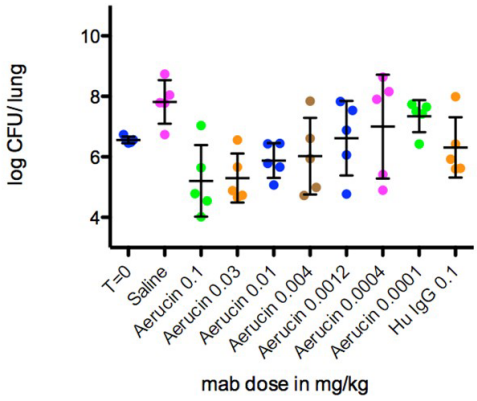
***Background.*** Anti-bacterial monoclonal antibodies can serve as a new treatment modality for difficult to treat infections. AR-105 is a fully human IgG1 monoclonal antibody (mAb) that binds to an extracellular polysaccharide epitope of *Pseudomonas aeruginosa* (PA) and was shown to mediate *in vitro* complement-dependent opsonophagocytic killing. AR-105 is currently being tested in a global Phase 2 clinical trial as an adjunctive treatment to standard of care antibiotics in ventilator-associated pneumonia patients. Here we present pre-clinical efficacy and clinical safety data for AR-105.

***Methods.*** Efficacy in nonclinical studies against PA pneumonia was tested in prophylactic and therapeutic mouse models, either as a stand-alone therapy or in combination with antibiotics. Mice were dosed intranasally or by intravenous infusion with AR-105 post or prior to infection with PA and survival or lung bacteriology were monitored. In a clinical Phase 1 open-label study, 16 healthy volunteers received 2, 8, or 20 mg/kg of AR-105. Adverse events, immunogenicity, and pharmacokinetic (PK) profiles were evaluated for up to 84 days following administration.

***Results.*** In the animal models, AR-105 reduced lung bacterial counts in a dose-dependent manner, and improved survival (80% in the treated group vs. 0% in the control group). Combination of AR-105 with antibiotics was more effective than monotherapy. In the Phase I study, no serious adverse events (AE) were observed in any cohort. Few AE were deemed related to the investigational drug, and all were mild and transient. AR-105 was found to be well tolerated in healthy volunteers with no anti-drug antibodies (ADA) detected. The PK profile was comparable with other human IgG1 mAbs, exhibiting a serum half-life of approximately 20 days.

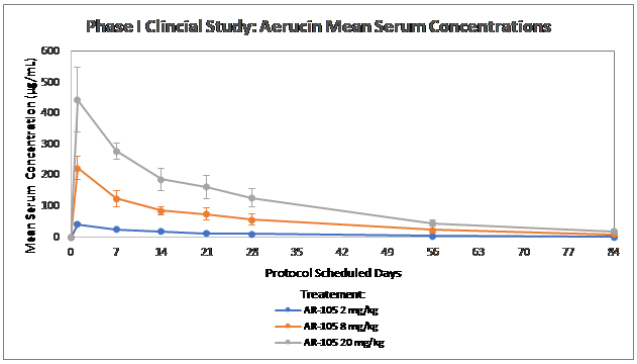
***Conclusion.*** AR-105 was confirmed to be effective in PA pneumonia animal models, either as stand-alone therapeutic or in combination with antibiotics. In the Phase 1 clinical study, AR-105 was shown to be safe and well-tolerated, with a PK profile similar to that of other IgG1 mAbs. AR-105 is a promising drug candidate for therapy of PA pneumonia.

