Conclusion. LEF appears to be as safe and effective as MOX in treating patients with *LP*, including when given as short-course (5 days) oral therapy.

Table 1. Diagnostic Modalities and Baseline Pathogen Categories in Patients With *L. pneumophila*

	Lefamulin	Moxifloxacin
microITT, n/N (%)	34/364 (9.3)	31/345 (9.0)
Diagnostic Modality,* n (%)		
Serology	15 (4.1)	22 (6.4)
Urine UAT	8 (2.2)	8 (2.3)
Urine UAT + serology	3 (0.8)	0
Sputum RT-PCR	2 (0.5)	0
Urine UAT + sputum RT-PCR	1 (0.3)	0
Sputum RT-PCR + serology	1 (0.3)	1 (0.3)
≥3 modalities	4 (1.0)	0
Pathogen Category, n (%)		
Monomicrobial	18 (4.9)	16 (4.6)
Polymicrobial[†]	16 (4.4)	15 (4.3)
microITT-2, n/N (%)	32/209 (15.3)	31/195 (15.9)
Diagnostic Modality, n (%)		
Serology	16 (7.7)	23 (11.8)
Urine UAT	9 (4.3)	8 (4.1)
Urine UAT + serology	5 (2.4)	0
≥3 modalities	2 (1.0)	0
ME, n/N (%)	29/319 (9.1)	26/306 (8.5)
Diagnostic Modality, n (%)		
Serology	15 (4.7)	19 (6.2)
Urine UAT	5 (1.6)	6 (2.0)
Urine UAT + serology	2 (0.6)	0
Sputum RT-PCR	2 (0.6)	0
Sputum RT-PCR + serology	1 (0.3)	1 (0.3)
≥3 modalities	4 (1.2)	0

LEF=lefamulin; *LP*=*L. pneumophila*; ME=microbiologically evaluable population includes all pts who met the criteria for both the microITT and the CE analysis sets; microITT=microbiological ITT population includes all pts who had ≥1 baseline pathogen known to cause CABP; microITT-2=microbiological ITT-2 population includes all pts who had ≥1 baseline pathogen known to cause CABP from a diagnostic method other than PCR; MOX=moxifloxacin; RT-PCR=real-time polymerase chain reaction; UAT=urine antigen test.
*Qualification of *LP* as a baseline pathogen with serology testing required a 4-fold or greater increase in *LP* antibody titer to ≥1:128 between the baseline and convalescent samples. In RT-PCR, sample had to test positive for the *ssrA* gene.
†Included >1 atypical pathogen only (6 LEF, 3 MOX); Gram-positive and atypical pathogens only (6 LEF, 9 MOX); Gram-negative and atypical pathogens only (4 LEF, 1 MOX); and Gram-positive, Gram-negative, and atypical pathogens (0 LEF, 2 MOX).

Figure 1. Patients with *L. pneumophila* at Baseline Achieving ECR and IACR
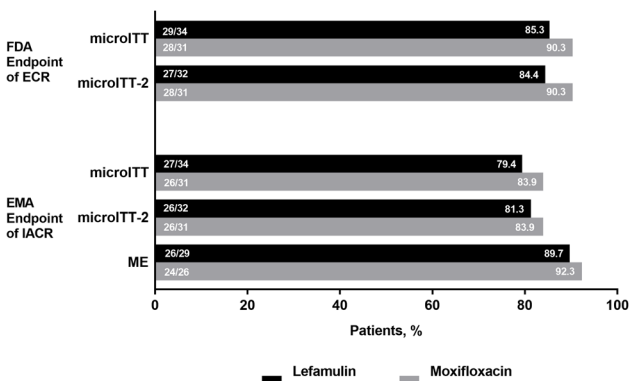
ECR=early clinical response; EMA=European Medicines Agency; FDA=Food and Drug Administration; IACR=investigator assessment of clinical response; ME=microbiologically evaluable population; microITT=microbiological intent-to-treat population.

Figure 2. Microbiological Response in Patients with *L. pneumophila* at Baseline
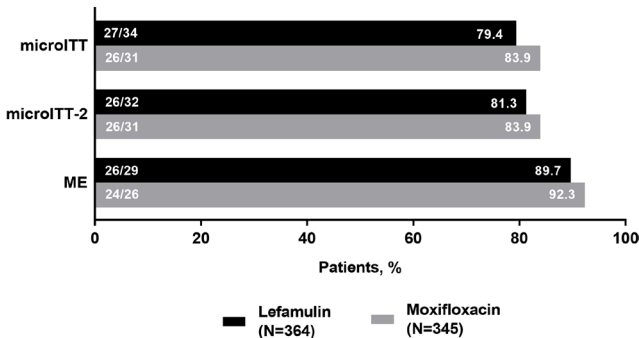
ME=microbiologically evaluable population; microITT=microbiological intent-to-treat population.

