Supplementary Online Content

Alexander E, Goldberg L, Das A, et al. Oral lefamulin vs moxifloxacin for early clinical response among adults with community-acquired bacterial pneumonia: the LEAP 2 randomized clinical trial. *JAMA*. doi:10.1001/jama.2019.15468

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Patients Who Met SIRS Criteria at Baseline (ITT Population)

Criterion, No. (%)	Lefamulin (n = 370)	Moxifloxacin (n = 368)
All patients who met SIRS criteria[a]	353 (95.4)	342 (92.9)
Temperature <36°C or >38°C	316 (85.4)	296 (80.4)
Heart rate >90 beats/min	202 (54.6)	203 (55.2)
Respiratory rate >20 breaths/min	341 (92.2)	343 (93.2)
WBC <4000 cells/mm^3, WBC >12,000 cells/mm^3, or immature PMNs >10%	89 (24.1)	92 (25.0)

Abbreviations: ITT, intent to treat; PMN, polymorphonuclear neutrophil; SIRS, systemic inflammatory response syndrome; WBC, white blood cell.
[a]Defined as ≥2 of the criteria/symptoms described in the table above.

eTable 2. Baseline CABP Pathogen Distribution (microITT Population)

	No. (%)[b]	
Baseline Pathogen[a]	**Lefamulin (n = 205)**	**Moxifloxacin (n = 186)**
Streptococcus pneumoniae	123 (60.0)	126 (67.7)
Penicillin susceptible	26/34 (76.5)[c]	38/46 (82.6)[c]
Penicillin resistant	5/34 (14.7)[c]	4/46 (8.7)[c]
Macrolide resistant[d]	8/34 (23.5)[c]	11/46 (23.9)[c]
Multidrug resistant[e]	8/34 (23.5)[c]	12/46 (26.1)[c]
Staphylococcus aureus	13 (6.3)	6 (3.2)
Methicillin susceptible	9/11 (81.8)[c]	2/3 (66.7)[c]
Methicillin resistant	2/11 (18.2)[c]	1/3 (33.3)[c]
Haemophilus influenzae	56 (27.3)	48 (25.8)
Moraxella catarrhalis	21 (10.2)	11 (5.9)
Mycoplasma pneumoniae	20 (9.8)	14 (7.5)
Legionella pneumophila	16 (7.8)	17 (9.1)
Chlamydophila pneumoniae	16 (7.8)	12 (6.5)
Monomicrobial infections	142 (69.3)	135 (72.6)
Polymicrobial infections	63 (30.7)	51 (27.4)

Abbreviations: CABP, community-acquired bacterial pneumonia; microITT, microbiological intent to treat; PCR, polymerase chain reaction.

[a]Baseline pathogens were identified by multiple diagnostic modalities including standard methods such as culture from adequate sputum, bronchoalveolar lavage, and pleural fluid or blood as well as urinary antigen testing (*S pneumonia*, *L pneumophila*), serological testing (*M pneumoniae*, *C pneumoniae*, *L pneumophila*), quantitative real-time PCR for all listed pathogens from sputum samples, and quantitative real-time PCR of nasopharyngeal swabs (*S pneumoniae*) and of oropharyngeal swabs (*M pneumoniae*). All non-culture based diagnostic methodologies used FDA-cleared diagnostic tests or have been validated and met acceptance criteria.

[b]Percentages were based on the number of patients in each treatment group. A patient could have had more than 1 pathogen. Multiple isolates of the same species from the same patient were counted only once for each phenotype and once for the overall tabulation of the genus and species.

[c]Susceptibility or resistance phenotypes were determined only for pathogens identified from cultures and with susceptibility testing results. Therefore, the number of isolates with a resistance phenotype was ultimately lower than the total number of organisms. For *S pneumonia,* the numbers of pathogens identified from cultures with susceptibility testing results were n = 34 for lefamulin and n = 46 for moxifloxacin; for *S aureus,* these were n = 11 for lefamulin and n = 3 for moxifloxacin.

[d]Resistant to azithromycin or erythromycin.