**AR-105 (Aerucin) reduces Bacterial Lung Counts in a Prophylactic Mouse Model**




**PK Characteristics of Aerucin by Dose Level**

| Parameter Statistics | Aerucin 2.0 mg/kg (N=5) | Aerucin 8.0 mg/kg (N=6) | Aerucin 20.0 mg/kg (N=5) |
|---|---|---|---|
| Cmax (µg/mL) | | | |
| Mean | 42.6737 | 223.5833 | 443.7230 |
| SD | 4.3644 | 37.0869 | 104.3782 |
| Tmax (h) | | | |
| Mean | 25.4 | 26.3 | 25.8 |
| SD | 0.89 | 1.51 | 0.84 |
| t½ (h) | | | |
| Mean | 426.3954 | 470.3799 | 498.2121 |
| SD | 98.3213 | 144.0327 | 87.1815 |
| AUC(0-last) (µg*h/mL) | | | |
| Mean | 19551.3567 | 97177.3962 | 249106.7305 |
| SD | 3454.7592 | 35656.1818 | 60768.8219 |
| AUC(0-inf) (µg*h/mL) | | | |
| Mean | 21195.2689 | 114797.6332 | 264250.3780 |
| SD | 2813.3058 | 35896.9289 | 67372.4678 |
| Cl (L/h) | | | |
| Mean | 8.6783 | 5.9588 | 6.3568 |
| SD | 0.9851 | 1.4862 | 1.8183 |
| λz (1/h) | | | |
| Mean | 0.0017 | 0.0016 | 0.0014 |
| SD | 0.0005 | 0.0005 | 0.0003 |
| MRT (h) | | | |
| Mean | 459.6475 | 425.2518 | 509.9929 |
| SD | 117.7048 | 143.5832 | 59.5586 |
| Vdss (mL) | | | |
| Mean | 3936.2764 | 2382.1174 | 3218.2642 |
| SD | 946.5306 | 427.3122 | 858.6019 |




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

**675. Efficacy of Human-Simulated Bronchopulmonary Exposures of Cefepime and Zidebactam (WCK 5222) Against Multidrug-Resistant (MDR) *Pseudomonas aeruginosa* (PSA) in a Neutropenic Murine Pneumonia Model**

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

***Background.*** WCK 5222 combines cefepime (FEP) with zidebactam (ZID), a bicycloacyl hydrazide β-lactam enhancer which binds PBP2 in PSA and inhibits class A and C β-lactamases. The *in vivo* efficacy of human-simulated bronchopulmonary exposures of WCK 5222 against MDR PSA, a recalcitrant pneumonia-causing pathogen with few treatment options, was investigated in a neutropenic murine pneumonia model.

***Methods.*** Thirteen clinical isolates of MDR PSA with FEP MIC ≥64 mg/L were studied in neutropenic CD-1 mice. FEP, ZID, and WCK 5222 MICs were measured by broth microdilution in triplicate. For *in vivo* experiments, lungs were intranasally inoculated with $10^7$–$10^8$ CFU/mL bacterial suspensions. Human-simulated regimens (HSR) of FEP and ZID alone and in combination which achieved epithelial lining fluid (ELF) exposures in mice approximating human ELF exposures after doses of 2 g FEP/1 g ZID as a 1 hour infusion at steady state were developed. For each regimen, groups of 6 mice were dosed subcutaneously 2 hours after inoculation for 24 hours, then sacrificed. Vehicle-dosed control mice were sacrificed at the start (0 hour) and end (24 hours) of the dosing period. Lungs were aseptically harvested and bacterial CFU/lungs were determined.

***Results.*** FEP MIC was >64 mg/L for all isolates, while ZID and WCK 5222 MICs ranged from 4–512 and 4–32 mg/L, respectively. Mean bacterial growth for all isolates at 0 hour was 6.68 $\log_{10}$ CFU/lungs. Mean changes ± SD in bacterial density at 24 hours compared with 0 hour controls for 12 isolates with WCK5222 MIC ≤16 mg/L were 2.08 ± 1.09, 1.09 ± 0.98, −0.92 ± 1.45, and −2.13 ± 0.75, for control, FEP, ZID, and WCK5222, respectively. Against these isolates, ZID yielded >1 $\log_{10}$ CFU/lungs reduction in 7/12, while activity was enhanced with WCK5222, producing >1 $\log_{10}$ CFU/lungs reduction in 11/12 and >2 $\log_{10}$ CFU/lungs reduction in 9/12. All isolates showed growth or stasis on FEP.

