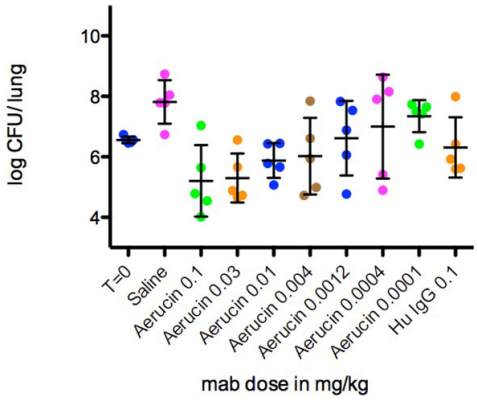
Background. Anti-bacterial monoclonal antibodies can serve as a new treatment modality for difficult to treat infections. AR-105 is a fully human IgG1 monoclonal antibody (mAb) that binds to an extracellular polysaccharide epitope of *Pseudomonas aeruginosa* (PA) and was shown to mediate *in vitro* complement-dependent 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.

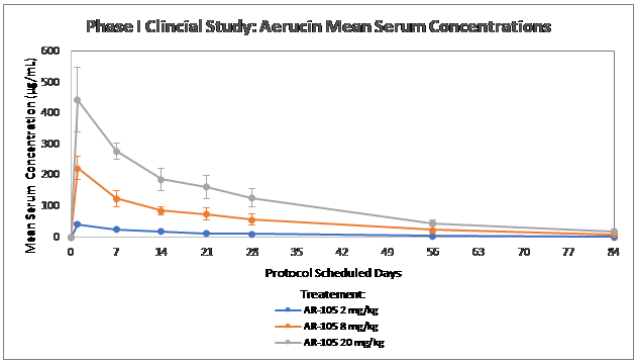
Conclusion. AR-105 was confirmed to be effective in PA pneumonia animal models, either as stand-alone therapeutic or in combination with antibiotics. In the Phase 1 clinical study, AR-105 was shown to be safe and well-tolerated, with a PK profile similar to that of other IgG1 mAbs. AR-105 is a promising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

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Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
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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