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Post Hoc Assessment of Time to Clinical Response (TTCR) Among Adults Hospitalized with Community-Acquired Bacterial Pneumonia Who Received Either Lefamulin (LEF) or Moxifloxacin (MOX) in Two Phase III Randomized, Double-Blind, Double-Dummy Clinical Trials

Thomas Lodise,[1] Sam Colman,[2] Daniel Stein,[3] David Fitts,[3] Lisa Goldberg,[3] Elizabeth Alexander,[3] Jennifer Schranz[3]

[1]Albany College of Pharmacy and Health Sciences, Albany, NY, USA; [2]Covance Market Access Services Inc., Gaithersburg, MD, USA; [3]Nabriva Therapeutics US, Inc., King of Prussia, PA, USA

Nabriva Therapeutics
Dublin, Ireland
www.nabriva.com

INTRODUCTION

- Alternatives to fluoroquinolones with intravenous (IV) and oral (PO) formulations for patients with community-acquired bacterial pneumonia (CABP) are needed given the increased safety concerns with fluoroquinolones[1,2]
- Lefamulin (LEF) is a first-in-class systemic pleuromutilin antibiotic in development for the treatment of adult patients with CABP. LEF was shown to be noninferior to moxifloxacin (MOX) based on the standard early and post treatment clinical response endpoints in two phase III Lefamulin Evaluation Against Pneumonia (LEAP) 1 and 2 clinical trials[3,4]
- Even though treatment duration and hospital discharge readiness status is not mandated by health authorities, evaluation of time to clinical response has been well described in the literature as an important effectiveness metric to inform clinicians about preferred administration route (ie, IV vs PO)[5,6]

OBJECTIVE

- This analysis sought to quantify time to clinical response (TTCR) among inpatients with CABP who received LEF or MOX in the LEAP 1 and LEAP 2 trials

METHODS

Study Design and Population

- A post hoc analysis using the pooled data from 2 completed and similar phase III clinical trials NAB-BC-3781-3101 (LEAP 1 henceforth) and NAB-BC-3781-3102 (LEAP 2 henceforth) **(Table 1)**

Table 1. LEAP 1 and LEAP 2 Study Characteristics

Study Characteristic	LEAP 1	LEAP 2
Design	Multicenter, multinational, randomized, double-blind, double-dummy, active-controlled, efficacy and safety study in patients with CABP. The planned enrollment was 738 patients. Eligible patients were randomized 1:1 to lefamulin or the comparator, moxifloxacin, using an interactive response technology	
	Randomized patients were stratified according to PORT risk class (risk class III vs IV and V), geographic region (US vs ex-US), and prior (single dose) short-acting antibiotic therapy for CABP vs none	Randomized patients were stratified according to PORT risk class (risk class II vs III/IV), geographic region (US vs ex-US), and prior (single dose) short-acting antibiotic therapy for CABP vs none
Key inclusion/exclusion criteria	Adult (≥18 years) had an acute illness (≤7 days duration) with at least 3 of the following symptoms consistent with a lower respiratory tract infection (new or worsening): • Dyspnea • New or increased cough • Purulent sputum production • Chest pain due to pneumonia Have at least 2 of the following vital sign abnormalities: • Fever (body temperature >38.0°C [100.4°F]) or hypothermia (body temperature <35.0°C [95.0°F]) • Hypotension (systomic blood pressure <90 mmHg) • Tachycardia (heart rate >100 beats/min) • Tachypnea (respiratory rate >20 breaths/min)	
	PORT risk class ≥III	PORT risk class II, III, or IV
Active treatment and duration	Lefamulin (IV) 150 mg q12h with possible switch to lefamulin (PO) 600 mg q12h after 3 days Duration: 5–10 days	Lefamulin (PO) 600 mg q12h Duration: 5 days
Comparator treatment	Moxifloxacin (IV) 400 mg q24h with possible switch to moxifloxacin (PO) 400 mg q24h after 3 days with or without adjunctive linezolid Duration: 5–10 days	Moxiflaxicin (PO) 400 mg q24h Duration: 7 days

CABP=community-acquired bacterial pneumonia; IV=intravenous; LEAP=Lefamulin Evaluation Against Pneumonia; PO=orat; PORT=Pneumonia Outcomes Research Team; q12h=every 12 hours.