***Conclusion.*** Human-simulated bronchopulmonary exposures of WCK5222 is effective against MDR PSA at MIC up to 16 mg/L in a neutropenic murine model. These data support the clinical development of WCK5222 for the treatment of pseudomonal lung infections, but further studies of PSA with high WCK5222 MIC are necessary to delineate the susceptibility breakpoint.

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

**676. Health-Related Quality of Life (HRQoL) as Measured by the 12-Item Medical Outcomes Study Short-Form (SF-12) Among Adults With Community-Acquired Bacterial Pneumonia (CABP) Who Received Either Lefamulin (LEF) or Moxifloxacin (MOX) in Two Phase 3 Randomized, Double-Blind, Double-Dummy Clinical Trials (LEAP 1 and 2)**

Thomas Lodise, PharmD, PhD[1]; Sam Colman, MSc[2]; Elizabeth Alexander, MD, MSc., FIDSA[3]; Daniel Stein, MD[3]; David Fitts, MPH, PhD[3]; Lisa Goldberg, MS[3]; Jennifer Schranz, MD[3]; [1]Albany College of Pharmacy and Health Sciences, Albany, New York; [2]Covance Market Access Services, Inc., Gaithersberg, Maryland; [3]Nabriva Therapeutics US, Inc., King of Prussia, Pennsylvania

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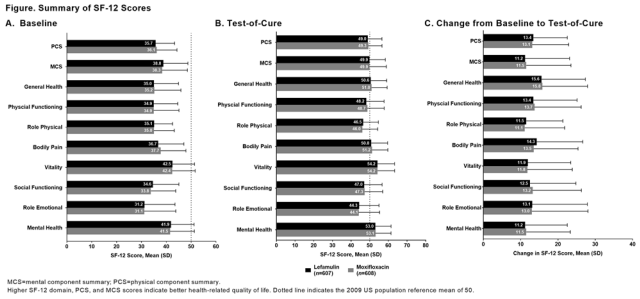
***Background.*** Interest in patient health experience as part of a benefit–risk assessment for new drug approvals is increasing. Patient-centeredness, a key metric in the 2010 Affordable Care Act, is also a growing area of focus in healthcare. LEF, a new antibiotic in development for treating adults with CABP, was noninferior to MOX based on clinical response endpoints in LEAP 1 and 2. HRQoL was prospectively incorporated and evaluated in both studies via SF-12, a well-known survey that measures general health status in 8 domains (physical function, role limitations due to physical

problems, bodily pain, general health, vitality, social function, role limitations due to emotional problems, and mental health).

***Methods.*** An exploratory analysis evaluated HRQoL in patients who received LEF or MOX in LEAP 1 (IV-PO treatment) and LEAP 2 (PO-only treatment). SF-12 was measured at baseline (BL) and test-of-cure (TOC; 5–10 days after last study drug dose). SF-12 outcomes assessed included the 8 domains, physical component summary (PCS), and mental component summary (MCS) scores. SF-12 scores were normalized to the 2009 US population reference mean (SD) of 50 (10). A 3-point change on any scale represents a clinically meaningful difference.

***Results.*** Analysis included 1,215 patients (LEF $n$ = 607; MOX $n$ = 608). At BL, all mean SF-12 scores in both treatment groups were well below the US reference mean, indicating a low HRQoL level, consistent with the acute illness of the study population (figure). Clinically meaningful and significant improvements from BL to TOC were observed in all domain, PCS, and MCS scores in both groups. Mean scores were close to the reference mean, indicating an average HRQoL level. No significant differences in mean score improvements from BL to TOC were seen for LEF vs. MOX. SF-12 score improvements at TOC across predefined subgroups (age, sex, number of comorbidities, study, and PORT risk class) were comparable between treatment groups.

