Organism (n)	MIC$_{50/90}$ (mg/L)					
	Lefamulin	Amoxicillin/ Clavulanic acid	Azithromycin/ Erythromycin*	Ceftaroline/ Ceftriaxone†	Moxifloxacin	Tetracycline/ Doxycycline‡
S. pneumoniae (1,441)	0.12/0.25	≤0.03/2	0.06/>16	0.03/1	0.12/0.25	0.5/>4
Penicillin resistant (156)	0.12/0.25	2/>4	16/>16	1/2	0.12/0.25	1/>4
Macrolide resistant (657)	0.12/0.25	0.25/4	8/>16	0.25/1	0.12/0.25	0.5/>4
Tetracycline resistant (293)	0.12/0.25	0.25/>4	>16/>16	0.25/2	0.12/0.25	>4/>4
S. aureus (297)	0.06/0.12	ND	4/>8	0.25/1	≤0.06/>4	0.12/0.5
MRSA (133)	0.06/0.12	ND	>8/>8	1/2	2/>4	0.12/1
Macrolide resistant (144)	0.06/0.12	ND	>8/>8	0.5/2	2/>4	0.12/1
Fluoroquinolone resistant (97)	0.06/0.12	ND	>8/>8	1/2	>4/>4	0.12/1
H. influenzae (382)	0.5/2	0.5/2	1/2	0.004/0.015	0.03/0.06	0.5/1
M. catarrhalis (165)	0.06/0.12	≤0.25/≤0.25	≤0.03/≤0.03	0.25/1	0.06/0.06	0.25/0.5
Beta-lactamase positive (161)	0.06/0.12	≤0.25/≤0.25	≤0.03/≤0.03	0.25/1	0.06/0.06	0.25/0.5
Beta-hemolytic streptococci (14)	0.03/0.06	ND	0.03/4	0.03/0.06	0.12/0.25	ND

MRSA=methicillin-resistant *S. aureus*; ND=not determined.

*Erythromycin for *S. pneumoniae*, *S. aureus*, and beta-hemolytic streptococci; azithromycin for *H. influenzae* and *M. catarrhalis*.

†Ceftriaxone for *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and beta-hemolytic streptococci; ceftaroline for *S. aureus*.

‡Tetracycline for *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*, doxycycline for *S. aureus*.

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704. Incidence and Patient Outcomes of *S. aureus* Isolates from Acute Bacterial Skin and Skin Structure Infections (ABSSSI) with High Iclaprim MIC values in Phase 3 REVIVE Trials

David B. Huang, MD, PhD[1]; Cedric Charrier, PhD[2]; Chloe Le Bras, Bachelor[3]; Stephen Hawser, PhD[3]; Stephanie S. Noviello, MD, MPH[4]; [1]Motif Bio / Rutgers New Jersey Medical School, Princeton, New Jersey; [2]IHMA Europe, Monthey, Valais, Switzerland; [3]IHMA, Monthey, Valais, Switzerland; [4]Motif BioSciences, Princeton, New Jersey

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Background. The incidence and outcomes of patients with *S. aureus* isolates with an iclaprim MIC >8 μg/mL, a concentration that is not systemically achievable, were determined among patients from two Phase 3 studies for the treatment of ABSSSI, REVIVE-1 and -2.

Methods. REVIVE-1 and REVIVE-2 studies were 600-patient, double-blinded, randomized (1:1), active-controlled trials among patients with ABSSSI that compared the safety and efficacy of iclaprim 80 mg fixed dose with vancomycin 15 mg/kg (adjusted for renal function), both administered intravenously over 2 hours every 12 hours for 5–14 days. Patients had a bacterial skin infection suspected or confirmed to be due to a Gram-positive pathogen with a lesion size ≥75 cm². An early clinical response (ECR) was defined as a ≥20% reduction in lesion size compared with baseline at the early time point (ETP) 48–72 hours after the start of administration of the study drug in the intent-to-treat (ITT) population. A clinical cure, defined as complete resolution of all signs and symptoms of ABSSSI was measured at the end of therapy (EOT) and test of cure (TOC) visit, 7–14 days after the last dose of study drug. At baseline, EOT and TOC visits, ABSSSIs were sampled for microbiological culture and broth microdilution susceptibility testing conducted in accordance with CLSI M7.