Disclosures. All authors: No reported disclosures.

---

664. Efficacy in Adults With Moderate to Severe Community-Acquired Bacterial Pneumonia (CABP) and Pneumonia Outcomes Research Team (PORT) Risk Class III to V: Results of a Pooled Analysis of Lefamulin Evaluation Against Pneumonia (LEAP) 1 and LEAP 2 Study Outcomes

Elizabeth Alexander, MD, MSc, FIDSA[1]; Jennifer Schranz, MD[1]; Anita F. Das, PhD[2]; Gregory J. Moran, MD, FACEP[3]; Christian Sandrock, MD[4]; Thomas M. File, Jr., MD[5]; Steven P. Gelone, PharmD[1]; [1]Nabriva Therapeutics US, Inc., King of Prussia, Pennsylvania; [2]Das Consulting, Guerneville, California; [3]Olive View-UCLA Medical Center, Sylmar, California; [4]UC Davis School of Medicine, Sacramento, California; [5]Summa Health, Akron, Ohio

Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
*Thursday, October 3, 2019: 12:15 PM*

Background. CABP, the second most common cause of hospitalization in the US, has prognoses ranging from rapid resolution to death, the likelihood of which can be estimated via PORT pneumonia severity index. Patients with PORT scores ≤III have predicted mortality rates <3% and may be managed as outpatients; those with scores of IV/V are often hospitalized, owing to higher predicted mortality rates (8%–31%). Lefamulin (LEF), a novel systemic antibiotic, was noninferior to moxifloxacin (MOX) for treatment of adults with CABP in 2 phase 3 trials (LEAP 1 and 2). We report the results of pooled analyses of LEAP 1/2 data in patients with PORT III and IV/V scores.

Methods. In LEAP 1, patients (PORT III–V) received IV LEF 150 mg for 5–7 d or MOX 400 mg for 7 d, with optional IV-to-oral switch. In LEAP 2, patients (PORT II–IV) received oral LEF 600 mg for 5 d or MOX 400 mg for 7 d. In both studies, randomization was stratified by PORT score. The studies assessed early clinical response (ECR; 96±24 h after first dose) in the intent-to-treat (ITT; all randomized patients) population (FDA primary endpoint) and investigator assessment of clinical response (IACR) success at test of cure (5–10 d after last dose) in the modified ITT (received ≥1 dose) and clinically evaluable (met predefined evaluability criteria) populations (EMA coprimary endpoints).

Results. Over 50% of patients (52.8% LEF; 51.9% MOX) were PORT III and >18% (18.7% LEF; 18.2% MOX) were PORT IV/V, reflective of the CABP population. As expected, PORT IV/V patients were older and more likely to have comorbidities (eg, moderate/severe renal impairment) vs. PORT III patients (Table 1). ECR and IACR response rates were high and similar for LEF and MOX in PORT III (Figure 1) and PORT IV/V (Figure 2) patients, with slightly higher rates in PORT III vs. PORT IV/V patients. LEF and MOX had similar safety profiles, with more adverse events overall in PORT IV/V vs. PORT III patients (Table 2). Mortality rates were low, with higher rates in PORT IV/V (4.2% LEF; 5.2% MOX) vs. PORT III (1.5% LEF; 0.6% MOX) patients.

Conclusion. ECR and IACR rates with LEF were high and similar to MOX in patients who are candidates for outpatient (PORT III) and inpatient (PORT IV/V) treatment; LEF may be an alternative oral and IV monotherapy option for empiric CABP treatment in both populations.

Figure 1. PORT Risk Class III Patients Achieving ECR* and IACR[†]
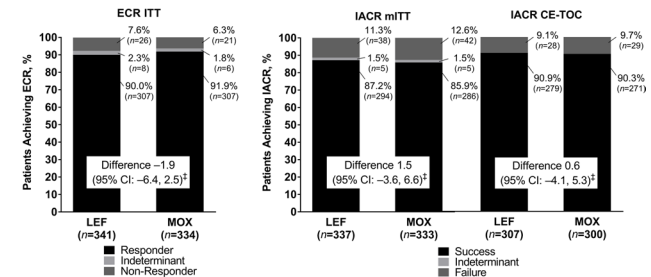
*Patients achieved ECR if they showed improvement in ≥2 CABP signs/symptoms, had no worsening in any CABP sign/symptom, and had not received a concomitant nonstudy antibiotic for CABP.
†IACR was classified as successful if CABP signs/symptoms resolved or improved such that no additional antibacterial therapy was administered for CABP.
‡Weighted treatment difference and confidence interval (CI) were computed using the method of Miettinen and Nurminen and adjusted for study, with the inverse variance of effect size as stratum weights.

