Table Mean (SD) Lefamulim and BC-8401 PK Parameters by Hepatic Functional Status Group

| PK Parameter | Normal (n=11) | Moderate (n=8) | Severe (n=8) |
|--------------|--------------|---------------|--------------|
| Lefamulim    |              |               |              |
| Cmax, ng/mL  | 2463 (403)   | 1746 (524)    | 1469 (325)   |
| tmax, h      | 1.0 (0.2)    | 1.1 (0.2)     | 1.0 (0.0)    |
| AUC, ng/mL   | 7615 (1584)  | 8233 (2286)   | 8938 (1640)  |
| Cl, L/h      | 20.5 (4.5)   | 19.6 (6.0)    | 17.4 (3.8)   |
| t1/2, h      | 11.5 (1.8)   | 13.5 (3.1)    | 17.5 (3.4)   |
| BC-8401      |              |               |              |
| Cmax, ng/mL  | 33.3 (9.7)   | 37.9 (41.2)   | 20.4 (12.3)  |
| tmax, h      | 1.3 (0.1)    | 1.5 (0.3)     | 1.4 (0.1)    |
| AUC, ng/mL   | 303 (116)    | 409 (463)     | 647 (441)    |
| t1/2, h      | 14.4 (4.5)   | 24.4 (20.0)   | 33.8 (14.8)  |

AUC=areas under the plasma concentration-time curve extrapolated through infinity; Cl=glomerular clearance; Cmax=maximum observed concentration; t1/2=terminal elimination half-life; tmax=time of maximum observed concentration.

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

Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
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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., ≥28 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 cefotaxime/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 isolates, the combination of CFDC and meropenem had synergistic effects of CFDC combined with other antibiotics against isolates with high CFDC MIC. The combination of CFDC with ceftazidime/avibactam and cefotaxime/tazobactam also showed strong synergy against these isolates, presumably due to the effect of MIC. The combination of CFDC with other β-lactam/β-lactam enhancer, may offer a solution.

Conclusion. Cefiderocol showed in vitro activity against a collection of 694 aerobic Gram-negative and Gram-positive clinical isolates, with an MIC90 value against all Gram-negative anaerobic isolates of 4 µg/mL, and against all Gram-positive anaerobic isolates of 2 µg/mL.

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

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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 (ceftipime/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 were also assessed using GDS for isolates nonsusceptible to β-lactams (MICs >8 mg/L, >4/4 mg/L, and >2 mg/L, respectively). Synergy was defined as a fractional inhibitory concentration index ≤ 0.5. Rates of β-lactam susceptibility were: AMK (67%), FOF (44%, MIC ≤ 64 mg/L), FEP (6%), C/T (33%), and MEM (33%). The combination of 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% in 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 (ceftipime 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.

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Background. Macromycosis 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-translation modification in eukaryotes. We previously reported the activity 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 sawarunazole (ISAV) and APX001A, respectively. ICR mice were immunosuppressed by cyclophosphamide (200 mg/kg) and cortisone acetate (500 mg/kg) on Days -2, +3, +8 relative to intratracheal infection with 2.5 × 10^6 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-aminothiozoline (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. 6% survival in placebo mice (n = 10, P < 0.05 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 APX001A 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, further investigation of APX001 against macromycosis is warranted.

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727. Potency of the β-Lactamase Inhibitor QPX7728 Is Minimally Affected by KPC Mutations That Reduce Potency of Ceftazidime–Avibactam
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Background. In the USA, 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-producing C. Enterobacteriaceae (K/C) resistant to C/A-R clinical isolates with mutations in blaKPC can be isolated in vitro and were reported in patients treated with C/A. QPX7728 (QXP) is a new ultra-broad-spectrum β-lactamase inhibitor based on a cyclic boronic acid carboxaphoraphone with a potent activity against serine cephalosporinases QXP in combination with meropenem (MER), MQR, or cefepime (FEF). F/EQ has potent activity against all types of CRE (KPC, MBLs and OXA-48). The objective of these studies was to evaluate the activity of QXP in combination with various antibiotics against KPC-producing strains with C/A-R due to mutations in blaKPC.

Methods. Ten strains of KPC-producing Klebsiella pneumoniae with C/A MICs from 0.5 µg/mL to 8 µg/mL were used in sensitivity studies using C/A at 2x–8x the MIC, CAZ (50 µg/mL) and MER and FEP MICs for these isolates were ≤0.125 to 2 µg/mL, respectively. Similarly, there was no more than 2-fold increase in MICs for these isolates. Overall, 95% of the 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 isolates were 4.5 ± 4.5 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<sub>50</sub> and MIC<sub>90</sub> 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.

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729. Comparing Length of Stay and Clinical Outcomes for Hospitalized Patients with Cystic Fibrosis in Bridgeport Hospital when Treating Viral Infections with BM or ISAV
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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 viruria. 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 included all patients 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 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 = 0.45), obstructive airway disease exacerbation (5.3 (4.8) vs. 4.8 (8.0) days, P = 0.56), elderly with multiple co-morbidities (5.0 (4.8) vs. 3.4 (6.8) days, P = 0.63), reactive airway disease (4.1 (4.8) vs. 7.4 (1.5) days, P = 0.02) or congestive heart failure exacerbation (9.8 (9.0) vs. 5.6 (5.0) days, P = 0.63).

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.

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