Lefamulin Efficacy and Safety in Adults With Community-Acquired Bacterial Pneumonia (CABP): Pooled Analysis of The Lefamulin Evaluation Against Pneumonia (LEAP) 1 and LEAP 2 Trials in Patients With Asthma or Chronic Obstructive Lung Disease (COPD)

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INTRODUCTION

- Patients with chronic respiratory diseases such as asthma and COPD are at increased risk of developing CABP; and comorbid COPD increases the risk of severe CABP and can aggravate clinical symptoms and complicate management[1,2]
- The ATS/IDSA guidelines[3] recommend patients with comorbidities be treated with a combination of beta-lactam *plus* macrolide or doxycycline OR monotherapy with a respiratory fluoroquinolone
- Increasing rates of bacterial resistance[4-6] and safety issues associated with fluoroquinolones have created a need for alternative treatment options[7,8]
- Lefamulin has potent and targeted *in vitro* activity against *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis,* and *Staphylococcus aureus* (methicillin susceptible and methicillin resistant), as well as the atypical pathogens *Mycoplasma pneumoniae, Chlamydophila pneumoniae*, and *Legionella pneumophila*; its activity is unaffected *in vitro* by an organism's resistance to other CABP antibiotic classes[9]
- Lefamulin has predictable pharmacokinetics after oral and IV administration with rapid plasma absorption and considerable penetration in the epithelial lining fluid of the lung[9]
- Lefamulin is the first pleuromutilin antibiotic approved for IV and oral use in adults with CABP based on the results of two noninferiority phase 3 trials, the Lefamulin Evaluation Against Pneumonia (LEAP) 1 and LEAP 2
- Understanding the outcomes of novel treatments, such as lefamulin, in patients with chronic respiratory diseases may help to better characterize patients commonly encountered in the clinic

OBJECTIVE

- To investigate the safety and efficacy of lefamulin in CABP patients who may be at risk for poor outcomes, pooled data from LEAP 1 and 2 were analyzed post hoc in patients with asthma or COPD

METHODS

Study Design and Efficacy in LEAP 1 & LEAP 2

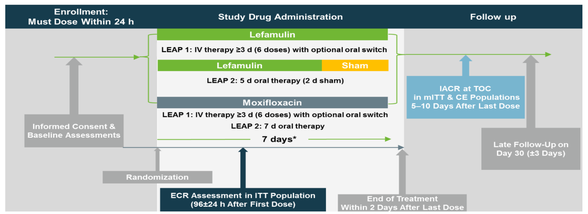
- Both studies were global, prospective, randomized, double-blind, double-dummy, non-inferiority phase 3 trials (**Figure 1**)
- The LEAP 1 study evaluated the efficacy and safety of lefamulin as monotherapy, with an IV-to-oral switch option, compared with moxifloxacin (± linezolid)[9]
  - Patients were randomized to receive lefamulin 150 mg IV every 12 hours (q12h) for 5–7 days or moxifloxacin 400 mg IV every 24 hours (q24h) for 7 days
- The LEAP 2 study evaluated the efficacy and safety of oral lefamulin monotherapy compared with oral moxifloxacin monotherapy[9]
  - Patients were randomized to receive oral lefamulin 600 mg q12h for 5 days or oral moxifloxacin 400 mg q24h for 7 days
- In both studies, the primary efficacy endpoint for the US FDA was ECR at 96±24 hours after first study drug dose in the ITT population
- The European Medicines Agency coprimary endpoints (FDA secondary endpoints) were IACR at the TOC assessment 5–10 days after the last dose of study drug in the mITT and clinically evaluable populations

Post Hoc Analysis

- Patients with asthma versus COPD were evaluated by demographics, baseline pathogens, rates of clinical response, and safety

METHODS (continued)

Figure 1. LEAP 1 and LEAP 2 Study Design



CE=clinically evaluable (patients who met predefined specified criteria related to adherence to the protocol); 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 episode of CABP); 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); mITT= modified ITT (All randomized patients who received ≥1 dose of study drug); TOC=test-of-cure visit.

RESULTS

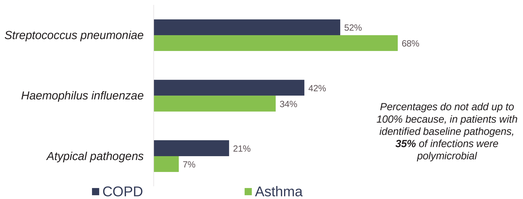
Patient Population

- Among 1289 randomized patients in the combined LEAP 1 and 2 trials, 84 (6.5%) had asthma and 154 (11.9%) had COPD
- Demographic data of asthma and COPD patients are shown in **Table 1.** Compared to patients with asthma, those with COPD were more likely to be aged ≥ 65 y (45% vs 61% respectively), be male (36% vs 67.5%), have a history of smoking (33% vs 73%), hypertension (45% vs 61%), or congestive heart failure (5% vs 15%); or have PORT risk class IV-V (20% vs 37%) and CURB-65 scores of 3-5 (7.1% vs 14.2%); patients in both cohorts were predominantly PORT III or greater

Microbiology

- *Streptococcus pneumoniae* was seen in the majority of patients, followed by *Haemophilus influenzae* **(Figure 2)**
- *S. pneumoniae* was more commonly identified in patients with asthma, while *H. influenzae* was more commonly identified in patients with COPD
- Atypical pathogens were more frequently identified in patients with COPD vs asthma

