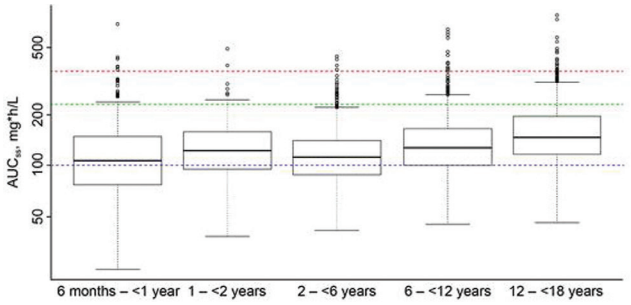
Figure: Box plot of predicted AUC_{ss} by age group for a 6 mg/kg dose (ages 6 months to <1 year) or 10 mg/kg dose (all other groups).



Dashed blue line is the lowest targeted median exposure. Dashed green and red line were the minimum (230 mg*h/L) and mean (330 mg*h/L) AUC_{ss} in a high-dose adult study (1116 mg) with increased toxicity. The box is the interquartile range (IQR) representing the 25th to 75th percentile. The whiskers represent the last point within 1.5 times the IQR of the 25th and 75th percentile. Circles represent all points beyond these thresholds.

Disclosures. **A. Desai**, Astellas Pharma, Inc.: Employee, Salary. **L. Kovanda**, Astellas Pharma, Inc.: Employee, Salary. **C. Lademacher**, Astellas Pharma, Inc.: Employee, Salary. **W. Hope**, F2G: Grant Investigator and Scientific Advisor, Consulting fee and Research grant. Astellas: Grant Investigator and Investigator, Grant recipient and Research grant. Pfizer: Grant Investigator, Research support. Gilead: Consultant and Scientific Advisor, Consulting fee. **P. Bonate**, Astellas Pharma, Inc.: Employee, Salary. **A. Edginton**, Astellas Pharma Global Development, Inc.: Independent Contractor, Consulting fee.

1397. Comparative Efficacy of Human-Simulated Epithelial Lining Fluid (ELF) Exposures of Tedizolid (TZD) Against Methicillin-resistant *Staphylococcus Aureus* (MRSA) in Neutropenic (I–) vs. Immunocompetent (I+) Murine Models of Pneumonia

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Background. TZD is an oxazolidinone with potent *in vitro* activity against Gram-positive pathogens, including MRSA. Limited data currently exist on the efficacy of TZD in the presence of neutropenia. Herein, we investigate the comparative efficacy of human-simulated ELF exposures of TZD against MRSA in I– and I+ murine models of pneumonia.

Methods. Four MRSA isolates with TZD broth microdilution MICs of 0.5 mg/L were studied. BALB/c mice in I– groups were made neutropenic with cyclophosphamide. Lungs of I– mice were inoculated intranasally with bacterial suspensions of 10^7 CFU/mL; a higher inoculum of 10^9 CFU/mL was required to induce infection in I+ mice. Single daily doses of TZD simulating human ELF exposures after doses of 200 mg q24h were determined in both I+ (40 mg/kg) and I– (32 mg/kg) models. Three hours after inoculation, human-simulated doses of TZD were administered q24h for up to 72 hours while control mice were vehicle dosed. A group of control and another of treatment ($n = 6$) per isolate were sacrificed at 24, 48, or 72 hours for lung harvest. Bacterial densities were determined by quantitative culture and averaged across all isolates. Mice that succumbed to infection before the scheduled time of sacrifice were included in the next group due for sacrifice. Changes in $\log_{10}$ CFU/lungs at 24 hours were compared with 0 hour controls.

Results. The average bacterial burdens at 0 hour were 5.86 ± 0.21 and 8.10 ± 0.24 $\log_{10}$ CFU/lungs among I– and I+ mice, respectively. At 24 hours, average burdens in control mice were comparable among I– and I+ mice at 7.91 ± 0.62 and 9.01 ± 0.69 $\log_{10}$CFU/lungs, respectively. Mean changes in bacterial density are reported in the table. No I+ control mice survived past 48 hours.

		Change in $\log_{10}$ CFU/Lungs (Mean ± SD)	
		I–	I+
24 hours	Control	2.06 ± 0.62	0.91 ± 0.69
	TZD	−1.18 ± 0.58	−1.23 ± 0.81
48 hours	Control	2.54 ± 0.31	0.61 ± 0.17
	TZD	−1.99 ± 0.90	−2.17 ± 0.84
72 hours	Control	2.85 ± 0.60	ND
	TZD	−2.78 ± 0.74	−3.64 ± 1.03

ND, no data.

Conclusion. Human-simulated ELF exposures of TZD demonstrated substantial and sustained efficacy in both I– and I+ murine models of pneumonia. These preclinical data utilizing clinically achievable bronchopulmonary exposures suggest that the efficacy of TZD for treatment of MRSA lung infections is not compromised by neutropenic status of the host. Further validation of these findings in patients is warranted.

