFU) before. However, patients who had an early S3 visit were excluded from LFU visits. Patients were assessed for efficacy and safety through at least 34 days after randomization.

RESULTS (continued)

Early Clinical Response

• The majority of patients in the LEAP 1 and LEAP 2 treatment groups met ECR criteria at Day 3, with >90% of patients in both groups meeting ECR criteria at Day 3, followed by convergence to >96% and >97% treatment success at Day 7 (Table 3).

• Mean symptom resolution time (SRT), which is reflective of clinical improvement, was 4.5 days in the LEAP 1 study and 4.7 days in the LEAP 2 study. The mean SRT calculated at the late follow-up visit was 7 days in both studies. The median SRT was 3 days in both studies.

• All patients were assessed as success if alive, with signs and symptoms of CABP resolved or improved such that no additional antibacterial therapy was needed.

• The majority of patients in the LEAP 1 and LEAP 2 studies met ECR criteria at Day 3, with >90% of patients in both groups meeting ECR criteria at Day 3, followed by convergence to >96% and >97% treatment success at Day 7.

Figure 1. LEAP 1 and LEAP 2 Study Design

Figure 2. Patients Meeting Criteria for Early Clinical Response by Visit (Pooled ITT Population)

Figure 3. Pooled Investigator Assessment of Clinical Response Success Rates

Figure 4. Patients With Resolution of 3 or More Baseline Signs/Symptoms of CABP by Visit (Pooled ITT Population)

CONCLUSIONS

• In this pooled analysis of 2 phase 3 LEAP studies (LEAP 1 and LEAP 2), efficacy results (ECR, MOX, and symptoms resolved) were similar in the LEAP 1 and 2 mITT groups, with high-risk enrollment and early clinical response rates consistent with LEAP 1 and 2 community-acquired pneumonia (CAP) and late follow-up results. Through the LFU visit, the majority of patients with CABP

• Consistently achieved clinical response and resolution at a single antimicrobial therapy, for which they were selected, which aligns with current guidelines for empirical and definitive treatment.

• The high percentage of patients with CABP with resolution of baseline symptoms suggests that symptoms can be an important indicator of how well patients respond to antibiotics for empiric treatment of CABP in adults.

REFERENCES


