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

Jennifer Schranz,1 Lisa Goldberg,1 Anita F. Das,1 Elizabeth Alexander,1 Gregory J. Morran,2 Christian Sandrock,4 Andrew F. Shorr,4 Steven P. Gelone1

Nabriva Therapeutics US, Inc, King of Prussia, PA, USA; 1Oxas Consulting, Guerneville, CA, USA; 2One View-VCLLA Medical Center, Sylvan, CA, USA; 3UC Davis School of Medicine, Sacramento, CA, USA; 4Medstar Washington Hospital Center, Washington, DC, USA

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Understanding the clinical and economic burden of community-acquired pneumonia is substantial,1–4 with annual costs estimated at $30.8 billion in the United States.1–4 Lefamulin (LEF), a novel semisynthetic pleuromutilin macrolide, is being developed as a new treatment option 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 fluorquinolone-associated disability (eg, tendon injury, aortic rupture, encephalopathy, and glucose homeostasis abnormalities).5–7

Lefamulin (LEF), a first-in-class pleuromutilin antibiotic, approved for intravenous (IV) and oral use in the treatment of adults with CABP, inhibits protein synthesis by binding selectively and specifically to the peptidyltransferase center of the 50S ribosomal subunit.8,9 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) (n=527);10 the LEAP 2 study evaluated the efficacy and safety of oral LEF monotherapy compared with oral MOX (n=517).11–13

METHODS

Study Design

– Both studies were prospective, randomized, double-blind, double dummy, phase 3 trials (Figure 1A–D).14

– Patients in LEAP 1 and LEAP 2 were enrolled at 66 centers (18 countries) and 59 centers (18 countries), respectively.

– In LEAP 1, patients were randomized to receive LEF 750 mg IV every 12 hours (q12h) for 7–10 days or oral MOX 400 mg q12h for 24 hours (q24h) for 7 days.

– Patients could switch to oral LEF therapy (MOX 600 mg q12h or q24h 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 Society (PORT) criteria II–IV or I–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 predose 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 all patients, and on Days 1 and 4 for Day 1 and Day 4 (patients) or 1 h after dose (subpatients).

– Clinically significant laboratory abnormalities were evaluated by the study investigator or a monitoring physician.

RESULTS

Patients

1283 patients randomized to LEF (n=646) and MOX (n=637) were included in the pooled intent-to-treat population – Patients demographics and disease characteristics were 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 (55.1%), white (79.3%), and with a mean (SD) age of 65.1 (12.8) 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, 39.6% had a history of chronic obstructive pulmonary disease, 36.9% had a history of liver enzyme elevation, 13.0% had a history of diabetes mellitus, and 5.7% had a history of erythromycin.

– 1283 patients randomized to LEF (n=646) and MOX (n=637) were included in the pooled safety analysis set.

Safety and Tolerability

Overview of TEAEs

– The overall rate of TEAEs was similar in the LEF (34.5%) and MOX (31.4%) treatment groups (Table 1).

– Patients were primarily mild to moderate in severity; only 3.3% of TEAEs were severe.

– Treatment-emergent adverse events were reported in 14.5% and 10.5% 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)

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