[e]Resistant to ≥2 of the following: oral penicillin, moxifloxacin, ceftriaxone, clindamycin, azithromycin or erythromycin, doxycycline, or trimethoprim/sulfamethoxazole.

eTable 3. Minimum Inhibitory Concentrations for Key Cultured CABP Pathogens (microITT Population)

		$MIC_{50/90}$,[b] µg/mL	
Pathogen[a]	**No.[c]**	**Lefamulin**	**Moxifloxacin**
Streptococcus pneumoniae	80	0.25/0.25	0.12/0.25
Penicillin susceptible	64	0.25/0.25	0.12/0.25
Penicillin intermediate	9	NC (0.12–0.5)	NC (0.12–0.25)
Penicillin resistant	9	NC (0.12–0.25)	NC (0.12–0.25)
Macrolide resistant[d]	19	0.25/0.25	0.12/0.25
Multidrug resistant[e]	20	0.25/0.25	0.12/0.25
Staphylococcus aureus	14	0.12/0.12	0.06/>2
Methicillin susceptible	11	0.12/0.12	0.06/0.06
Methicillin resistant	3	NC (0.12–0.12)	NC (0.06–>2)
Haemophilus influenzae	24	1/2	0.03/0.03
Moraxella catarrhalis	5	NC (0.06–0.25)	NC (0.03–0.06)
Mycoplasma pneumoniae	11	≤0.001/≤0.001	0.12/0.25
Legionella pneumophila	2	NC (0.5–1)	NC (0.03–0.03)

Abbreviations: CABP, community-acquired bacterial pneumonia; MIC, minimum inhibitory concentration; MIC_{50}, MIC required to inhibit 50% of isolates; MIC_{90}, MIC required to inhibit 90% of isolates; microITT, microbiological intent to treat; NC, not calculated because of small sample size.

[a]Number of patients with a baseline pathogen isolated from adequate sputum (for *L pneumophila*, adequacy of sputum was not required), nasopharyngeal swab (*S pneumoniae* only), oropharyngeal swab (*M pneumoniae* only), blood, bronchoalveolar lavage, and/or pleural fluid via culture. A patient could have had >1 pathogen. Multiple isolates of the same species and phenotype from the same patient were counted only once, regardless of source, using the isolate with the highest MIC to study drug received. Percentage of susceptible and resistant was based on total number of given pathogens tested.

[b]MIC_{50} and MIC_{90} values are reported only for pathogens with ≥10 isolates in the relevant group. For pathogen groups with <10 isolates, the range of MIC values is provided in parentheses. Susceptibilities for moxifloxacin are based on Clinical and Laboratory Standards Institute breakpoints, 2017. Oral penicillin breakpoints were applied.

[c]No. of pathogens collected from both treatment groups.

[d]Resistant to azithromycin or erythromycin.

[e]Resistant to ≥2 of the following: oral penicillin, moxifloxacin, ceftriaxone, clindamycin, azithromycin or erythromycin, doxycycline, or trimethoprim/sulfamethoxazole.

eTable 4. Results From Hierarchical Modeling Analysis[a]

Outcome[b]	Lefamulin n/N_1 (%)	Moxifloxacin n/N_1 (%)	Between-Group Treatment Difference (two-sided 95% CI)
Early clinical response, responder rate (ITT population)			
Site 1 only (*P*=.0213)	0/3 (0)	0	
Site 2 only (*P*=.0109)	3/4 (75.0)	4/8 (50.0)	
All sites included	336/370 (90.8)	334/368 (90.8)	0.1 (–4.4 to 4.5)[c]
Site 2 excluded	333/366 (91.0)	330/360 (91.7)	–0.7 (–5.0 to 3.7)[c]
Investigator assessment of clinical response at TOC, success rate (mITT population)			
Site 2 only (*P*=.0006)	2/4 (50.0)	3/8 (37.5)	
Site 3 only (*P*=.0465)	1/2 (50.0)	1/3 (33.3)	
Site 4 only (*P*=.0200)	0/2 (0)	0/1 (0)	
Site 5 only (*P*=.0465)	0/2 (0)	2/3 (66.7)	
All sites included	322/368 (87.5)	328/368 (89.1)	–1.6 (–6.3 to 3.1)[d]
Site 2 excluded	320/364 (87.9)	325/360 (90.3)	–2.4 (–7.0 to 2.2)[d]
Investigator assessment of clinical response at TOC, success rate (CE population)			
Site 2 only (*P*=.0006)	1/3 (33.3)	1/4 (25.0)	
Site 5 only (*P*=.0159)	0/2 (0)	2/3 (66.7)	
Site 6 only (*P*=.0394)	0	0/2 (0)	
All sites included	296/330 (89.7)	305/326 (93.6)	–3.9 (–8.2 to 0.5)[d]
Site 2 excluded	295/327 (90.2)	304/322 (94.4)	–4.2 (–8.3 to 0.1)[d]