Figure 2. PORT Risk Class IV/V Patients Achieving ECR* and IACR[†]
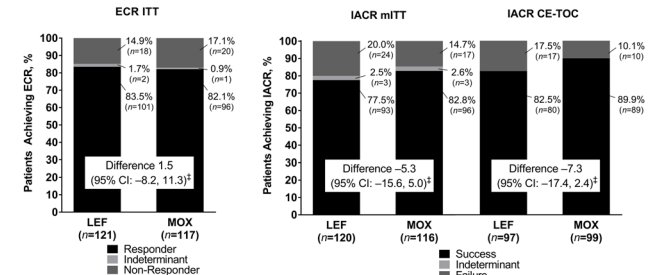
*Patients achieved ECR if they showed improvement in ≥2 CABP signs/symptoms, had no worsening in any CABP sign/symptom, and had not received a concomitant nonstudy antibiotic for CABP.
†IACR was classified as successful if CABP signs/symptoms resolved or improved such that no additional antibacterial therapy was administered for CABP.
‡Weighted treatment difference and confidence interval (CI) were computed using the method of Miettinen and Nurminen and adjusted for study, with the inverse variance of effect size as stratum weights.

Table 1. Baseline Patient Demographics and Characteristics

	LEF		MOX	
	PORT III patients (*n*=341)	PORT IV/V patients (*n*=121)	PORT III patients (*n*=334)	PORT IV/V patients (*n*=117)
Analysis population				
Age, years, mean (SD)	60.7 (15.3)	69.1 (14.2)	58.8 (14.3)	70.7 (12.6)
Male, *n* (%)	202 (59.2)	86 (71.1)	183 (54.8)	71 (60.7)
White, *n* (%)	277 (81.2)	92 (76.0)	277 (82.9)	96 (82.1)
Renal Status,* *n* (%)				
Normal function	148 (43.4)	34 (28.1)	166 (49.7)	25 (21.4)
Mild impairment	129 (37.8)	30 (24.8)	104 (31.1)	36 (30.8)
Moderate impairment	61 (17.9)	51 (42.1)	63 (18.9)	51 (43.6)
Severe impairment	3 (0.9)	4 (3.3)	1 (0.3)	4 (3.4)
SIRS, *n* (%)	330 (96.8)	116 (95.9)	318 (95.2)	108 (92.3)

Data for PORT I/II pts not shown.
*Normal: CrCl ≥90 mL/min; mild impairment: CrCl 60–<90 mL/min; moderate impairment: CrCl 30–<60 mL/min; severe impairment: CrCL<30 mL/min.

Table 2. TEAEs in PORT Risk Class III and IV/V Patients

	LEF		MOX	
	PORT III pts (*n*=337)	PORT IV/V pts (*n*=120)	PORT III pts (*n*=333)	PORT IV/V pts (*n*=116)
Patients with ≥1, *n* (%)				
Any TEAE	97 (28.8)	55 (45.8)	98 (29.4)	51 (44.0)
TEAE severity				
Mild	56 (16.6)	24 (20.0)	62 (18.6)	26 (22.4)
Moderate	32 (9.5)	18 (15.0)	26 (7.8)	14 (12.1)
Severe	9 (2.7)	13 (10.8)	10 (3.0)	11 (9.5)
Serious TEAE	12 (3.6)	15 (12.5)	14 (4.2)	13 (11.2)
TEAE leading to study drug discontinuation	8 (2.4)	9 (7.5)	8 (2.4)	8 (6.9)
TEAE leading to death by study Day 28	3 (0.9)	5 (4.2)	2 (0.6)	5 (4.3)
TEAE leading to death (over entire study duration)	5 (1.5)*	5 (4.2)	2 (0.6)	6 (5.2)†

TEAE=treatment-emergent adverse event.
*Two patients in the lefamulin group had a TEAE leading to death after study Day 28: one on study Day 32 and one on study Day 57.
†One patient in the moxifloxacin group had a TEAE leading to death on study Day 48.

Disclosures. **All authors:** No reported disclosures.

