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Oral Lefamulin Is Safe and Effective in the Treatment of Adults With Community-Acquired Bacterial Pneumonia (CABP): Results of Lefamulin Evaluation Against Pneumonia (LEAP 2) Study

Elizabeth Alexander,[1] Lisa Goldberg,[1] Anita Das,[2] Gregory J. Moran,[3] Christian Sandrock,[4] Leanne B. Gasink,[1] Patricia Spera,[1] Carolyn Sweeney,[1] Susanne Paukner,[5] Wolfgang W. Wicha,[5] Jennifer Schranz[1]

[1]Nabriva Therapeutics US, Inc., King of Prussia, PA, USA; [2]Das Consulting, Guerneville, CA, USA; [3]Olive View-UCLA Medical Center, Los Angeles, CA, USA; [4]UC Davis School of Medicine, Sacramento, CA, USA; [5]Nabriva Therapeutics GmbH, Vienna, Austria

Nabriva Therapeutics
Dublin, Ireland
www.nabriva.com

INTRODUCTION

- Community-acquired bacterial pneumonia (CABP) causes substantial morbidity, mortality, and economic burden and has been among the leading causes of infection-related death in the United States for the past 20 years[1-3]
- Increasing rates of bacterial resistance, combined with increasing safety concerns associated with fluoroquinolones, have created a need for new treatment options[4-8]
- Lefamulin, a first-in-class pleuromutilin for intravenous (IV) and oral use in humans, inhibits bacterial protein synthesis by a unique conserved interaction with the bacterial ribosome[9]
- Lefamulin rapidly penetrates the epithelial lining fluid after IV or oral administration[10,11] and is active against most common Gram-positive, Gram-negative, and atypical CABP-causing pathogens, including strains resistant to other antimicrobial classes[12-16]
- The LEAP 1 study in adults with moderate to severe (Pneumonia Outcomes Research Team [PORT] risk class ≥III) CABP demonstrated that lefamulin was noninferior to moxifloxacin when both groups initiated IV therapy with optional IV-to-oral switch[17]

OBJECTIVE

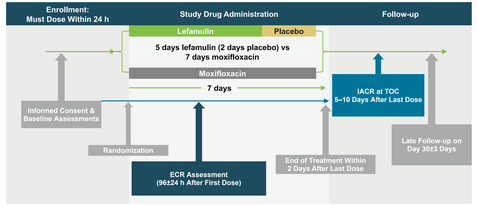
- To evaluate the efficacy and safety of a 5-day oral regimen of oral lefamulin vs a 7-day oral regimen of moxifloxacin in adults with CABP

METHODS

Study Design

- LEAP 2 was a prospective, multicenter, double-blind, double-dummy phase 3 study in adults with CABP with PORT risk class II–IV (NCT02813694; EudraCT 2015-004782-92; **Figure 1**)
- Patients were randomized to oral lefamulin 600 mg every 12 hours (q12h) for 5 days or oral moxifloxacin 400 mg every 24 hours (q24h) for 7 days **(Figure 1)**. Randomization was stratified by PORT risk class (II vs. III/IV), geographic region (US vs ex-US) and prior short-acting antibiotic therapy for CABP vs none

Figure 1. Study Design



ECR=early clinical response; IACR=investigator assessment of clinical response; TOC=test-of-cure visit.

Patients

- Key inclusion criteria
  - Patients ≥18 years of age with PORT risk class II–IV (with ≥50% III or IV) radiographically documented pneumonia, acute illness (≤7 days) with ≥3 CABP symptoms (dyspnea, new or increased cough, purulent sputum production, and chest pain), ≥2 vital sign abnormalities (fever or hypothermia, hypotension, tachycardia, or tachypnea), hypoxemia, and physical exam or laboratory evidence of pneumonia

METHODS (continued)

- Key exclusion criteria
  - Receipt of >1 dose of a short-acting oral or IV antibacterial for CABP within 72 hours before randomization, hospitalization for ≥2 days within 90 days, confirmed or suspected methicillin-resistant *Staphylococcus aureus*, being at risk of major cardiac events/dysfunction, having significant hepatic, immunologic, or hematologic diseases, and severe renal impairment (estimated creatinine clearance <30mL/min)