Abbreviations: CE, clinically evaluable; CI, confidence interval; ECR, early clinical response; IACR, investigator assessment of clinical response; ITT, intent to treat; mITT, modified intent to treat; PORT, Pneumonia Outcomes Research Team; TOC, test of cure.

[a]Rates of ECR and IACR success at individual sites are shown for those sites with *P*<.05 from the hierarchical modeling analysis; overall rates of ECR and IACR success excluding sites with potential site effects are shown for those sites with *P*<.05 from the hierarchical modeling analysis and >5 randomized patients.

[b]*P* value is from the hierarchical modeling procedure.

[c]Treatment difference = difference in rates of ECR responder (lefamulin treatment group – moxifloxacin treatment group). Two-sided 95% CI was computed using a continuity corrected Z-test.

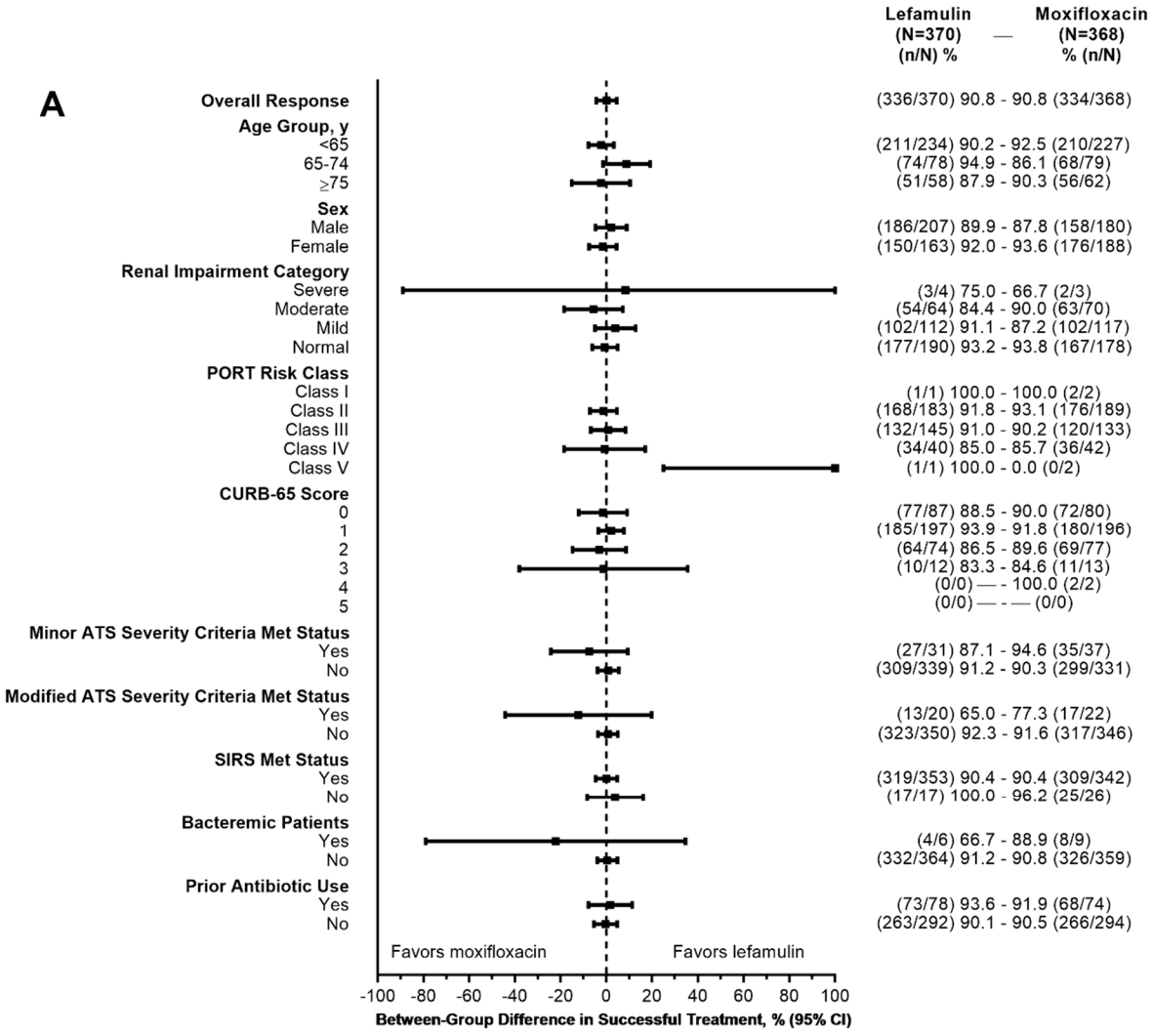
[d]Treatment difference = difference in rates of IACR success (lefamulin treatment group – moxifloxacin treatment group). Two-sided 95% CI was computed using the method of Miettinen and Nurminen with Cochran-Mantel-Haenszel weights as stratum weights and adjusted for the stratification factors of prior antibiotic use and PORT risk class.

