GNB, however its ability to improve patient outcomes may be attenuated if initiation is delayed or it is reserved for salvage therapy. We sought to determine the impact of delayed C/T initiation on 30-day mortality in patients with MDR GNB infections.

Methods. This was a multicenter, retrospective cohort study including adult patients treated with C/T (≥72 hours) for suspected or confirmed MDR GNB (resistant to ≥1 drug from ≥3 classes) infections between January 2015 and February 2018. Classification and regression tree (CART) analysis was used to determine the time point of C/T initiation from index culture or diagnosis most predictive of 30-day mortality. Clinical characteristics and outcomes were compared between patients receiving early or delayed C/T, defined by the CART time point. Multivariable logistic regression was conducted to determine the independent association between early C/T initiation and 30-day mortality.

Results. A total of 144 patients were included. The median (IQR) age was 61 (49, 71) years with a male (65%) and African American (53%) predominance. The most common source of infection was respiratory (64%) and MDR *Pseudomonas aeruginosa* was isolated from 92% of cultures. A breakpoint in time was identified of 119 hours where 30-day mortality was significantly increased (11.8% vs. 26.2%; $P = 0.032$). Absence of prior infection or colonization with MDR GNB was the only variable independently associated with delayed C/T (*a*OR 3.28, 95% CI 1.53, 7.01). After adjustment for confounding variables, delayed C/T was associated with a > 3-fold increase in 30-day mortality (*a*OR 3.22, 95% CI 1.11, 9.40).

Conclusion. These data suggest that delaying C/T initiation by approximately 5 days substantially increases the risk of mortality in patients with MDR GNB infections, underscoring the importance of early appropriate therapy and the need for incorporation of C/T into automated susceptibility testing panels to support earlier initiation.

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2385. Ceftazidime–Avibactam in Combination With Fosfomycin: A Novel Therapeutic Strategy Against Multidrug-Resistant *Pseudomonas aeruginosa*

Krisztina M. Papp-Wallace, PhD[1,2]; Elise T. Zeiser, BS, MPH[2]; Scott A. Becka, BS[2]; Steven T. Park, MS[3]; Marisa L. Winkler, MD/PhD[4]; Kevin Nguyen, BS[5]; Indresh Singh, MS[5]; Granger Sutton, PhD[5]; Derrick E. Fouts, PhD[5]; Evelyn J. Ellis-Grosse, PhD[6]; George L. Drusano, MD[7]; David S. Perlin, PhD[3] and Robert A. Bonomo, MD[2,8]; [1]Medicine, Case Western Reserve University, Cleveland, Ohio, [2]Research, Louis Stokes Cleveland Veteran's Affairs Medical Center, Cleveland, Ohio, [3]Public Health Research Institute, New Jersey Medical School, Rutgers Biomedical and Health Sciences, Newark, New Jersey, [4]Brigham and Women's Hospital, Boston, Massachusetts, [5]J Craig Venter Institute, Rockville, Maryland, [6]Zavante Therapeutics, Inc., San Diego, California, [7]Institute for Therapeutic Innovation, Lake Nona, Florida, [8]Case Western Reserve University, Cleveland, Ohio

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Background. By targeting penicillin binding protein-3, the AmpC β-lactamase, and MurA, another enzyme involved in cell wall synthesis, with the ceftazidime–avibactam–fosfomycin combination, we previously overcame multidrug resistance (MDR) *in vitro* in an archived collection of *Pseudomonas aeruginosa* clinical isolates. Here, we further validate the ceftazidime–avibactam–fosfomycin combination using the MDR *P. aeruginosa* clinical isolate, CL232.

Methods. Whole genome and transcriptome sequencing, checkerboard analysis, and determination of mutation frequency as well as mutation prevention concentration were conducted. In addition, the ceftazidime–avibactam–fosfomycin combination was tested in a neutropenic thigh murine infection model with a high bacterial burden (2×10^7 colony forming units (CFUs)) of MDR *P. aeruginosa* clinical isolate CL232.