Assessments

- The primary efficacy endpoint for the US Food and Drug Administration (FDA) was early clinical response (ECR) at 96±24 hours after first study drug dose in the intent-to-treat (ITT) population (all randomized patients)
  - Patients were classified as responders if they were alive, showed improvement in ≥2 of 4 CABP symptoms, had no worsening of any CABP symptom, and did not receive a nonstudy antibacterial for the current CABP episode; as nonresponders if these criteria were not met; and as indeterminate if data were missing
- The European Medicines Agency (EMA) coprimary endpoints (FDA secondary endpoints) were investigator assessment of clinical response (IACR) at test of cure (TOC; 5–10 days after last study drug dose) in the modified ITT (mITT; all randomized patients who received ≥1 study drug dose) and clinically evaluable (CE; patients who met predefined "per-protocol" criteria) populations
  - Patients were classified as a success if they had improved or resolved CABP without additional antibacterials or as a failure if they died from any cause or if a nonstudy antibacterial was required for the current CABP episode. Patients lost to follow-up or with insufficient data were classified as indeterminate
- For ECR and IACR, lefamulin noninferiority vs moxifloxacin was concluded if the lower limit of the 2-sided 95% CI for the treatment difference exceeded –10%
- Other endpoints included ECR by PORT risk class in the ITT population, ECR in the microbiological ITT population (microITT; all patients in the ITT population with ≥1 baseline CABP pathogen detected), and IACR at TOC in the microITT population
- Multiple diagnostic techniques were used to maximize pathogen detection at baseline, including:
  - Culture of typical Gram-positive and Gram-negative organisms from adequate sputum samples (defined by Gram-stain), blood, from oropharyngeal swabs (*Mycoplasma pneumoniae*) and nasopharyngeal swabs (*Streptococcus pneumoniae*)
  - Serological testing (4-fold increase of IgG) for *Chlamydophila pneumoniae, M. pneumoniae*, and *Legionella pneumophila*
  - Urine antigen testing for detection of *S. pneumoniae* and *L. pneumophila*
  - Quantitative single-plex real-time PCR of sputum and nasopharyngeal samples for the detection of the most relevant bacterial pathogens causing CABP

Safety

- Treatment-emergent adverse events (TEAEs), laboratory results, and 12-lead electrocardiograms were monitored during the study, and 28-day all-cause mortality was evaluated in the safety population (all randomized and treated patients)

RESULTS

Patients and Baseline Characteristics

- Of 738 patients randomized, 370 were randomized to lefamulin and 368 were randomized to moxifloxacin
- Demographics and baseline characteristics were well balanced between treatment groups **(Table 1)**
  - 53% of patients (391/738) were included in the microITT population (lefamulin, 55.4% [205/370]; moxifloxacin, 50.5% [186/368])

RESULTS (continued)

Table 1. Demographic and Baseline Characteristics (ITT Population)

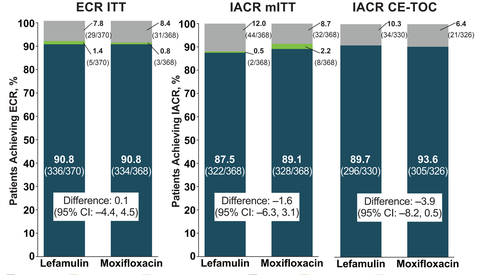
Characteristic	Lefamulin (*n*=370)	Moxifloxacin (*n*=368)
Male, *n* (%)	207 (55.9)	180 (48.9)
Age, mean (SD), y	57.4 (16.4)	57.7 (16.2)
Comorbidities, *n* (%)		
Vascular disorders	138 (37.3)	145 (39.4)
Renal impairment (CrCl <60 mL/min)	68 (18.4)	73 (19.8)
Diabetes	48 (13.0)	51 (13.9)
Cardiac disorders	46 (12.4)	53 (14.4)
COPD	38 (10.3)	33 (9.0)
Asthma	23 (6.2)	29 (7.9)
Current or previous smoker, *n* (%)	163 (44.1)	135 (36.7)
PORT risk class, *n* (%)		
I	1 (0.3)	2 (0.5)
II	183 (49.5)	189 (51.4)
III	145 (39.2)	133 (36.1)
IV	40 (10.8)	42 (11.4)
V	1 (0.3)	2 (0.5)
Minor ATS criteria for severity met,* *n* (%)	31 (8.4)	37 (10.1)
SIRS criteria met,† *n* (%)	353 (95.4)	342 (92.9)
Bacteremia at baseline, *n* (%)	6 (1.6)	9 (2.4)
Multilobar pneumonia, *n* (%)	88 (23.8)	101 (27.4)

ATS=American Thoracic Society; COPD=chronic obstructive pulmonary disease; CrCl=creatinine clearance; ITT=intent to treat; PORT=Pneumonia Outcomes Research Team; SIRS=systemic inflammatory response syndrome; WBC=white blood cell.
*Defined as presence of ≥3 of the following 9 criteria at baseline: respiratory rate ≥30 breaths/min, O_2 saturation <90% or PaO_2 <60 mmHg, BUN ≥20 mg/dL, WBC <4000 cells/mm³, confusion, multilobar infiltrates, platelets <100,000 cells/mm³, temperature <36°C, systolic blood pressure <90 mmHg.
†Defined as ≥2 of the following 4 symptoms at baseline: temperature <36°C or >38°C; heart rate >90 beats/min; respiratory rate >20 breaths/min; WBC <4000 cells/mm³, WBC >12,000 cells/mm³, or immature polymorphonuclear neutrophils >10%.