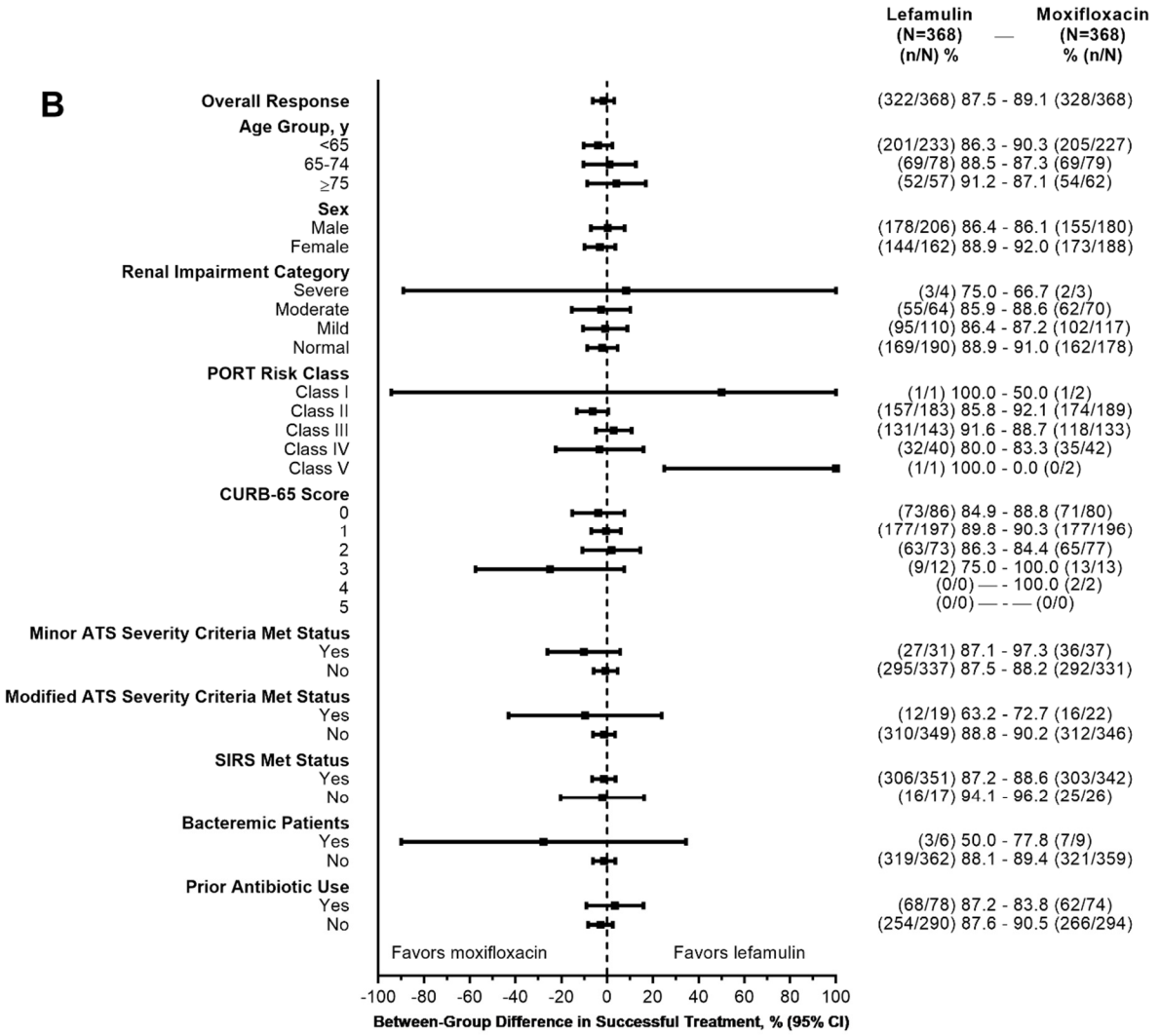
eTable 5. Results for Selected Laboratory Parameters (Safety Analysis Set)