Figure 2. Baseline Pathogens from the Pooled LEAP 1 and LEAP 2 Studies



RESULTS (continued)

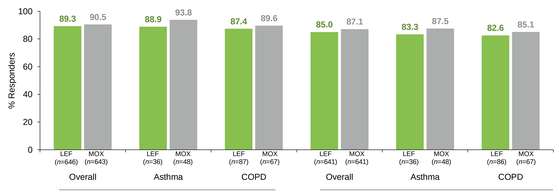
Table 1. Demographics and Baseline Patient Characteristics

Parameter	Asthma		COPD	
	Lefamulin *n* = 36	Moxifloxacin *n* = 48	Lefamulin *n* = 87	Moxifloxacin *n* = 67
Age, yr, median (range)	64 (21-84)	62 (25-88)	68 (37-89)	66 (49-93)
Age ≥ 65 years	17 (47.2)	21 (43.8)	54 (62.1)	40 (59.7)
Male, *n* (%)	14 (38.9)	17 (35.4)	64 (73.6)	40 (59.7)
PORT risk class, *n (%)*				
II	12 (33.3)	12 (25.0)	14 (16.1)	15 (22.4)
III	16 (44.4)	27 (56.3)	44 (50.6)	24 (35.8)
IV-V	8 (22.2)	9 (18.8)	29 (33.3)	28 (41.8)
CURB-65 score, *n (%)*				
0-2	34 (94.4)	44 (91.7)	76 (87.4)	56 (83.6)
3-5	2 (5.6)	4 (8.3)	11 (12.6)	11 (16.4)
Comorbidities/Characteristics, *n* (%)				
Hypertension	15 (41.7)	23 (47.9)	51 (58.6)	44 (65.7)
Diabetes	6 (16.7)	9 (18.8)	14 (16.1)	14 (20.9)
Smoking history	14 (38.9)	14 (29.2)	67 (77.0)	45 (67.2)
Congestive heart failure	2 (5.6)	2 (4.2)	12 (13.8)	11 (16.4)
History of arrhythmia	3 (8.3)	4 (8.3)	8 (9.2)	6 (9.0)

PORT, Pneumonia Outcomes Research Team; CURB-65, Confusion, Uremia, Respiratory Rate, Blood Pressure, 65 years of age and older

- The results of the pooled data from LEAP 1 and LEAP 2 demonstrated comparable efficacy across all clinical endpoints (ECR and IACR at TOC) within a given treatment arm (i.e., lefamulin or moxifloxacin), whether evaluating the overall population or those with chronic respiratory disease **(Figure 3)**

Figure 3. Rates of Clinical Response



[a] ECR assessed in the intent-to-treat (ITT) population (all randomized patients), with response defined as alive, showing improvement in ≥ 2 CABP symptoms, no CABP symptom worsening, and receipt of no nonstudy antibiotic for CABP treatment.
[b] IACR assessed in the modified ITT population (all randomized patients who received any study drug), with response defined as alive and CABP signs/symptoms resolved or improved such that no additional antibiotic was administered for the current CABP episode.
ECR=early clinical response; IACR=investigator assessment of clinical response; LEF=lefamulin; MOX=moxifloxacin; TOC=test of cure.

RESULTS (continued)

Safety

- Consistent with the overall lefamulin safety profile, the most common TEAEs in patients with asthma or COPD were gastrointestinal **(Table 2)**

Table 2. Treatment-Emergent Adverse Events (TEAEs)

n (%)	Asthma		COPD	
	Lefamulin (n=36)	Moxifloxacin (n=48)	Lefamulin (n=87)	Moxifloxacin (n=67)
All TEAEs	15 (41.7)	15 (31.3)	30 (34.9)	29 (43.3)
Mild	5 (13.9)	8 (16.7)	10 (11.6)	16 (23.9)
Moderate	8 (22.2)	5 (10.4)	13 (15.1)	10 (14.9)
Severe	2 (5.6)	2 (4.2)	7 (8.1)	3 (4.5)
TEAEs by preferred term (≥2% in any group)				
Diarrhea	4 (11.1)	3 (6.3)	5 (5.8)	5 (7.5)
TEAEs by system organ class				
Gastrointestinal distress	7 (19.4)	9 (18.8)	7 (8.1)	9 (13.4)

CONCLUSIONS

- In the two global phase 3 studies, LEAP 1 and LEAP 2, lefamulin, the first-in-class systemic pleuromutilin, showed high clinical response rates and a safety profile that was comparable to a respiratory fluoroquinolone
- Lefamulin efficacy was unaffected by the presence of asthma or COPD and was comparable to that observed for moxifloxacin
- Lefamulin is indicated as a short-course 5-day oral therapy, has targeted activity against the most common causes of CABP, including atypical and drug-resistant strains, and has the ability to facilitate transitions of care with both the IV and oral formulation
- Lefamulin provides an alternative to fluoroquinolones in patients with asthma or COPD including those at risk for severe CABP

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Disclosures

D.M., S.G., are employees/stockholders in Nabriva Therapeutics plc. C.S., G.M., G.W., T.F., has served as a consultant for Nabriva Therapeutics during the design and execution within the LEAP programs.

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