- Additional inclusion criteria for this analysis:
  - Meet CABP disease and other study criteria in LEAP 1 and LEAP 2 trials
  - Pneumonia Outcomes Research Team (PORT) risk class pneumonia severity index of II, III or IV at baseline
  - Hospitalized at baseline and received at least 24 hours of therapy (unless due to death)

METHODS (continued)

Patient Data

- Data elements included enrollment region, demographics, medical history and comorbidities, physical examination, laboratory findings, prior antibiotic therapy, previous episodes of pneumonia, severity of illness based on the PORT scoring system and CURB-65 (confusion, urea, respiratory rate, blood pressure, age over 65), and microbiological culture results
- Patients' vital signs and 4 cardinal CABP symptoms (ie, cough, shortness of breath, chest pain, and sputum production) were collected on admission and each subsequent day for up to 10 days

Outcomes

- Clinical response was achieved when the following criteria were met:
  - Alive
  - Clinical stability (temperature ≤38.0°C and ≥35.0°C, heart rate ≤100 bpm, systolic blood pressure ≥90 mmHg, respiratory rate ≤24 breaths/min, oxygen saturation ≥90%, arterial PaO_2 ≥60 mmHg)
  - Improvement in at least 2 cardinal CABP symptoms (ie, cough, shortness of breath, chest pain, or sputum production) and none worsening
  - No receipt of a concomitant antibiotic (other than adjunctive linezolid) for treatment of the current episode of CABP
- A patient was considered to have achieved the outcome of interest on a given day if all components of the outcome of interest were achieved on that day
- Patients who died or did not show clinical improvement between Day 2 and end of treatment (EOT) were censored at the last evaluable outcome assessment
  - Patients who received a concomitant antibiotic for treatment of the current episode of CABP were censored at the earliest of the date of concomitant antibiotic for treatment or at the last evaluable outcome assessment

Statistical Analysis Plan

- Descriptive analysis was conducted on the study sample for baseline characteristics, including: 1) demographics, 2) geographic region, 3) medical history, 4) physical examination and laboratory findings, 5) prior antibiotic therapy, 6) previous episodes of pneumonia, 7) severity of illness, and 8) microbiological culture results
- Kaplan-Meier time-to-event analyses (overall and by subgroup)
  - TTCR, a proxy for hospital discharge readiness
  - Time to clinical stability
  - Time to clinical improvement
- Cox proportional-hazards analyses were conducted controlling for baseline characteristics having a variation in 10% or more between treatment groups

RESULTS

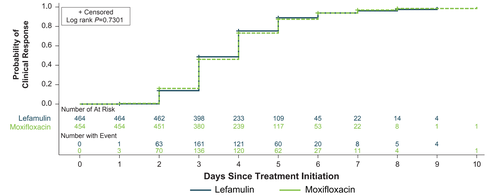
Baseline Disease Characteristics

- Demographics and baseline characteristics were generally well balanced between treatment groups **(Table 2)**

Time to Clinical Response

- The median (interquartile range, IQR) time from treatment initiation to clinical response was 4 (3–4) days for LEF and 4 (3–5) for MOX (P=0.7301, log rank test) **(Figure 1)**
- Nearly all patients had clinical response between treatment initiation and EOT: 95.5% and 95.6% for LEF and MOX, respectively

Figure 1. Time to Clinical Response (Overall)



RESULTS (continued)

- In the Cox regression, there was no difference in TTCR between treatments after adjustment for baseline covariates (hazard ratio, 1.04; 95% confidence interval, 0.91–1.20; P=0.5323) **(Table 3)**
- These results were generally consistent within the subgroups assessed **(Table 4)**