Disclosures. **D. P. Nicolau**, Merck: Consultant, Grant Investigator and Speaker's Bureau, Consulting fee, Research grant and Speaker honorarium.

1398. β-Lactam Probability of Target Attainment (PTA) and Penetration into Epithelial Lining Fluid (ELF) Based on Multiple Bronchoalveolar Lavage (BAL) Sampling Time Points in a Swine Pneumonia Model

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Background. Defining ELF concentrations is desired for antibiotics developed for pneumonia. For ethical reasons, BAL sampling in humans is routinely done at a single time point, thereby creating ambiguity in the precise ELF profile. It is unknown if additional sampling of the ELF would lead to more accurate estimates of exposure. The swine pneumonia model was used to characterize the full ELF profiles (5-BAL) of two β-lactams for comparison with models employing 1-BAL (1B) and 2-BAL (2B) sampling time points only.

Methods. Sixteen ventilated swine were infected with *Pseudomonas aeruginosa* to establish pneumonia and then treated for 72 hours with ceftolozane/tazobactam (C/T) 50 mg/kg q8h ($n = 8$) or piperacillin/tazobactam (TZP) 200 mg/kg q8h ($n = 8$). Plasma and BAL concentrations were measured in each swine at 1, 2, 4, 6, and 8 hours after the first dose. Urea correction was used to calculate ELF values. Ceftolozane and piperacillin plasma and ELF data were fitted to a two compartment model using the nonparametric adaptive grid program in Pmetrics. Hypothetical models were refitted after randomly selecting either 1B or 2B sampling time points from each swine. A 5,000 subject Monte-Carlo simulation was performed for each model to define PTA (60% free time above the MIC) and ELF penetration [area under the curve in ELF (AUC_{ELF}) vs. free AUC_{plasma}]. The KS-test was used to analyze distribution differences, reporting maximum vertical deviation (D) as percent difference; $D < 20\%$ was defined as negligible.

Results. Thirty-two C/T and 34 TZP plasma samples and 29 and 32 BAL samples were available for the full model, respectively; 1B and 2B sampling models used eight and 16 BAL samples. All models adequately fitted the data. C/T PTA at 4 mg/L was 94.8, 96.1, and 98.0%, for the full, 1B and 2B models. TZP PTA at 16 mg/L was 55.8, 46.8, and 46.7%, respectively. C/T median [interquartile range] penetration differences were negligible between the full (65% [25−−109]) and 1B (72% [45−−125], $D = 15\%$) or 2B models (62% [32−−111], $D = 6\%$). TZP penetration differences were also minimal between the full (32% [9−−67]) and 1B (17% [5−−49], $D = 18\%$) or 2B models (27% [9−−44], $D = 15\%$).

Conclusion. These data suggest that antibiotic ELF models constructed from a single BAL time point result in similar exposure estimates to full ELF profiles.

Disclosures. **G. Li Bassi**, MSD: Grant Investigator, Grant recipient. **A. Torres**, MSD: Grant Investigator, Grant recipient.

1399. Efficacy of Daptomycin Combination with β-Lactams for Daptomycin-resistant *Enterococcus faecium* Harboring LiaSR Substitutions

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Background. Daptomycin (DAP) is one of the mainstay treatments for *Enterococcus faecium* infections. However, development of resistance threatens its continued viability as a treatment option. Although the mechanisms of DAP resistance in enterococci are not fully comprehended, they are associated with alterations in cell envelope phospholipids assembly which leads to repulsion of the drug from cell exterior and diversion from the cell septum. Previous data suggest that combination of DAP with β-lactams has the potential to improve patient outcomes. In this investigation, we

sought to evaluate combinations of DAP with ampicillin (AMP), ceftaroline (CPT), and ertapenem (ERT).

Methods. *E. faecium* R497 harboring liaSFR mutations (DAP MIC of 16 mg/L) was evaluated in a simulated endocardial vegetation (SEV) pharmacokinetic and pharmacodynamic model over 336 hours at a starting inoculum of 10^9 log10 CFU/g of SEV. DAP alone at 10 mg/kg/day or DAP (6, 8, 10 mg/kg/day) in combination with AMP (2 g continuous infusion), CPT 600 mg q12h or ERT 1 g q24h were evaluated. The emergence of DAP resistance was determined daily over the course of the 14-day experiment.

Results. DAP alone was not bactericidal and high-level DAP resistance was observed (MIC increase from 16 to 256 µg/mL) for all DAP alone regimens. Combination of DAP+AMP offered a significant reduction in $\log_{10}$CFU/g amounts (up to 7 $\log_{10}$ CFU/g and to detection limits) in 24 hours in DAP10+AMP model with no further emergence of DAP resistance. Even in DAP 6 mg/kg/day with AMP (2 g), dramatic killing with no further emergence of resistance was observed. Neither CPT nor ERT in combination with DAP was effective against this strain. At higher doses of DAP (14 mg/kg/day) + CPT or ERT, a temporary (0–48 hours) CFU/g reduction was observed followed by regrowth and the further emergence of DAP resistance.