***Conclusion.*** Our data indicate that adults with CABP experienced HRQoL improvements with LEF that were comparable with MOX, and treatment with either agent resulted in return to normal HRQoL. When combined with overall study results, these data suggest LEF as a potential alternative to MOX for treatment of adults with CABP.




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

### 677. Activity of Novel β-Lactamase Inhibitor QPX7728 Combined with β-Lactam Agents When Tested Against Carbapenem-Resistant *Enterobacteriaceae* (CRE) Isolates

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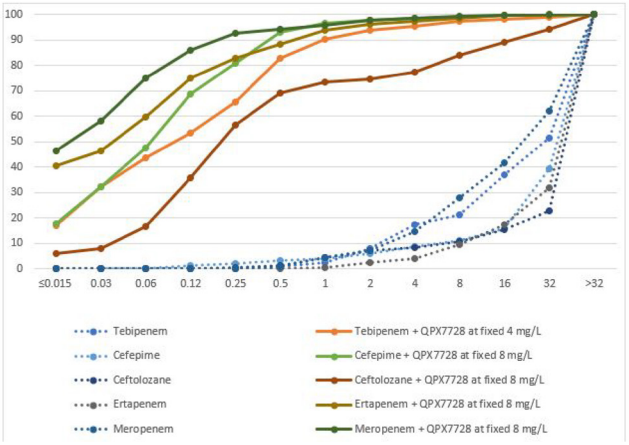
***Background.*** CREs have been described worldwide and these isolates are often multidrug resistant with few therapeutic options remaining active against them. New β-lactam (BL)/β-lactamase inhibitor (BLI) combinations recently approved are active against KPC and some OXA-48 producers, but not against isolates producing metallo-β-lactamases (MBLs). We evaluated the activity of QPX7728 (QPX), a novel BLI paired with various BLs against a collection of CRE isolates characterized for the presence of carbapenemases.

***Methods.*** A total of 508 CRE clinical isolates were susceptibility (S) tested by reference broth microdilution methods against meropenem (MER), tebipenem (TEB), cefepime (FEP), ceftolozane (TOL), and ertapenem (ETP), and meropenem (MEM) combined with QPX at fixed 2, 4, and 8 mg/L. Agents were provided by Qpex Biopharma except for FEP, ETP, and MEM. Carbapenemases were detected using PCR/sequencing or whole-genome sequencing.

***Results.*** All BLs had limited activity against CRE isolates ($MIC_{50/90}$, ≥32/>32 mg/L) and QPX lowered the MIC for all agents (figure). Against 157 isolates carrying serine-carbapenemase (SCarb) genes (153 KPC-producers), MEM or ETP plus QPX at fixed 4 or 8 mg/L displayed $MIC_{50}$ at ≤ 0.03 mg/L and $MIC_{90}$ ranging from 0.12 to 0.5 mg/L. QPX lowered the FEP or TOL $MIC_{50}$ to ≤ 0.25 mg/L and $MIC_{90}$ to 0.25, 0.5 or 1 mg/L depending on the BLI concentration. Over 98.0% of the 150 isolates harboring OXA-48-like genes were inhibited by FEP, TOL, ETP or MEM plus QPX at ≤2 mg/L. Similarly, MEM, FEP, TOL and ETP + QPX inhibited >98.0% of the 51 CREs that did not carry carbapenemases at ≤2 mg/L when using a higher BLI concentration. The activity of FEP ($MIC_{50/90}$, 0.06/1 mg/L), ETP ($MIC_{50/90}$, 0.03/4 mg/L), and MEM ($MIC_{50/90}$, ≤ 0.015/2 mg/L) was mostly restored when 8 mg/L of QPX was combined with these agents and tested against 150 MBL-producing isolates.