Results. The incidence of culture confirmed *S. aureus* isolates among patients with ABSSSI with an iclaprim MIC >8 μg/mL was 2.0% (16/790). Six were MSSA and 10 were MRSA. The clinical outcomes of these infections included ECR of 63% (10/16), EOT response of 81.3% (13/16) and the TOC response of 75% (12/16). For microbiological outcomes of these infections, the end of therapy response was 92.9% (13/14) and the test of cure response was 92.3% (12/13). In comparison, there was less variation in vancomycin MICs among the *S. aureus* isolates. For patients who were randomized to vancomycin and had a pathogen identified from their ABSSSI, the pooled ECR was 82.6% (242 of 293) at a vancomycin MIC of 0.5–1 μg/mL and one isolate from a patient with ECR had a MIC of 2 μg/mL.

Conclusion. Patients receiving iclaprim had good clinical and microbiological responses against *S. aureus* isolates with an iclaprim MIC >8 μg/mL, which are uncommon (2.0%).

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705. Pharmacokinetics (PK) and Safety of Lefamulin (LEF) After Single Intravenous Dose Administration in Subjects With Impaired Renal Function and in Those Requiring Hemodialysis

Wolfgang Wicha, MSc[1]; Thomas C. Marbury, MD[2]; James A. Dowell, PhD[3]; Lori Lykens, BS[4]; Cathie Leister, MS[3]; James Ermer, MS[3]; Steven P. Gelone, PharmD[4]; [1]Nabriva Therapeutics GmbH, Vienna, Wien, Austria; [2]Orlando Clinical Research Center, Orlando, Florida; [3]Pharmacology Development Services, LLC, Collegeville, Pennsylvania; [4]Nabriva Therapeutics US, Inc., King of Prussia, Pennsylvania

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Background. Renal comorbidities are common in patients hospitalized with community-acquired bacterial pneumonia (CABP). LEF, a novel pleuromutilin antibiotic (IV/oral), was generally well tolerated and noninferior to moxifloxacin in two phase 3 studies of adults with CABP. We investigated the PK and safety of LEF and its main metabolite, BC-8041, in subjects with severe renal impairment and those requiring hemodialysis (HD).

Methods. In this open-label study, subjects were allocated to 1 of 3 groups based on renal function level. Severe subjects (estimated glomerular filtration rate <30 mL/

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minute/1.73 m², not on HD, Severe) were matched (gender, age, and weight) to subjects with normal renal function (estimated creatinine clearance ≥90 mL/minute, Normal). Subjects in the Normal and Severe groups received a single 1-hour 150 mg LEF infusion. Subjects in the HD group started HD within 1 hour after LEF infusion ("On-dialysis") and on a nondialysis day ("Off-dialysis"). Blood and urine samples were collected predose and over a 36-hour period postdose for PK analysis; LEF and BC-8041 were assayed in plasma and urine with validated methods. Safety assessments included treatment-emergent adverse events (TEAEs), labs, vital signs, and electrocardiograms.

Results. 23 subjects enrolled in and completed the study (*n* = 7, Normal; *n* = 8, Severe; *n* = 8, HD). LEF and BC-8041 pharmacokinetic parameters (table) were comparable between the Normal and Severe groups and between the On-dialysis and Off-dialysis treatment periods for the HD group. The majority of LEF and BC-8041 were excreted nonrenally in Normal and Severe subjects and were not measurably filtered into dialysate. TEAEs were reported in 2 (28.6%) subjects in the Normal group, 4 (50%) in the Severe group, and 4 (50%) in the HD group. None of the TEAEs were serious or led to study drug discontinuation. Within 4 h post-dose, the maximum mean change from baseline in the QTcF interval was 8.9, 6.6, 15.9, and 17.6 msec in the normal, severe, on-dialysis, and off-dialysis groups, respectively.

Conclusion. No dosage adjustment is required for LEF when treating subjects with severe renal impairment, and LEF can be administered without regard to HD timing. LEF was generally well tolerated in all subjects regardless of renal function status.