665. *In vitro* Activity of Omadacycline Against Recent (2018) Bacterial Pathogens from the United States and Europe Obtained from Skin and Skin Structure, Respiratory, and Urinary Tract Infections

Michael D. Huband, BS[1]; Michael A. Pfaller, MD[1]; Jennifer M. Streit, BS[1]; Helio S. Sader, MD, PhD[1]; Robert K. Flamm, PhD[2]; [1]JMI Laboratoryoratories, North Liberty, Iowa; [2]United States Committee on Antimicrobial Susceptibility Testing (USCAST), North Liberty, Iowa

Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
Thursday, October 3, 2019: 12:15 PM

Background. Omadacycline (OMC) was FDA approved to treat acute bacterial skin and skin structure infection (ABSSSI) and community-acquired bacterial pneumonia (CABP) for indicated organisms in 2018. Phase 2 OMC clinical trials for uncomplicated urinary tract infection (uUTI; NCT03425396) and acute pyelonephritis (NCT03757234) are ongoing. OMC is active against bacterial isolates expressing common tetracycline, penicillin, fluoroquinolone, and macrolide resistance mechanisms.

Methods. Isolates (14,000) were collected in 2018 from 31 medical centers located in the United States and 38 medical centers in Europe, including 3,458 staphylococci, 1,551 streptococci, 746 enterococci, 574 *Haemophilus* spp., and 5,690 *Enterobacterales* isolates. One isolate per patient infection episode was tested. Identifications were confirmed by MALDI-TOF MS and susceptibility testing was performed using CLSI broth microdilution methods.

Results. OMC (MIC$_{50/90}$, 0.12/0.25 mg/L) was highly active against *S. aureus* isolates from skin and skin structure infection (SSSI; 99.3% susceptible [S]) including MRSA (97.7%S) and MSSA (99.9%S) (table). Similarly, OMC demonstrated potent activity against *S. aureus* isolates from respiratory tract infection (RTI; MIC$_{50/90}$, 0.12/0.25 mg/L) including MSSA (98.2%S). All *S. lugdunensis* isolates from SSSI were S (100.0%) to OMC. All *Streptococcus* anginosus group (100.0%) and 97.6% of *S. pyogenes* isolates from SSSI were S to OMC as were 98.0% of *S. pneumoniae* from RTI. No streptococci were resistant (R) to OMC. OMC (MIC$_{50/90}$ 0.12/0.25 mg/L) had potent activity against *E. faecalis* isolates from SSSI (99.0%S). OMC S against *E. cloacae* and *K. pneumoniae* isolates from SSSI was 92.1% S and 89.4% S, respectively. Similarly, 86.2% of *K. pneumoniae* isolates from RTI were S to OMC. Susceptibility of *H. influenzae* isolates from RTI to OMC was 99.8%S (no isolates were R). ≥90.0% of *E. coli* (MIC$_{50/90}$, 1/2 mg/L) and *K. pneumoniae* (MIC$_{50/90}$, 2/4 mg/L) UTI isolates were inhibited by ≤4 mg/L of OMC.

Conclusion. OMC was highly active against bacterial pathogens associated with ABSSSI, CABP, and UTI including staphylococci (97.7%-100.0%S), streptococci (97.6%-100.0%S), *E. faecalis* (99.0%S). *E. cloacae* (92.1%S), *K. pneumoniae* (86.2%-89.4%S), and *E. coli.*

Organism (no. of isolates)	Infection type	MIC$_{50}$	MIC$_{90}$	%S	%R	FDA Breakpoint Applied
S. aureus (1,475)	SSSI	0.12	0.25	99.3	0.2	ABSSSI
MRSA (432)	SSSI	0.12	0.25	97.7	0.7	ABSSSI
MSSA (1,043)	SSSI	0.12	0.25	99.9	0.0	ABSSSI
S. aureus (699)	RTI	0.12	0.25	95.3	2.9	CABP[a]
MRSA (248)	RTI	0.12	0.5	89.9	7.3	CABP[a]
MSSA (451)	RTI	0.12	0.25	98.2	0.4	CABP
S. lugdunensis (29)	SSSI	0.06	0.06	100.0	0.0	ABSSSI
S. anginosus gr (13)	SSSI	0.06	0.12	100.0	0.0	ABSSSI
S. pyogenes (125)	SSSI	0.06	0.12	97.6	0.0	ABSSSI
S. pneumoniae (794)	RTI	0.06	0.12	98.0	0.0	CABP
E. faecalis (101)	SSSI	0.12	0.25	99.0	0.0	ABSSSI
H. influenzae (512)	RTI	0.5	1	99.8	0.0	CABP
E. cloacae (89)	SSSI	2	4	92.1	3.4	ABSSSI
K. pneumoniae (141)	SSSI	2	8	89.4	5.7	ABSSSI
K. pneumoniae (290)	RTI	2	8	86.2	7.9	CABP
K. pneumoniae (275)	UTI	2	4	--	--	
E. coli (865)	UTI	1	2	--	--	

[a] Omadacycline CABP breakpoint for MSSA applied for comparison purposes.

