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

PK Parameter	Normal (n=11)	Moderate (n=8)	Severe (n=8)
Lefamulin			
C_{max}, ng/mL	2463 (403)	1746 (524)	1468 (328)
t_{max}, h	1.0 (0.2)	1.1 (0.2)	1.0 (0.0)
AUC, h•ng/mL	7615 (1554)	8233 (2286)	8938 (1640)
CL, L/h	20.5 (4.5)	19.6 (6.0)	17.4 (3.8)
$t_{1/2}$, h	11.5 (1.8)	13.6 (3.1)	17.5 (3.4)
BC-8041			
C_{max}, ng/mL	33.3 (9.7)	37.9 (41.2)	20.4 (12.3)
t_{max}, h	1.3 (0.1)	1.5 (0.3)	1.4 (0.1)
AUC, h•ng/mL	303 (116)	499 (463)	647 (441)
$t_{1/2}$, h	14.4 (4.5)	24.4 (20.0)	33.8 (14.8)

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; $t_{1/2}$=terminal elimination half-life; t_{max}=time of maximum observed concentration.

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

723. Synergistic Effect of Cefiderocol Combined With Other Antibiotics Against Cefiderocol High MIC Isolates From the Multi-National SIDERO-WT Studies

Yoshinori Yamano, PhD[1]; Masakatsu Tsuji, PhD[1]; Roger Echols, MD[2]; [1]Shionogi & Co., Ltd., Osaka, Osaka, Japan; [2]Infectious Disease Drug Development Consulting LLC, Easton, Connecticut

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

Background. Cefiderocol (CFDC) is a novel siderophore cephalosporin, which demonstrated potent activity at MICs of ≤4 µg/mL against ≥99% of the Gram-negative clinical isolates, including carbapenem-resistant Enterobacteriaceae spp. and nonfermenters in a multi-national SIDERO-WT study. In this study, we evaluated the synergistic effects of CFDC combined with other antibiotics against isolates with high CFDC MIC (i.e., ≥8 µg/mL).

Methods. The combination effects of CFDC and other antibiotics were evaluated by several ***Methods.*** (1) broth microdilution method in the presence of β-lactamase inhibitors avibactam and/or picolinic acid, (2) checkerboard method or time-kill assays in the presence of amikacin, meropenem, colistin, ceftazidime/avibactam or ceftolozane/tazobactam, (3) chemostat model reproducing humanized antibiotic exposures. Iron-depleted cation-adjusted Mueller–Hinton broth was used as the standard medium for CFDC as recommended by the Clinical Laboratory and Standard Institute (CLSI).

Results. A total of 39 CFDC nonsusceptible (NS) isolates were found among 9,205 isolates in the SIDERO-WT-2014 study. Among 28 CFDC-NS *A. baumannii*, 25 isolates were PER producers mainly from Russia and Turkey. Among 9 CFDC-NS Enterobacteriaceae, 5 isolates were NDM-producers from Turkey. Against all 34 non-NDM-producing isolates, the addition of avibactam significantly reduced CFDC MIC. The combination of CFDC with ceftazidime/avibactam and ceftolozane/tazobactam also showed strong synergy against these isolates, presumably due to the effect of β-lactamase inhibition. In addition, CFDC had synergistic effects with meropenem against 42.9% (9 of 21) of carbapenem NS isolates. Against the CFDC-NS isolates, including PER-producing *A. baumannii*, the combination of CFDC and meropenem under humanized drug exposures (chemostat model) showed synergistic effect leading to sustained eradication of bacteria over 24 hours.

Conclusion. Even against the non-NDM-producing CFDC-NS isolates, including PER-producing *A. baumannii*, the combinations of CFDC with ceftazidime/avibactam, ceftolozane/tazobactam, or meropenem were effective due to synergistic effects. The mechanism of CFDC-meropenem synergy against *A. baumannii* is not known.

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

724. The *In Vitro* Activity of Gepotidacin and Comparator Agents Against Anaerobic Bacterial Isolates

Meredith Hackel, MPH[1]; Michele A. Canino, MS, MBA[2]; Daniel F. Sahm, PhD[1]; Nicole Scangarella-Oman, MS[3]; [1]IHMA, Inc., Schaumburg, Illinois; [2]Janssen Biotech, Inc., Malverne, Pennsylvania; [3]GlaxoSmithKline Pharmaceuticals, Collegeville, Pennsylvania,

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

Background. Gepotidacin (GSK2140944) is a first in class novel triazaacenaphthylene bacterial type II topoisomerase inhibitor in clinical development for the treatment of gonorrhea and uncomplicated UTI (acute cystitis). Gepotidacin selectively inhibits bacterial DNA gyrase and topoisomerase IV by a unique mechanism not utilized by any currently approved therapeutic agent and demonstrates *in vitro* activity against most target pathogens resistant to established antibacterials, including fluoroquinolones. This study assessed the *in vitro* activity of gepotidacin and comparators against a collection of 649 Gram-positive and Gram-negative anaerobic bacterial clinical isolates.

