Lefamulin (Pleuromutilin-Class Antibiotic) Is an Empiric, Monotherapeutic Treatment Option for Community-Acquired Bacterial Pneumonia Caused by *Streptococcus pneumoniae*, Including Drug-Resistant Strains

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INTRODUCTION & PURPOSE

- Community-acquired bacterial pneumonia (CABP) is associated with substantial morbidity, mortality, and economic burden and is among the leading causes of infection-related death in the US[1,2]
- *S. pneumoniae (SP)* is the most common bacterial cause of CABP.[3] Because of the significant healthcare burden associated with *SP*, the US CDC designated drug-resistant *SP* a serious threat [4]
- The ATS/IDSA guidelines recommend macrolide monotherapy in patients without comorbidities only when local *SP* resistance is <25%.[3] However, the rate of macrolide-resistance was recently observed to be 39.5% across the US[5]
- Increasing rates of bacterial resistance[2] and safety issues associated with fluoroquinolones have created a need for new treatment options[6,7]
- Lefamulin, a first-in-class pleuromutilin for intravenous (IV) and oral use in humans, inhibits protein synthesis by binding centrally to the peptidyl transferase center of the 50S ribosomal subunit [8]
- Lefamulin has potent *in vitro* activity against *SP*, *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]
- The favorable pharmacokinetics and spectrum of activity of lefamulin led to its investigation in two phase 3 trials in adults with CABP and ultimately FDA approval for this indication

OBJECTIVE

- Given the need for monotherapy treatment options, we report efficacy outcomes overall from the Lefamulin Evaluation Against Pneumonia (LEAP) phase 3 clinical program together with a focus in patients with *SP* including those with resistant strains in the pooled LEAP 1 and LEAP 2 analyses

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

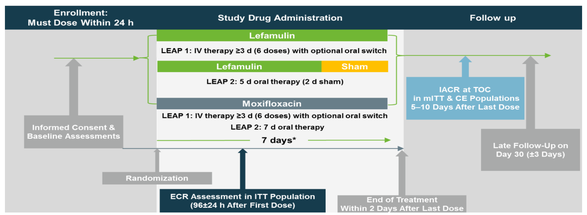
Analysis of Patients with *S. pneumoniae* from LEAP Trial Program

- The microbiological intent-to-treat (microITT) population included all patients with a baseline CABP pathogen detected by ≥1 method (i.e., culture, quantitative real-time PCR, urine antigen testing, and IgG serology)
- MICs for lefamulin and moxifloxacin were determined using broth microdilution according to the Clinical and Laboratory Standards Institute, with susceptibilities based on 2017 CLSI breakpoints[10] for penicillin, the oral breakpoint was applied, and macrolide resistance was defined as resistance to azithromycin or erythromycin

METHODS (continued)

- Multi-drug resistance was defined as resistant to ≥2 of the following: oral penicillin, moxifloxacin, ceftriaxone, clindamycin, azithromycin or erythromycin, doxycycline, or trimethoprim/sulfamethoxazole
- We evaluated the ECR and IACR for both lefamulin and moxifloxacin in the microITT population found to be positive with *SP* at baseline (i.e., collected within 24hr of the first dose of study drug), as well as various subgroups of those patients based on the resistance phenotypes of their *SP* isolates

Figure 1. LEAP 1 and LEAP 2 Study Design

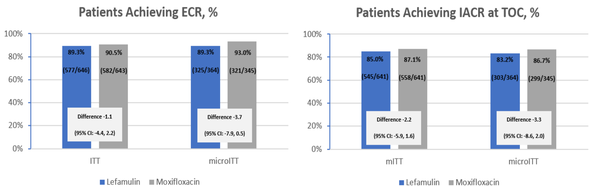


CE=clinically evaluable (patients who met predefined specified criteria related to adherence to the protocol); ECR=early clinical response (patient assessed as responder if alive, showed improvement in ≥2 CABP signs and symptoms, no worsening in any CABP sign or symptom, and no receipt of a concomitant 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 (Overall pooled LEAP trial program)

- The results of the overall pooled data of the LEAP 1 and LEAP 2 studies demonstrated comparable efficacy across all clinical endpoints achieving non-inferiority between lefamulin and moxifloxacin **(Figure 2)**
- There were 1010 baseline CABP pathogens detected in 709/1289 (55.0%) patients. The most frequently isolated baseline pathogens were *SP* (439/1010 [43.5%] pathogens; 439/709 [61.9%] patients) followed by *H. influenzae* (212/1010 [21.0%] pathogens; 212/709 [29.9%] patients). *M. catarrhalis* and the atypical pathogens were less common and identified in similar percentages (5.7%–7.2%) of pathogens. Similar to the overall population in the phase 3 program ECR + IACR at TOC were similar and high across treatments and among pathogens