Disclosures. **All authors:** No reported disclosures.

666. Efficacy and Safety of Cefiderocol According to Renal Impairment in Patients With Complicated Urinary Tract Infection (cUTI) in a Phase 2 Study

Simon Portsmouth, MD[1]; Roger Echols, MD[2]; Mitsuaki Machida, MS[3]; Juan Camilo Arjona Ferreira, MD[1]; Mari Ariyasu, BPharm[3]; Tsutae Den Nagata, MD[3]; [1]Shionogi Inc., Florham Park, New Jersey; [2]Infectious Disease Drug Development Consulting LLC, Easton, Connecticut; [3]Shionogi & Co. Ltd., Osaka, Osaka, Japan

Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
Thursday, October 3, 2019: 12:15 PM

Background. Cefiderocol, a novel siderophore cephalosporin with broad activity against Gram-negative bacteria, requires dose adjustment in patients with renal impairment or augmented renal clearance, similarly to other β-lactams. The efficacy and safety of cefiderocol were assessed according to degree of renal impairment as part of a pivotal study vs. imipenem–cilastatin (IPM/CS) in patients with cUTI (NCT02321800).

Methods. A total of 448 randomized adults with cUTI received cefiderocol (2 g) or IPM/CS (1 g / 1 g), IV, q8h, for 7–14 days (safety population), with 371 patients in the microbiological intent-to-treat (Micro-ITT) population. Dose adjustments were made based on body weight (to enable IPM/CS blinding) and creatinine clearance (CrCL). The composite (clinical and microbiological) outcome at a test of cure (TOC; 7 days after treatment cessation) was analyzed by CrCL subgroup. Adverse events (AEs) according to renal subgroup were monitored throughout the study.

Results. A treatment difference in the composite outcome at TOC in favor of cefiderocol vs. IPM/CS was observed across renal subgroups (table), with greater differences in moderate and severe groups, consistent with that observed in the overall population (*n* = 371; 18.0%, 95% confidence interval: 7.5; 28.5). The incidence of AEs in the cefiderocol group was comparable across all renal subgroups. Conversely, AE incidence increased with the degree of impairment in the IPM/CS group (table).

Conclusion. In contrast to IPM/CS, the efficacy of cefiderocol was maintained across all renal function subgroups with no increase in the rate of AEs. These findings underscore the efficacy and safety of cefiderocol in patients with renal impairment and support the adequacy of the dose adjustment.

Table.

	Renal subgroup, CrCL mL/min			
	>80 (Normal)	>50–80 (Mild)	30–50 (Moderate)	<30 (Severe)
Composite outcome at TOC, Micro-ITT population, n/N (%)				
Cefiderocol (n=250)	97/124 (78.2)	49/78 (62.8)	30/41 (73.2)	5/7 (71.4)
IPM/CS (n=119)	31/51 (60.8)	22/41 (53.7)	11/23 (47.8)	1/4 (25.0)
Difference (95% CI)	17.4 (2.2; 32.7)	9.2 (–9.5; 27.8)	25.3 (0.8; 49.9)	46.4 (na)
AEs, safety population, n/N (%)				
Cefiderocol (n=298)	62/152 (40.8)	35/89 (39.3)	22/49 (44.9)	3/8 (37.5)
IPM/CS (n=148)	26/63 (41.3)	27/50 (54.0)	18/28 (64.3)	5/7 (71.4)

na: not available

Disclosures. **All authors:** No reported disclosures.

667. Preclinical Pharmacokinetic and Pharmacodynamic Characterization of EDP-938, a Novel and Potent NonFusion Replication Inhibitor of Respiratory Syncytial Virus

Li-Juan Jiang, PhD; Lisha Xu, BSc; Meng Huang, PhD; Shucha Zhang, PhD; Yang Li, PhD; Indy Zang, PhD; Jonathan Kibel, BSc; Madison Adams, BSc[1]; Noelle Labrecque, BSc[1]; Michael Rhodin, PhD[1]; Nicole McAllister, BSc[1];