Methods. A total of 649 clinically significant Gram-negative (333) and Gram-positive (316) anaerobic clinical isolates previously collected and frozen at –70°C were tested. Isolates came from North America (315/48.5%) and Europe (334/51.5%) and were collected between 2000 and 2017. Minimum inhibitory concentrations (MICs) for gepotidacin and 6 comparators were determined by agar dilution (AD) for all isolates, and by both AD and broth microdilution (BMD) for *Bacteroides* spp. according to CLSI guidelines (CLSI M11-A8). Most *Lactobacillus* spp. tested in this study require anaerobic conditions for growth and were tested by anaerobic AD.

Results. The *in vitro* activity results of gepotidacin and comparators are shown in the table below. The gepotidacin MIC_{90} for all Gram-negative anaerobic isolates tested in this study was 4 µg/mL and for the comparators tested was as follows: ceftriaxone 512 µg/mL, clindamycin >8 µg/mL, imipenem 0.5 µg/mL, metronidazole 2 µg/mL, moxifloxacin 8 µg/mL and piperacillin–tazobactam 16 µg/mL. Gepotidacin had the lowest MIC_{90} (2 µg/mL) for the Gram-positive anaerobic isolates compared with the other antibiotics tested, with the exception of metronidazole (MIC_{90} = 0.5 µg/mL).

Conclusion. Gepotidacin showed *in vitro* activity against a collection of 649 anaerobic Gram-negative and Gram-positive clinical isolates, with an MIC_{90} value against all Gram-negative anaerobic isolates of 4 µg/mL, and against all Gram-positive anaerobic isolates of 2 µg/mL.

Organism (n)	MIC_{90}(% susceptible)						
	GEP	CRO	CLI	IMI	MET	MOX	PTZ
All Gram-negative anaerobes (333)	4 (na)	512 (58.6)	> 8 (73.3)	0.5 (99.1)	2 (98.5)	8 (78.1)	16 (97.6)
Bacteroides fragilis group (191)	4 (na)	>512 (34.0)	>8 (64.4)	1 (99.0)	1 (100)	8 (71.7)	8 (99.0)
All Gram-positive anaerobes (225)	2 (na)	256 (46.2)	> 8 (66.2)	8 (87.6)	0.5 (98.7)	> 8 (68)	16 (100)
Lactobacillus spp. (91)	1 (na)	64 (na)	4 (na)	2 (na)	> 16 (na)	4 (na)	4 (na)
Clostridioides difficile (100)	2 (na)	128 (1.0)	>8 (37.0)	8 (72.0)	1 (100)	>8 (56.0)	8 (100)
Peptostreptococcus anaerobius (26)	0.03 (na)	≤8 (100)	>8 (88.0)	2 (100)	0.5 (100)	8 (72.0)	16 (100)

MIC_{90} in µg/mL; GEP, gepotidacin; CRO, ceftriaxone; CLI, clindamycin; IMI, imipenem; MET, metronidazole; MOX, moxifloxacin; PTZ, piperacillin-tazobactam (tazobactam tested as a fixed 4 µg/mL); na, no breakpoints available

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

725. WCK 5222 (Cefepime/Zidebactam): An *In Vitro* Assessment of Activity Compared with Current Dual-Antibiotic Options Against Multidrug-Resistant *Pseudomonas aeruginosa*

Elias M. Mullane; Lindsay M. Avery, PharmD; David P. Nicolau, PharmD; Hartford Hospital, Hartford, Connecticut

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

Background. *Pseudomonas aeruginosa* (PSA) is an opportunistic pathogen known to cause complications in critically ill patients worldwide. In those at risk of infection with multidrug-resistant strains (MDR-PSA), dual antibiotic therapy is often considered. However, this practice may contribute to rising resistance rates and poor outcomes if empirical selection is suboptimal. WCK 5222 (cefepime/zidebactam), a novel β-lactam/β-lactam enhancer, may offer a solution.