Table 2. Patient Characteristics

Characteristic	Lefamulin (n=468)	Moxifloxacin (n=458)
Mean (SD) age, y	59.7 (16.34)	59.4 (15.63)
Sex, *n* (%)		
Male	278 (59.4)	253 (55.2)
Race, *n* (%)		
White	410 (87.6)	392 (85.6)
Black or African American	10 (2.1)	17 (3.7)
Asian	38 (8.1)	36 (7.9)
American Indian or Alaska Native	7 (1.5)	6 (1.3)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)
Other	3 (0.6)	7 (1.5)
Mean (SD) weight, kg	76.5 (18.56)	74.6 (18.28)
Mean (SD) BMI, kg/m^2	26.7 (5.51)	26.4 (5.77)
Renal status, *n* (%)		
Severe impairment (CrCl <30 mL/min)	5 (1.1)	3 (0.7)
Moderate impairment (CrCl 30–<60 mL/min)	94 (20.1)	101 (22.1)
Mild impairment (CrCl 60–<90 mL/min)	147 (31.4)	145 (31.7)
Normal function (CrCl ≥90 mL/min)	221 (47.2)	209 (45.6)
Missing renal function data	1	0
PORT risk class, *n* (%)		
II	97 (20.7)	95 (20.7)
III	279 (59.6)	272 (59.4)
IV	92 (19.7)	91 (19.9)
CURB-65 score,* *n* (%)		
0	74 (15.8)	64 (14.0)
1	227 (48.5)	225 (49.1)
2	138 (29.5)	138 (30.1)
3	29 (6.2)	27 (5.9)
4	0 (0.0)	4 (0.9)
5	0 (0.0)	0 (0.0)
Patients meeting minor ATS severity criteria,† *n* (%)	62 (13.2)	57 (12.4)
Patients meeting modified ATS severity criteria,‡ *n* (%)	45 (9.6)	49 (10.7)
Patients meeting SIRS criteria,§ *n* (%)	458 (97.9)	439 (95.9)
Patients with bacteremia, *n* (%)	11 (2.4)	10 (2.2)
Prior antibiotic use, *n* (%)		
Use	116 (24.8)	112 (24.5)
No Use	352 (75.2)	346 (75.5)

ATS=American Thoracic Society; BMI=body mass index; CrCl=creatinine clearance; PORT=Pneumonia Outcomes Research Team; SD=standard deviation; SIRS=systemic inflammatory response syndrome.
*Defined as blood urea nitrogen >19 mg/dL, respiratory rate ≥30 breaths/min, blood pressure <90 mmHg systolic or ≤60 mmHg diastolic, and age ≥65 years.
†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 (defined as infiltrates present in any two locations, except lingula and left upper lobe is not multilobar. Lingula and other location is multilobar), platelets <100,000 cells/mm³, temperature <36°C, systolic blood pressure <90 mmHg.
‡Defined as presence of ≥3 of the following 6 criteria at baseline: respiratory rate ≥30 breaths/min, SpO_2/FiO_2 <274 where SpO_2/FiO_2 = 64+0.84 (PaO_2/FiO_2)), BUN ≥20 mg/dL, confusion, age ≥65 years, multilobar infiltrates.
§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, or WBC >12,000 cells/mm³, or immature PMNs >10%.

Table 3. Cox Proportional Hazards Analysis of Time to Clinical Response*

Time to Clinical Response (days)	Lefamulin (n=468)	Moxifloxacin (n=458)	P-value
Overall, *n*	464	454	
Clinical Response, *n* (%)	443 (95.5)	434 (95.6)	
Hazard Ratio – adjusted (95% CI)	1.04 (0.91, 1.20)	reference	0.5323
Hazard Ratio – unadjusted (95% CI)	1.02 (0.89, 1.16)	reference	0.7906

CI=confidence interval; PORT=Pneumonia Outcomes Research Team.
*The hazard ratio was evaluated using a Cox proportional hazards model of time to clinical improvement on treatment controlling for study ID, age categories, sex, region of enrollment, prior pneumonia, prior antibiotic use ≤72 hours prior to randomization, PORT classification, procalcitonin, and tobacco history. The hazard ratio compared the event for patients taking lefamulin to those taking moxifloxacin.