Conclusion. Combination of DAP + AMP offered the most encouraging results against *E. faecium* R497. A DAP dose sparring effect was noted with DAP + AMP but not with CPT or ERT. The reason for the discrepancy is unknown and is under further investigation. Further evaluation of DAP plus β-lactam therapy is warranted to discover the most optimized DAP and β-lactam therapy to improve patient outcome and prevent the emergence of resistance.

Disclosures. **B. Murray**, Paratek pharmaceuticals: Consultant and Scientific Advisor, Consulting fee and Speaker honorarium; Forest/Actavis: Grant Investigator, Grant recipient; Cubist/Merck: Grant Investigator, Grant recipient. **C. Arias**, Merck & Co., Inc.: Grant Investigator, Research support; MeMed: Grant Investigator, Research support; Allergan: Grant Investigator, Research support; **M. J. Rybak**, Allergan: Consultant, Grant Investigator and Speaker's Bureau, Research grant and Research support; Achaogen: Consultant, Grant Investigator and Speaker's Bureau, Consulting fee, Research grant and Research support; Bayer: Consultant, Grant Investigator and Speaker's Bureau, Consulting fee, Research grant and Research support; Melinta: Consultant, Grant Investigator and Speaker's Bureau, Consulting fee, Research grant and Research support; Merck: Consultant, Grant Investigator and Speaker's Bureau, Consulting fee, Research grant and Research support; Theravance: Consultant, Grant Investigator and Speaker's Bureau, Consulting fee, Research grant and Research support; Sunovian: Consultant, Grant Investigator and Speaker's Bureau, Consulting fee, Research grant and Research support; Zavante: Consultant, Grant Investigator and Speaker's Bureau, Consulting fee, Research grant and Research support; NIAID: Consultant, Grant Investigator and Speaker's Bureau, Consulting fee, Research grant and Research support

1400. Mass Balance, Metabolism, and Excretion of [^{14}C]-Plazomicin in Healthy Human Subjects

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Background. Plazomicin is a next-generation aminoglycoside (AG) with a structure that protects it from common AG resistance mechanisms in Enterobacteriaceae, and with in vitro activity against extended spectrum β-lactamase-producing and carbapenem-resistant Enterobacteriaceae. The purpose of this study was to evaluate the metabolism and excretion of plazomicin in healthy human subjects.

Methods. Six healthy male subjects were administered a single 30-minute intravenous infusion of 15 mg/kg [^{14}C]-plazomicin (~100 µCi/dose). Following administration, blood (and plasma), urine, and feces were collected for 7 days. Total radioactivity was analyzed by liquid scintillation counting; plazomicin concentration was analyzed by a validated liquid chromatography–tandem mass spectrometry method; and metabolite profiling was conducted by accelerator mass spectrometry (AMS).

Results. The majority of the total administered radioactivity was recovered in urine (89.1%), with negligible amounts (<0.2%) excreted in feces. Radioactivity was rapidly eliminated, with ~56% of the total radioactivity recovered in urine within the first 4 hours postdose and >85% recovered in urine by 48 hours postdose. Analysis of nonradiolabeled plazomicin demonstrated that 97.5% of the dose was recovered as unchanged parent drug in urine by the end of the last sampling interval. Metabolite profiling of plasma and urine using AMS showed that [^{14}C]-plazomicin was the only definable peak present, accounting for 94.3% and 93.6%, respectively, of the total carbon content.

Conclusion. Mass balance was achieved for ^{14}C-labeled and for nonradiolabeled plazomicin as the majority of the administered dose was recovered in urine, with negligible amounts in the feces. Plazomicin was eliminated as unchanged drug by the kidneys and thus did not appear to be metabolized to any appreciable extent. No metabolites were detected by AMS and plazomicin was the only definable peak present in plasma and urine.

Disclosures. **T. Choi**, Achaogen, Inc.: Employee, Salary. **J. D. Seroogy**, Achaogen, Inc.: Employee and Shareholder, Salary. **M. Sanghvi**, Xceleron: Employee, Salary. **S. V. Dhuria**, Achaogen, Inc.: Employee, Salary.

1401. A Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Pharmacokinetics of Single and Repeat Doses of VNRX-5133 in Healthy Subjects

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Background. VNRX-5133 is a novel, non-β-lactam, β-lactamase inhibitor with potent and selective direct inhibitory activity against serine- and metallo-β-lactamases. VNRX-5133, combined with the β-lactam antibiotic cefepime, is being developed for the treatment of serious infections due to multidrug-resistant Gram-negative bacteria, including ESBL-producing organisms and carbapenem-resistant Enterobacteriaceae and *Pseudomonas aeruginosa*. This study evaluated the safety and pharmacokinetics (PK) of VNRX-5133 after single and multiple intravenous (IV) doses.