Methods. Minimum inhibitory concentrations (MICs) were determined for WCK 5222, amikacin (AMK), fosfomycin (FOF), cefepime (FEP), ceftolozane/tazobactam (C/T), and meropenem (MEM) against 18 clinical PSA isolates using gradient diffusion strip (GDS) methods. Activities of FEP, C/T, and MEM in combination with AMK and FOF were assessed using GDS for isolates nonsusceptible to the β-lactam (MICs >8 mg/L, >4/4 mg/L, and >2 mg/L, respectively). Synergy was defined as a fractional inhibitory concentration index ≤ 0.5. Instances of restored β-lactam susceptibility when tested in combination were compared with the proportion of WCK 5222 MICs ≤ 8 mg/L.

Results. WCK 5222 MICs ranged from 2 to 32 mg/L (MIC_{50}, 8 mg/L). Rates of susceptibility were: AMK (67%), FOF (44%, MIC ≤ 64 mg/L), FEP (6%), C/T (33%), MEM (0%). Combinations with C/T most frequently demonstrated synergy (C/T-FOF, 42%; C/T-AMK, 33%) and restored C/T susceptibility was observed in 42% of assessments with FOF and in 50% with AMK. For FEP combinations, synergy was observed in 29% and 18% of assessments with FOF and AMK, respectively, with restored susceptibility in 6% for both combinations. Synergy occurred in 11% and 6% of assessments of MEM with FOF and AMK, respectively, with zero instances of restored susceptibility. In total, β-lactam susceptibility was restored in 14% (13/94) of combinations compared with 78% (14/18) of WCK 5222 MICs ≤ 8 mg/L.

Conclusion. In a selection of MDR-PSA isolates that included carbapenem- and C/T-resistant strains, WCK 5222 MICs ≤ 8 mg/L (cefepime susceptible) were observed more frequently than restoration of susceptibility in select β-lactams in combination with FOF or AMK. WCK 5222 monotherapy may offer enhanced coverage of MDR-PSA over empirically selected combination therapies.

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

726. APX001 (Fosmanogepix) Is Effective in an Immunosuppressed Mouse Model of *Rhizopus oryzae* Infection

Teklegiorgis Gebremariam, MS[1]; Sondus Alkhazraji, PhD[1]; Yiyou Gu, PhD[1]; Abdullah Alqarihi, MS[1]; Zeinab Mamouei, PhD[1]; Karen J. Shaw, PhD[2]; Ashraf S. Ibrahim, PhD[1]; [1]LA Biomed. Res. Inst. at Harbor-UCLA Med Ctr., Torrance, California; [2]Amplyx Pharmaceuticals, San Diego, California

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

Background. Mucormycosis is a life-threatening infection that predominantly occurs in immunocompromised hosts. The antifungal APX001A (manogepix) inhibits Gwt1, an enzyme required for the conserved glycosylphosphatidyl inositol (GPI) post-translational modification in eukaryotes. We previously reported the activity of APX001 (fosmanogepix, the prodrug of APX001A) against *Rhizopus delemar* (minimum effective concentration [MEC] = 0.25 μg/mL). Here we assessed the activity against *R. oryzae,* which has an elevated MEC value.

Methods. *R. oryzae* 99–892 MIC and MEC values were 0.125 μg/mL and 4.0 μg/mL for isavuconazole (ISAV) and APX001A, respectively. ICR mice were immunosuppressed with cyclophosphamide (200 mg/kg) and cortisone acetate (500 mg/kg) on Days -2, +3, and +8 relative to intratracheal infection with 2.5×10^5 cells of *R. oryzae* 99–892. For survival studies, treatment with 104 mg/kg APX001 was compared with ISAV (110 mg/kg TID). Oral treatment started on Day +1 through Day +7, relative to infection for survival studies, and through Day +4 for tissue fungal burden studies (assessed by conidial equivalent [CE] using qPCR). Placebo mice received vehicle control. To extend the half-life of APX001, mice were administered 50 mg/kg of the cytochrome P450 inhibitor 1-aminobenzotriazole (ABT) 2 h prior to APX001 administration.

Results. APX001 and ISAV equally prolonged median survival time of mice (n = 20) vs. placebo (12 and 14 days for APX001 and ISAV, respectively, vs. 8 days for placebo). Furthermore, APX001 and ISAV treatment both resulted in 30% 21-day survival vs. 0% survival of placebo mice ($P < 0.05$ by log-rank test). Both drug treatments resulted in ~1.5 $\log_{10}$ reduction in lung and brain CE vs. placebo-treated mice (n = 10, $P < 0.005$ by Wilcoxon rank-sum test).