Efficacy

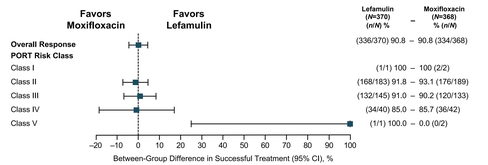
- Lefamulin met the primary objective of noninferiority vs moxifloxacin with high response (ECR) and success (IACR) rates in both groups **(Figure 2)**
- High ECR rates were observed across all PORT risk classes **(Figure 3)**
  - Consistently high responses were also observed by age, sex, prior antibiotic use, severity indices, and renal status (data not shown)
  - Similar results were observed for IACR at TOC (data not shown)
- Lefamulin demonstrated high response rates overall and by common CABP pathogens **(Table 2)**

Figure 2. ECR and IACR at TOC



CE-TOC=clinically evaluable at test-of-cure visit; ECR=early clinical response; EMA=European Medicines Agency; FDA=Food and Drug Administration; IACR=investigator assessment of clinical response; ITT=intent to treat; mITT=modified ITT.

Figure 3. ECR by PORT Risk Class (ITT Population)



CI=confidence interval; ECR=early clinical response; ITT=intent to treat; PORT=Pneumonia Outcomes Research Team.

Table 2. ECR and IACR by Baseline CABP Pathogen (microITT Population)

Pathogen, *n/N* (%)*	ECR		IACR	
	Lefamulin (*n*=205)	Moxifloxacin (*n*=186)	Lefamulin (*n*=205)	Moxifloxacin (*n*=186)
Overall response	186 (90.7)	173 (93.0)	176 (85.9)	163 (87.6)
Treatment difference (95% CI)	–2.3 (–8.2, 3.6)		–1.8 (–8.7, 5.1)	
Streptococcus pneumoniae	110/123 (89.4)	115/126 (91.3)	105/123 (85.4)	108/126 (85.7)
Staphylococcus aureus	13/13 (100)	6/6 (100)	12/13 (92.3)	5/6 (83.3)
Haemophilus influenzae	50/56 (89.3)	44/48 (91.7)	52/56 (92.9)	40/48 (83.3)
Moraxella catarrhalis	18/21 (85.7)	11/11 (100)	17/21 (81.0)	11/11 (100)
Atypicals				
Mycoplasma pneumoniae	20/20 (100)	14/14 (100)	19/20 (95.0)	14/14 (100)
Legionella pneumophila	13/16 (81.3)	16/17 (94.1)	13/16 (81.3)	15/17 (88.2)
Chlamydophila pneumoniae	15/16 (93.8)	12/12 (100)	12/16 (75.0)	10/12 (83.3)

CABP=community-acquired bacterial pneumonia; ECR=early clinical response; IACR=investigator assessment of clinical response; microITT=microbiological intent to treat.
*A patient could have had >1 pathogen (~30% of patients had a polymicrobial infection). Multiple isolates of the same species from the same patient were counted once for each phenotype and once for the overall tabulation of the genus and species. Phenotypes were only determined for pathogens identified from cultures and with susceptibility testing results. Reporting the number of patients who were responders (ECR) or who had success (IACR)/ total number of patients with a specific baseline pathogen.

Safety

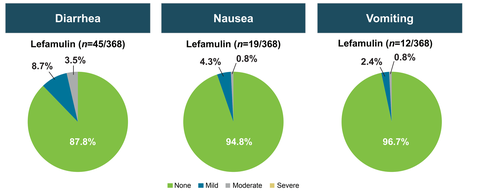
- Both agents had similar safety profiles **(Table 3)**, with low rates of study drug discontinuation observed
- The most frequent TEAEs in the lefamulin treatment group were gastrointestinal events, which were mild to moderate in severity **(Figure 4)**
  - No other TEAEs were reported at frequencies >2% in either treatment group
- Postbaseline elevations in alanine aminotransferase and aspartate aminotransferase were infrequent, transient, and similar in both treatment groups; no patient met the laboratory criteria for Hy's law
- Small increases in QT interval corrected according to Fridericia (QTcF) were seen, but increases were consistently smaller with lefamulin vs moxifloxacin, and no associated cardiac arrhythmias were observed

Table 3. Overview of TEAEs (Safety Population)

Patients With ≥1, *n* (%)	Lefamulin (*n*=368)	Moxifloxacin (*n*=368)
TEAEs	120 (32.6)	92 (25.0)
TEAEs leading to discontinuation of study drug	12 (3.3)	9 (2.4)
TEAEs leading to withdrawal from trial	5 (1.4)	5 (1.4)
Serious TEAEs	17 (4.6)	18 (4.9)
Deaths within 28 d	3 (0.8)	3 (0.8)

TEAEs=treatment-emergent adverse events.

Figure 4. Gastrointestinal TEAEs (Safety Population)



Diarrhea was generally of short duration (median, 2 days) and none led to discontinuation of lefamulin.

Nausea/vomiting was generally mild.
No patients discontinued due to nausea; 2 discontinued due to vomiting.

TEAEs=treatment-emergent adverse events.

CONCLUSIONS

- Oral lefamulin 5-day therapy was as efficacious as a 7-day course of moxifloxacin in the treatment of CABP, with high responses across subpopulations, PORT classes and against the most common typical and atypical CABP pathogens
- Oral lefamulin 5-day therapy was generally well tolerated, with low discontinuation rates due to TEAEs
- Lefamulin shows promise as an oral or IV-to-oral empiric monotherapy for CABP

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