Results. Checkerboard analysis revealed slight synergy with fractional inhibitory concentration index of 0.53 for 25–6.25 μg/mL of ceftazidime–avibactam combined with 12.5 μg/mL of fosfomycin. Accordingly, the resistance elements in *P. aeruginosa* CL232 were analyzed via whole-genome sequencing (WGS) and transcriptome sequencing (RNAseq). WGS of CL232 revealed mutations in genes (e.g., *oprD*, *ampR*) that contribute to β-lactam resistance. Moreover, expression of the AmpC β-lactamase and the MexAB-OprM efflux pump were upregulated (~2–6-fold). The potential for the development of ceftazidime–avibactam-fosfomycin resistance was assessed *in vitro*. Fosfomycin alone was found to have a high mutation frequency 1.9×10^{-5}; however, the addition of ceftazidime–avibactam reduced this frequency by 3-logs. In addition, the ceftazidime–avibactam–fosfomycin combination possessed the lowest mutation prevention concentration at 64 mg/L–4 mg/L–64 mg/L. In a neutropenic thigh murine infection model, the ceftazidime–avibactam–fosfomycin combination was found to reduce CFUs by 5–6 logs compared with vehicle-treated mice, while ceftazidime–avibactam and fosfomycin dosed separately decreased CFUs by ~1 log and 2–3 logs, respectively.

Conclusion. The combination of ceftazidime–avibactam–fosfomycin is highly likely to offer patients who suffer from infections with a high bacteria burdens (i.e., pneumonia) a therapeutic hope against MDR *P. aeruginosa*.

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2386. Efficacy of Lefamulin (LEF) vs. Moxifloxacin (MOX) Against Common Pathogens in Adults With Community-Acquired Bacterial Pneumonia (CABP): Results From the Phase 3 Lefamulin Evaluation Against Pneumonia (LEAP 1) Study

Thomas File, MD[1]; Lisa Goldberg, MS[2]; Susanne Paukner, PhD[3]; Anita Das, PhD[4]; Steven P. Gelone, PharmD[2]; John Saviski, MS[2]; Carolyn Sweeney, BS[2]; Elyse Seltzer, MD[5]; George H. Talbot, MD[6] and Leanne B. Gasink, MD[2]; [1]Summa Health, Akron, Ohio, [2]Nabriva Therapeutics US, King of Prussia, Pennsylvania, [3]Nabriva Therapeutics GmbH, Vienna, Austria, [4]Das Consulting, Guerneville, California, [5]Urogen Pharma, New York, New York, [6]Talbot Advisors LLC, Anna Maria, New York

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Background. New CABP treatments with targeted activity and improved tolerability are needed. LEF, a novel pleuromutilin antibiotic that binds to a conserved region of the bacterial ribosome, is in development for IV or oral CABP treatment. This Phase 3 clinical study evaluated the efficacy of LEF vs. MOX in adults with CABP.

Methods. In this multicenter, randomized, double-blind study, 551 adult patients with CABP (Patient Outcomes Research Team Risk Class ≥III) were randomized to LEF 150 mg IV Q12 hours ($n = 276$) or MOX 400 mg IV Q24 hours ($n = 275$). After 6 IV doses, qualifying patients could be switched to oral therapy. Adjunctive linezolid was given with MOX for suspected methicillin-resistant *S. aureus*.

Primary outcomes were early clinical response (ECR) in the intent-to-treat (ITT) population (FDA endpoint), and investigator assessment of clinical response (IACR) at test of cure in the modified ITT (mITT) and clinically evaluable (CE-TOC) populations (co-primary EMA endpoints). The microITT population included all patients with a baseline CABP pathogen detected by respiratory tract or blood culture, urinary antigen test, serology, and real-time PCR from sputum, oropharyngeal and nasopharyngeal swabs. The microITT2 population included patients with a CABP pathogen detected by methods excluding PCR. Confirmatory identification and susceptibility testing of isolates, serology, and PCR were performed by a central laboratory.