Conclusion. Despite a higher MEC value, APX001 showed significant efficacy against *R. oryzae* that was as protective as ISAV in immunosuppressed mice. Given the previously reported activity of APX001 against a strain of *R. delemar* with a lower MEC value,APX001 has now been shown to be efficacious against both species of *Rhizopus*, which together are responsible for ~60–70% of isolates causing lethal mucormycosis. Thus, continued investigation of APX001 against mucormycosis is warranted.

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

727. Potency of the β-Lactamase Inhibitor QPX7728 Is Minimally Affected by KPC Mutations that Reduce Potency of Ceftazidime–Avibactam

Olga Lomovskaya, PhD; Kirk J. Nelson, BS Biology;
Debora Rubio-Aparicio, BSC Microbiology; QPEX Biopharma, San Diego, California

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

Background. In the United States, carbapenem-resistant Enterobacteriaceae (CRE) are mainly represented by KPC-producing strains and ceftazidime–avibactam (C/A) is increasingly used to treat infections caused by KPC-producers. C/A resistant (C/A-R) mutants with mutations in bla_{KPC} can be isolated *in vitro* and were reported in patients treated with C/A. QPX7728 (QPX) is a new ultra-broad-spectrum β-lactamase inhibitor based on a cyclic boronic acid pharmacophore with a potent activity against serine and metallo-β-lactamases. QPX in combination with meropenem (MER), M/Q, or cefepime (FEP), F/Q, has potent activity against all types of CRE (KPC, MBLs and OXA-48). The objective of these studies was to evaluate the activity of QPX in combination with various antibiotics against KPC-producing strains with C/A-R due to mutations in bla_{KPC}.

Methods. Ten strains of KPC-producing *Klebsiella pneumoniae* with C/A MIC varied from 0.5 μg/mL to 8 μg/mL were used in resistance studies using C/A at 2x–8x the MIC (with avibactam [AVI] fixed at 4 μg/mL). Mutations in bla_{KPC} were identified by sequence analysis. Ceftazidime (CAZ), MER and FEP MIC alone and with AVI and QPX (both BLIs at 4 μg/mL) were determined using the reference broth microdilution method. Five C/A-R clinical isolates with mutations in bla_{KPC} were also included in the panel.

Results. Mutations in bla_{KPC} that result in C/A resistance were selected in all strains. Mutants had 4- to 64-fold (16-fold average) increase in C/A MIC that varied from 16 to 128 μg/mL. In contrast, there was a 2-fold increase for CAZ-QPX MICs (MICs between ≤0.125 to 2 μg/mL. Similarly, there was no more than 2-fold increase in MER/QPX and FEP/QPX MICs, and the majority of mutants did not have an increase in MER/QPX or FEP/QPX MICs (MICs varied from ≤0.125 to 1 μg/mL). For five clinical C/A-R isolates, C/A, M/Q and F/Q MIC varied from 16 to ≥128 μg/mL, ≤0.125 to 4 μg/mL, and ≤0.125 to 2 μg/mL, respectively.

Conclusion. These data indicate that KPC mutations that affect the potency of C/A have minimal effect on the potency of QPX7728 combinations with either CAZ, MER or FEP indicating the potential differences in binding sites for these inhibitors in KPC. Further studies of QPX combinations are in progress.

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

728. Activity of Eravacycline Against Contemporary Gram-Negative Clinical Isolates From New York City Hospitals

Alejandro Iregui, MD; Zeb Khan, MD; David Landman, MD; John M. Quale, MD;
SUNY Downstate Medical Center, Brooklyn, New York

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

Background. Antibiotic-resistant Gram-negative bacteria, including KPC-producing *Enterobacteriaceae* and carbapenem-resistant *A. baumannii*, have been problematic hospital pathogens in NYC and other areas. Eravacycline (ERV), a fluorocycline antibiotic released in the USA in 2018, has demonstrated *in vitro* activity against many of these strains. We tested the activity of ERV against a recent collection of clinical isolates from NYC hospitals.

Methods. For a 3-month period in 2017, all unique patient isolates of *E. coli*, *K. pneumoniae*, *Enterobacter* spp., and *A. baumannii* were collected from 7 hospitals in Brooklyn, NY. MICs were performed by broth microdilution for ERV and Tigecycline (TGC) and agar dilution for other antibiotics according to CLSI methodology. Cephalosporin-resistant isolates were screened by PCR for common carbapenemases.