***Conclusion.*** QPX restored the activity of several BLs when tested against 508 CRE isolates that include 157 harboring SCarb, 150 OXA-48-like-producers, and 150 MBL-producing isolates. Further development of this BLI with inhibitory activity against all carbapenemase types seems warranted.




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

### 678. Galactomannan Is a Biomarker of APX001 (Fosmanogepix) Efficacy in Treating Experimental Invasive Pulmonary Aspergillosis

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

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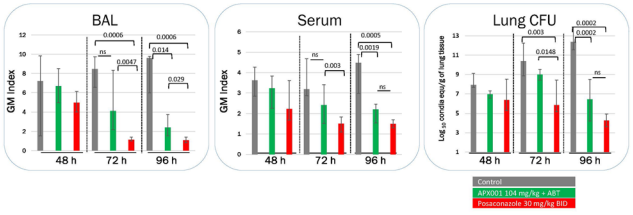
***Background.*** Invasive pulmonary aspergillosis (IPA) is a serious fungal infection afflicting immunocompromised patients. Galactomannan (GM) detection in biological samples using the Platelia ELISA has been shown to predict therapy response by azoles, and polyenes. We previously reported on the activity of APX001 (fosmanogepix) in treating murine IPA. Here, we investigated the potential use of GM as a biomarker of APX001 efficacy in an immunosuppressed murine model of IPA.

***Methods.*** ICR mice ($n$ = 8/group) were immunosuppressed with cyclophosphamide and cortisone acetate on days −2, and +3, relative to infection with *Aspergillus fumigatus* via inhalation. Treatment with placebo (diluent control), APX001 (104 mg/kg, PO, a human equivalent dose), or posaconazole (POSA, 30 mg/kg, BID [equivalent to 6× the humanized dose]) began 16-hour post-infection and continued daily. To extend the half-life of APX001, mice were administered 50 mg/kg of the cytochrome P450 inhibitor 1-aminobenzotriazole (ABT) 2 hours prior to APX001 administration. Mice were sacrificed 48-, 72-, or 96-hour post-infection and their lungs, bronchoalveolar lavage (BAL) and sera were collected. Lung fungal burden was determined by conidial equivalent (CE) using qPCR, while GM was determined using the Platelia ELISA.

***Results.*** Compared with placebo, APX001 or POSA treatment resulted in a gradual decrease in tissue fungal burden over time with APX001 or POSA showing significant reduction as early as 96 and 72 hours, respectively ($P$ < 0.005). Although the super-therapeutic dose of POSA resulted in faster reduction in lung fungal burden after 72 hours, both drugs resulted in similar reduction (~6–7 log) in lung CE vs. placebo after 96 hours. Changes in GM levels in BAL or serum samples mirrored reductions in lung CFU with significant decrease seen after 96 hours or 72 hours for APX001 or POSA, respectively, vs. placebo ($P$ < 0.02) (figure).

***Conclusion.*** A human equivalent dose of APX001 and a super humanized dose of POSA resulted in a time-dependent reduction of lung fungal burden and GM levels when compared with placebo. These results show that GM can be used as a biomarker of APX001 efficacy in immunosuppressed mice.




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

### 679. *In vitro* Activity of Cefiderocol (CFDC), a Novel Siderophore Cephalosporin, Against Difficult-to-Treat-Resistant (DTR) Gram-Negative Bacterial Pathogens From the Multi-National Sentinel Surveillance Study, SIDERO-WT (2014–2017)

Christopher Longshaw, PhD[1]; Masakatsu Tsuji, PhD[2]; Meredith M. Hackel, PhD[3]; Daniel F. Sahm, PhD, D(ABMM), FAAM [3]; Yoshinori Yamano, PhD[2]; [1]Shionogi Europe, London, UK; [2]Shionogi & Co., Ltd., Osaka, Japan; [3]International Health Management Associates, Inc., Schaumburg, Illinois