Figure 2. Pooled LEAP 1 and LEAP 2 Efficacy Results for ECR and IACR at TOC



RESULTS (*S. pneumoniae* cohort)

Patient Population

- There were a total of 1289 patients in the combined LEAP 1 and 2 trials, with 1010 baseline CABP pathogens detected in 709 (55.0%) patients
- Of the 709 patients, *SP* was identified in 439 patients and was the most frequently observed pathogen occurring at a rate of 61.9% (Lefamulin, n=216/439; Moxifloxacin, n=223/439)
- Demographic data of *SP* patients are shown in **Table 1,** where 71.6% of patients had PORT risk class ≥3 and patients with CURB-65 classification ≥2 amounted to 33.2%

Table 1. Demographics & Baseline Characteristics of Patients Infected with SP

Parameter	Lefamulin *n* = 216	Moxifloxacin *n* = 223	Overall *n* = 439
Age, yr, median (range)	62 (19-97)	58 (20-90)	60 (19-97)
Male, *n* **(%)**	133 (61.6)	124 (55.6)	257 (58.5)
PORT risk class, *n (%)*			
I	1 (0.5)	1 (0.5)	2 (0.5)
II	52 (24.1)	71 (31.8)	123 (28)
III	119 (55.1)	108 (48.4)	227 (51.7)
IV/V	44 (20.4)	43 (19.3)	87 (19.8)
CURB-65 score, *n (%)*			
0	36 (16.7)	38 (17.0)	74 (16.9)
1	113 (52.3)	106 (47.5)	219 (49.9)
2	55 (25.5)	61 (27.4)	116 (26.4)
3-4	12 (5.6)	18 (8.1)	30 (6.8)
Comorbidities/Characteristics, *n* (%)			
Congestive Heart Failure	14 (6.5)	26 (11.7)	40 (9.1)
Asthma/COPD	38 (17.6)	37 (16.6)	75 (17.1)
Diabetes	22 (10.2)	33 (14.8)	55 (12.5)
Hypertension	73 (33.8)	76 (34.1)	149 (33.9)
Smoking History	104 (48.1)	106 (47.5)	210 (47.8)

PORT, Pneumonia Outcomes Research Team; CURB, Confusion Uremia Respiratory rate Blood Pressure Age ≥ 65

Microbiologic Assessment

- *In vitro* data for cultured strains of *SP* indicated that resistance to macrolides, penicillin, or the multi-drug resistant phenotype had no bearing on lefamulin or moxifloxacin activity **(Table 2)**

Table 2. MIC Data for *SP* Isolates from the Pooled LEAP 1 and LEAP 2 Studies

Baseline Pathogen	Lefamulin		Moxifloxacin	
	n	$MIC_{50/90}$ (μg/mL)	*n*	$MIC_{50/90}$ (μg/mL)
S. pneumoniae	130	0.25/0.5	130	0.12/0.25
Macrolide resistant	31	0.25/0.25	31	0.12/0.25
Multidrug resistant	32	0.25/0.25	32	0.12/0.25
Penicillin resistant	14	0.25/0.25	14	0.12/0.25

RESULTS (continued)

Outcomes Assessment

- Clinical outcomes in the *SP* cohort were high and similar between treatment groups, irrespective of macrolide- penicillin- or multidrug-resistance **(Table 3)**

Table 3. LEAP 1 & LEAP 2 Pooled Analysis of Efficacy Against *SP* in Patients with CABP

Baseline Pathogen, % (*n/N*)	ECR		IACR at TOC	
	Lefamulin	Moxifloxacin	Lefamulin	Moxifloxacin
*S. pneumoniae**	88.9 (192/216)	92.4 (206/223)	85.2 (184/216)	86.5 (193/223)
Macrolide resistant	92.9 (13/14)	82.4 (14/17)	92.9 (13/14)	82.4 (14/17)
Multidrug resistant	100 (14/14)	83.3 (15/18)	100 (14/14)	83.3 (15/18)
Penicillin resistant	– (7/7)	– (6/7)	– (7/7)	– (4/7)

*ECR p = 0.275; IACR at TOC p = 0.785

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 that were comparable to a respiratory fluoroquinolone
- Evaluating *SP* isolates from these studies, we found potent *in vitro* activity for both lefamulin and moxifloxacin across macrolide-resistant, penicillin-resistant, and multi-drug resistant strains
- Corroborating this *in vitro* activity, the clinical success rates were also high and similar between lefamulin and moxifloxacin within the *S. pneumoniae* cohort including those resistant subgroups
- Given it 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 the ability to facility transitions of care with both the IV and oral formulation, lefamulin represents an alternative monotherapy option for empiric as well as pathogen-targeted treatment of CABP

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Disclosures

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

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