	No. of Patients Meeting Criteria/Total No. of Patients (%)	
Parameter	**Lefamulin**	**Moxifloxacin**
Any postbaseline ALT value		
>3× ULN	15/355 (4.2)	17/361 (4.7)
>5× ULN	7/355 (2.0)	3/361 (0.8)
>10× ULN	1/355 (0.3)	0/361
Any postbaseline AST value		
>3× ULN	12/355 (3.4)	8/361 (2.2)
>5× ULN	6/355 (1.7)	5/361 (1.4)
>10× ULN	1/355 (0.3)	0/361
Any postbaseline total bilirubin value		
>1.5× ULN	3/355 (0.8)	3/361 (0.8)
>2× ULN	2/355 (0.6)	0/361
Any postbaseline ALP value		
>2× ULN	14/357 (3.9)	6/362 (1.7)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

eFigure. Early Clinical Response by Baseline Variables in the ITT Population (A) and Investigator Assessment of Clinical Response by Baseline Variables in the mITT Population at Test of Cure (B)





Abbreviations: ATS, American Thoracic Society; CURB, confusion of new onset, blood urea nitrogen >19 mg/dL, respiratory rate ≥30 breaths/min, blood pressure <90 mmHg systolic or ≤60 mmHg diastolic, age ≥65; ITT, intent to treat; mITT, modified intent to treat; PORT, Pneumonia Outcomes Research Team; SIRS, systemic inflammatory response syndrome.

eText. Post Hoc Hierarchical Modeling Analysis

In this study, 99 clinical sites randomized ≥1 patient in the study, with 50 sites randomizing <5 patients. Because this study was conducted at multiple study sites, post hoc analyses of early clinical response (ECR) and investigator assessment of clinical response (IACR) were conducted using hierarchical modeling to evaluate the potential for site effects.

Early Clinical Response

The hierarchical model identified 2 sites as having a potential for site effects (*P*<.05; Table). Site 1 randomized no patients in the moxifloxacin group. Site 2 randomized 12 patients in the intent-to-treat (ITT) population, with ECR rates of 3/4 (75%) for lefamulin vs 4/8 (50%) for moxifloxacin. Exclusion of site 2 from the analysis did not affect the results and lefamulin remained noninferior to moxifloxacin.

Investigator Assessment of Clinical Response

The hierarchical model identified 4 sites (Sites 2, 3, 4, and 5) with *P*<.05 in the modified ITT (mITT) population at test of cure (TOC) (Table). However, only site 2 randomized >5 patients (the same site 2 identified for the ECR analysis; this site randomized 12 patients in the mITT population). The rates of IACR success in site 2 were 2/4 (50%) for lefamulin vs 3/8 (37.5%) for moxifloxacin. Exclusion of site 2 from the analysis did not affect the results and lefamulin remained noninferior to moxifloxacin.

The hierarchical model identified 3 sites (Sites 2, 5, and 6) with *P*<.05 in the clinically evaluable (CE) population at TOC (Table). However, only site 2 randomized >5 patients (the same site as identified for the ECR analysis; this site randomized 7 patients in the CE population). Exclusion

of site 2 from the analysis did not affect the results and lefamulin remained noninferior to moxifloxacin.