Table 4. Kaplan Meier Plot of Time to Clinical Response by Subgroup

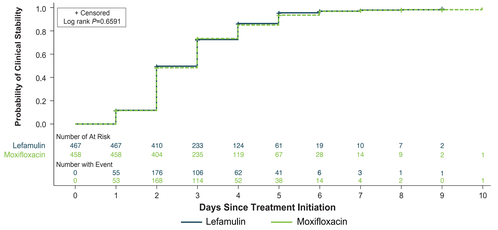
Time to Clinical Response (days)/ Subgroup*	Lefamulin (n=468) Median (IQR)	Moxifloxacin (n=458) Median (IQR)
Overall, *n*	4.00 (3.00–4.00)	4.00 (3.00–5.00)
Monomicrobial infection	3.00 (3.00–4.00)	4.00 (3.00–4.00)
Gram-positive pathogen only	4.00 (3.00–4.00)	4.00 (3.00–4.00)
Gram-negative pathogen only	3.00 (3.00–4.00)	3.00 (3.00–4.00)
Gram-negative fastidious pathogen only	3.00 (3.00–4.00)	3.00 (3.00–4.00)
Atypical pathogen only†	3.00 (3.00–5.00)	3.00 (3.00–5.00)
Typical pathogen only	3.00 (3.00–4.00)	3.00 (3.00–4.00)
Polymicrobial infection	4.00 (3.00–5.00)	4.00 (3.00–5.00)
Gram-positive and fastidious Gram-negative pathogens	3.00 (3.00–5.00)	4.00 (2.00–5.00)
Gram-positive and atypical pathogens	4.00 (3.00–5.00)	3.00 (3.00–5.00)
Streptococcus pneumoniae	4.00 (3.00–5.00)	4.00 (3.00–5.00)
Methicillin-susceptible *Staphylococcus aureus*	4.50 (3.50–5.00)	3.00 (2.00–5.00)
PORT II	4.00 (3.00–4.00)	4.00 (3.00–4.00)
PORT III	4.00 (3.00–4.00)	4.00 (3.00–5.00)
PORT IV	4.00 (3.00–5.00)	4.00 (3.00–5.00)
CURB 65‡ ≥2	4.00 (3.00–4.00)	4.00 (3.00–5.00)
CURB 65 <2	4.00 (3.00–4.00)	4.00 (3.00–4.00)
LEAP 1	4.00 (3.00–4.00)	4.00 (3.00–5.00)
LEAP 2	4.00 (3.00–4.00)	4.00 (3.00–5.00)
Minor ATS severity criteria§ – Yes	3.50 (3.00–4.50)	4.00 (3.00–5.00)
Minor ATS severity criteria – No	4.00 (3.00–4.00)	4.00 (3.00–5.00)
Modified ATS severity criteria‖ – Yes	4.00 (3.00–5.00)	4.00 (3.00–5.00)
Modified ATS severity criteria – No	4.00 (3.00–4.00)	4.00 (3.00–5.00)

ATS=American Thoracic Society; IQR=interquartile range; LEAP=Lefamulin Evaluation Against Pneumonia; PORT=Pneumonia Outcomes Research Team.
*All log rank test P-values were ≥0.3548.
†Defined as *Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Chlamydophila pneumoniae*.
‡Defined as blood urea nitrogen >19 mg/dL, respiratory rate ≥30 breaths/min, blood pressure <90 mmHg systolic or ≤60 mmHg diastolic, and age ≥65 years.
§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 (defined as infiltrates present in any two locations, except lingula and left upper lobe is not multilobar. Lingula and other location is multilobar), platelets <100,000 cells/mm³, temperature <36°C, systolic blood pressure <90 mmHg.
‖Defined as presence of ≥3 of the following 6 criteria at baseline: respiratory rate ≥30 breaths/min, SpO_2/FiO_2 <274 where SpO_2/FiO_2 = 64+0.84 (PaO_2/FiO_2)), BUN ≥20 mg/dL, confusion, age ≥65 years, multilobar infiltrates.

Time to Clinical Stability

- The median (IQR) time from treatment initiation to clinical stability was 3 (2–4) days in both the LEF and MOX treatment groups (P=0.6591, log rank test) **(Figure 2)**
- Nearly all patients reached clinical stability between treatment initiation and EOT: 96.6% and 97.4% for LEF and MOX, respectively

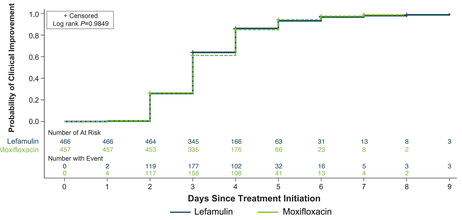
Figure 2. Time to Clinical Stability



Clinical Improvement

- The median (IQR) time from treatment initiation to clinical improvement was 3 (2–4) days in both the LEF and MOX treatment groups (P=0.9849, log rank test) **(Figure 3)**
- Nearly all patients had a clinical improvement between treatment initiation and EOT: 98.5% and 97.8% for LEF and MOX, respectively

Figure 3. Time to Clinical Improvement



CONCLUSIONS

- Clinical response to LEF is rapid and comparable to MOX with response across multiple inpatient types who present with CABP
- LEF provides an effective new IV and PO monotherapy option for empiric treatment of adults with CABP

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