Table. Mean (SD) Lefamulin and BC-8041 PK Parameters by Renal Functional Status Group

PK Parameter	Normal (n=7)	Severe (n=8)	Hemodialysis (n=8)	
			On-Dialysis	Off-Dialysis
Lefamulin				
C$_{max}$, ng/mL	3182 (697)	3138 (990)	3341 (916)	2893 (653)
t$_{max}$, h	1.0 (0.0)	1.1 (0.1)	1.0 (0.0)	1.0 (0.0)
AUC, h•ng/mL	9004 (2591)	12262 (7798)	8955 (3103)	8606 (2815)
CL, L/h	17.9 (5.4)	15.7 (7.2)	18.6 (6.4)	19.0 (5.6)
t$_{1/2}$, h	10.1 (1.9)	9.4 (0.9)	9.3 (1.4)	9.1 (0.9)
BC-8041				
C$_{max}$, ng/mL	48.7 (12.8)	56.1 (15.7)	60.0 (40.0)	51.2 (21.9)
t$_{max}$, h	1.3 (0.0)	1.3 (0.1)	1.4 (0.1)	1.4 (0.3)
AUC, h•ng/mL	413 (134)	695 (448)	734 (716)	643 (408)
t$_{1/2}$, h	13.5 (4.5)	11.4 (2.2)	15.1 (4.4)	12.8 (2.0)

AUC=area under the plasma concentration-time curve extrapolated through infinity; CL=systemic clearance (observed) estimated using AUC; C$_{max}$=maximum observed concentration; PK=pharmacokinetic; SD=standard deviation; t$_{1/2}$=elimination half-life; t$_{max}$=time of maximum observed concentration.

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706. *In Vitro* Activity of Ceftazidime–Avibactam and Comparator Agents Against MDR *Enterobacteriaceae* and *Pseudomonas aeruginosa* Collected in Latin America During the ATLAS Global Surveillance Program 2016–2017

Sibylle Lob, PhD[1]; Krystyna Kazmierczak, PhD[1]; Gregory Stone, PhD[2]; Daniel F. Sahm, PhD[1]; [1]IHMA, Inc., Schaumburg, Illinois; [2]Pfizer, Inc., Groton, Connecticut

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Background. Ceftazidime–avibactam (CAZ-AVI) is a β-lactam/non-β-lactam β-lactamase inhibitor combination that can inhibit class A, C and some class D β-lactamases. Resistance caused by these β-lactamases often results in multidrug-resistance (MDR). This study evaluated the *in vitro* activity of CAZ-AVI and comparators against MDR *Enterobacteriaceae* and *Pseudomonas aeruginosa* isolates collected from patients in Latin America.

Methods. Nonduplicate clinical isolates were collected in 2016–2017 in 6 countries in Latin America. Susceptibility testing was performed using CLSI broth microdilution and interpreted using CLSI 2019 and FDA (tigecycline) breakpoints. MDR was defined as nonsusceptible (NS) (intermediate or resistant) to ≥3 of 7 sentinel drugs: amikacin, aztreonam, cefepime, levofloxacin, colistin, meropenem, and piperacillin–tazobactam.

Results. The activity of CAZ-AVI and comparators against all isolates and MDR subsets is shown in the table. MDR rates ranged from 28.4% among *E. cloacae* to 41.5% among *K. pneumoniae*. CAZ-AVI was active against >97% of *Enterobacteriaceae* isolates and maintained activity against >92% of MDR isolates of the examined species. No other tested drug consistently exceeded this activity. Among *P. aeruginosa*, CAZ-AVI was active against 87% of all isolates and 63% of MDR isolates; only colistin was more active. The two most common MDR phenotypes among *Enterobacteriaceae* were (1) NS to aztreonam, cefepime, and levofloxacin (*n* = 580, 41% of all MDR *Enterobacteriaceae;* 100% susceptible to CAZ-AVI) and (2) NS to aztreonam, cefepime, levofloxacin, and piperacillin–tazobactam (*n* = 301, 21% of all MDR isolates; 99.7% susceptible to CAZ-AVI). The two most common MDR phenotypes among *P. aeruginosa* were (1) NS to all sentinel drugs except colistin (*n* = 154, 33% of all MDR isolates;