Results. LEF was noninferior to MOX for ECR and IACR (LEF 87.3% [ITT], 81.7% [mITT], 86.9% [CE-TOC]; MOX 90.2% [ITT], 84.2% [mITT], 89.4% [CE-TOC]). The most common pathogen identified was *S. pneumoniae*. In the microITT population ($n = 159$ per arm), LEF and MOX demonstrated similar ECR and IACR rates (figure). LEF was efficacious against *S. pneumoniae* (including resistant phenotypes), *H. influenzae, M. catarrhalis, S. aureus*, and atypical pathogens. In the microITT2 population, response rates remained similar across baseline pathogens but showed more variation likely due to smaller sample sizes.

Conclusion. In this first Phase 3 clinical trial, LEF showed similar efficacy to MOX against the most commonly identified CABP pathogens. LEF demonstrates promise as a targeted monotherapy for the treatment of CABP in adults.

Efficiency of Lefamulin and Moxifloxacin Against Community-Acquired Bacterial Pneumonia Pathogens

	ECR				IACR			
	Lefamulin		Moxifloxacin		Lefamulin		Moxifloxacin	
Baseline pathogen, rate* (n/N)	microITT	microITT2	microITT	microITT2	microITT	microITT2	microITT	microITT2
Streptococcus pneumoniae (SP)	**88.2%** (82/93)	**85.7%** (36/42)	**93.8%** (91/97)	**88.6%** (39/44)	**84.9%** (79/93)	**81.0%** (34/42)	**87.6%** (85/97)	**86.4%** (38/44)
Multidrug-Resistant SP (MDRSP)	– (6/6)	– (6/6)	– (5/6)	– (5/6)	– (6/6)	– (6/6)	– (4/6)	– (4/6)
Staphylococcus aureus (SA)	– (10/10)	– (7/7)	– (4/4)	– (3/3)	– (8/10)	– (6/7)	– (4/4)	– (3/3)
Methicillin-Susceptible SA (MSSA)	– (7/7)	– (7/7)	– (3/3)	– (3/3)	– (6/7)	– (6/7)	– (3/3)	– **(3/3)**
Haemophilus influenzae	**92.2%** (47/51)	– (6/6)	**94.7%** (54/57)	– (5/6)	**84.3%** (43/51)	– **(5/6)**	**84.2%** (48/57)	– (6/6)
Moraxella catarrhalis	**92.0%** (23/25)	– (0/1)	**100%** (11/11)	– (1/1)	**80.0%** (20/25)	– (0/1)	**100%** (11/11)	– (1/1)
Mycoplasma pneumoniae	**84.2%** (16/19)	**92.3%** (12/13)	**90.0%** (18/20)	**91.7%** (11/12)	**84.2%** (16/19)	**84.6%** (11/13)	**95.0%** (19/20)	**91.7%** (11/12)
Chlamydophila pneumoniae	**90.9%** (10/11)	– (8/9)	**94.7%** (18/19)	**93.3%** (14/15)	**72.7%** **(8/11)**	– (7/9)	**68.4%** (13/19)	**73.3%** (11/15)
Legionella pneumophila	**88.9%** (16/18)	**88.2%** (15/17)	**85.7%** (12/14)	**85.7%** (12/14)	**77.8%** (14/18)	**82.4%** (14/17)	**78.6%** (11/14)	**78.6%** (11/14)

*Number of patients in each microITT treatment group = 159 for lefamulin and moxifloxacin ± linezolid; Number of patients in each microITT2 treatment group = 92 for lefamulin and 85 for moxifloxacin ± linezolid; n/N = patients with a response of success / patients with a specific baseline pathogen. ECR=early clinical response; IACR=investigator assessment of clinical response; microITT=patients in ITT population with ≥1 baseline CABP pathogen; microITT2=patients in ITT population with ≥1 baseline CABP pathogen confirmed by methods excluding PCR.

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