Methods. This was a Phase 1, randomized, single-center, double-blind, placebo-controlled, sequential group study in healthy subjects. In a single ascending dose (SAD), phase subjects received 62.5, 125, 250, 500, 1000, and 1500 mg VNRX-5133 via a 2-hour IV infusion. In a multiple ascending dose (MAD) phase, subjects received 250, 500, and 750 mg VNRX-5133 q8h for 10 days. PK samples were collected predose and at frequent intervals. Safety was assessed from adverse events (AEs), laboratory tests, physical examination, vital signs, and electrocardiogram (ECG).

Results. All subjects completed the SAD (n = 48) and the MAD phases (n = 36). VNRX-5133 plasma exposure exhibited dose proportionality and linearity. Total clearance (CL) was ~6 L/h and volume of distribution (Vz) was ~30 to 50 L. The $t_{1/2}$ based on a noncompartmental analysis was ~6.5 hours. Modeling of VNRX-5133 plasma concentrations showed that the PK fit a 2-compartment model with most of the drug exposure accounted for within the initial phase of ~2 hours. Minimal accumulation of VNRX-5133 was observed following q8h dosing over 10 days. In the SAD phase, AEs occurred in four subjects (33.3%) with placebo and seven (19.4%) with VNRX-5133. In the MAD phase, AEs occurred in three subjects (33.3%) with placebo and eight (29.6%) with VNRX-5133. The most common AEs with VNRX-5133 were headache (11.1%), nausea (7.4%), and constipation (7.4%).

Conclusion. After single doses of 62.5–1,500 mg and multiple doses of 250–750 mg q8h, VNRX-5133 demonstrated a linear and dose-proportional PK profile with low variability. No safety issues were identified.

Disclosures. **B. Geibel**, VenatoRx Pharmaceuticals, Inc.: Employee, Salary. **J. Dowell**, VenatoRx Pharmaceuticals, Inc.: Consultant, Consulting fee. **D. Dickerson**, VenatoRx Pharmaceuticals, Inc.: Research Contractor, Research support. **T. Henkel**, VenatoRx Pharmaceuticals, Inc.: Employee, Salary

1402. Cystatin C Improves Estimation of Vancomycin Clearance in Critically Ill Children Using a Population Pharmacokinetic Modeling Approach

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Background. Vancomycin (VAN) is renally eliminated and clearance (CL) correlates with glomerular filtration rate (GFR). The bedside Schwartz equation (Schwartz_{bed}), currently used to estimate GFR in children, relies solely on creatinine (Cr) and is inaccurate in critical illness. We compared the Schwartz_{bed} against various GFR-estimating equations that incorporate the novel biomarker cystatin C (CysC) in a population pharmacokinetic (PK) model of VAN CL in critically ill children.

Methods. Children 2–18 years of age receiving intravenous VAN in the Children's Hospital of Philadelphia PICU were enrolled. Three PK samples were collected during a single steady-state dosing interval in addition to VAN concentrations collected for clinical care. A sample was obtained prior to and during PK sampling for the measurement of CysC and Cr. VAN concentrations, dosing histories, and covariates (age, height, weight, sex, eGFR) were analyzed using nonlinear mixed-effects modeling with NONMEM v7.4. Model evaluation/selection was based on successful convergence, precision of the parameter estimates, the Akaike Information Criteria (AIC), and comparison of goodness-of-fit diagnostic plots of models including Schwartz_{bed} and other published Cr- and CysC-based eGFR equations.

Results. We enrolled 20 subjects age 12.7 years (range: 3.9–18.2); six were female. Median VAN dosing at PK sampling was 57.4 mg/kg/day (range: 26.4–80.1). Median Cr was 0.35 mg/dL (IQR 0.3–0.5) and CysC was 0.5 mg/L (IQR 0.4–0.8); correlation between Cr and CysC was poor (0.24). Population PK data were described by a two-compartment model with allometric scaling for all parameters. The full age spectrum equation using both Cr and CysC [eGFR = $107.3/((Cr/Q_{Cr})*0.5 + (CysC/Q_{CysC})*0.5)$; Q_{Cr} and Q_{CysC} are normal values for age] as a covariate on CL had the largest reduction in AIC compared with Schwartz_{bed} (ΔAIC −11.571) and provided best model fit. Typical population PK parameters (95% CI) normalized to 70 kg were 0.13 L/minute (0.11,0.14), 24.5 L (7.7,41.5), and 0.14 L/minute (0.01, 0.28) for CL, V1, and Q, respectively.