Results. The susceptibility results for tetracycline and ERV are listed in the Table. Overall, 95% of the *Enterobacteriaceae* were inhibited by ≤ 0.5 μg/mL of ERV, the FDA-suggested breakpoint. Of 1,876 isolates of *E. coli*, 4 possessed KPC. ERV MICs for these 4 isolates were 0.125–0.25 μg/mL. Of 518 isolates of *K. pneumoniae*, 20 possessed KPC. The ERV MIC_{50} and MIC_{90} for these isolates were 1 and 1 μg/mL, respectively. Of 172 isolates of *Enterobacter* spp., 3 possessed KPC. ERV MICs for these 3 isolates were 0.5–1 μg/mL. Of 45 isolates of *A. baumannii*, 11 isolates possessed a carbapenemase (OXA23 in 8, OXA24 in 2, and KPC in 1). The ERV MIC_{50} and MIC_{90} for these isolates were 1 and 2 μg/mL, respectively. Overall, ERV MICs were two-fold lower than TGC MICs for *A. baumannii*.

Conclusion. ERV possesses significant *in vitro* activity against contemporary clinical isolates of *Enterobacteriaceae* and *A. baumannii* from NYC, including many carbapenemase producing strains.

	MIC_{50}	MIC_{90}	Range	Percent susceptible
	μg/ml			
E. coli (n=1876)				
Tetracycline	2	>8	≤0.25 - >8	60%
Eravacycline	0.25	0.5	≤0.015 - 2	
K. pneumoniae (n=518)				
Tetracycline	2	>8	≤0.25 - >8	73%
Eravacycline	0.5	1	0.06 - 4	
Enterobacter spp. (n=172)				
Tetracycline	4	>8	1 - >8	67%
Eravacycline	0.5	1	0.125 - 4	
A. baumannii (n=45)				
Tetracycline	>8	>8	2 - >8	29%
Tigecycline	0.5	4	0.125 - 8	
Eravacycline	0.25	2	0.03 - 4	

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

729. Comparing Length of Stay and Clinical Outcomes for Hospitalized Patients at Bridgeport Hospital who Received Baloxavir Marboxil (BM) or Oseltamivir Phosphate (OP) During the 2018–2019 Influenza Season

Arun C. Nachiappan, MBBS, BSc(Hons); Wei-Teng Yang, MD, MPH; Yale-New Haven Health Bridgeport Hospital, Bridgeport, Connecticut

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

Background. BM has been approved for the management of acute uncomplicated influenza in otherwise healthy individuals between age 12 and 64, and found to have a greater reduction in viremia. The original trial excluded hospitalized patients and those with co-morbidities.

Methods. This is a single-center, retrospective analysis of hospitalized patients diagnosed with influenza between October 1, 2018 and March 31, 2019. This study excluded those diagnosed before the addition of BM to the hospital formulary; those who were not treated with antivirals, treated before admission, or treated with both antivirals; those younger than 12 years old; and those who remain hospitalized. The relationship between length of stay and antiviral used was ascertained using t-test and multivariate linear regression. Due to heterogeneity in reasons for hospitalization, analysis was stratified by the main reasons for hospitalization. T-test and Wilcoxon's rank-sum test were used for continuous variables, and Pearson's chi-squared test was used for categorical variables. The significance level was 0.05.

Results. The study population (n = 145) has a mean age of 66.5 years; of whom, 43% are male. In terms of patient characteristics, those treated with BM (n = 105) vs. OP (n = 40) were older, less frequently admitted to ICU and of differing ethnic composition. The length of stay was similar in those treated with BM vs. OP in both univariate and multivariate linear regression (5.5 (5.3) vs. 8.2 (11.4) days, $P = 0.33$). In addition, the length of stay was similar in those treated with BM vs. OP when stratified by reasons for hospitalization: pneumonia/bronchitis (6.6 (7.1) vs. 8.2 (9.2) days, P = 0.43), obstructive airway disease exacerbation (5.5 (4.8) vs. 4.8 (8.0) days, $P = 0.56$), elderly with multiple co-morbidities (5.0 (4.0) vs. 3.4 (6.8) days, $P = 0.63$), reactive airway disease (4.1 (4.8) vs. 7.4 (1.5) days, $P = 0.27$) or congestive heart failure exacerbation (9.8 (9.0) vs. 5.6 (5.0) days, $P = 0.43$).

Conclusion. In hospitalized patients with co-morbidities diagnosed with influenza, there was no difference in length of stay in those who received BM vs. OP. This highlights the need to clarify the role of BM in this population, particularly given its comparable symptom reduction, greater cost, and the emergence of PA138T viral mutant.

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

730. Cefiderocol for the Treatment of *Achromobacter xylosoxidans* Infections in Two Lung Transplant Patients with Cystic Fibrosis

Nathaniel C. Warner, MD[1]; Luther Bartelt, MD[2]; Anne Lachiewicz, MD, MPH[1];