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