Methods. Data from the two Phase 1 studies used previously to develop the model were pooled with data from an additional Phase 1 study and the STRIVE trial in patients with candidemia and/or IC. The population PK model was refined using NONMEM Version 7.2. The ability of covariates such as body size, age, sex, albumin, markers of liver and renal function, and infection status to explain a portion of the interindividual variability on select PK parameters was explored using stepwise forward selection ($\alpha = 0.01$) and backward elimination ($\alpha = 0.001$). The final model was externally validated by comparing model-based predictions to observed data from STRIVE, which were not available during model development.

Results. The final population PK model was a linear, four-compartment model with zero order IV input. Albumin was the most important predictor of the interindividual variability in RZF PK as significant relationships were found between serum albumin concentration and clearance, volume of the central compartment, volume of peripheral compartment 1, and volume of peripheral compartment 2. Additional relationships were found between PK parameters and sex, body weight, and infection status. The model provided precise and unbiased fits to the observed data (Figure 1). Differences in predicted median AUC across a wide range of covariate values were modest (Figure 2). The final model was also able to predict the central tendency and variability in RZF concentration–time data from patients with candidemia and/or IC not included in the model development (Figure 3).

Conclusion. A population PK model describing RZF PK in healthy subjects and patients with candidemia and/or IC was successfully developed. This model was utilized for subsequent PK-PD target attainment analyses to support dose selection for RZF.

Figure 1. Goodness of fit plots for final RZF population PK model

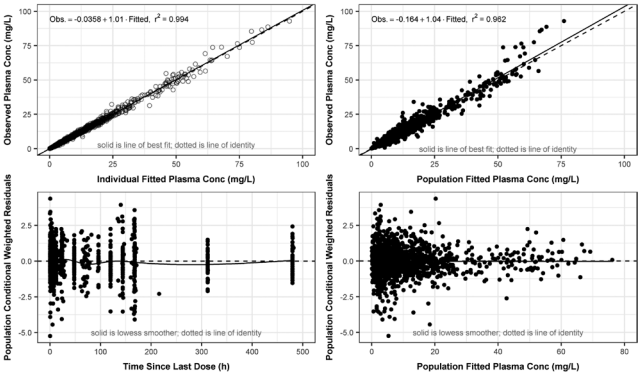


Figure 2. Forest plot of covariate effects on RZF Week 1 Plasma AUC

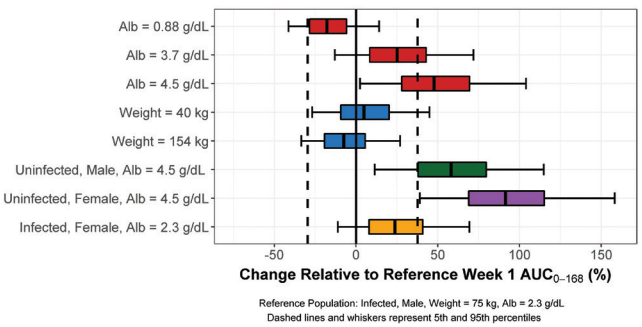
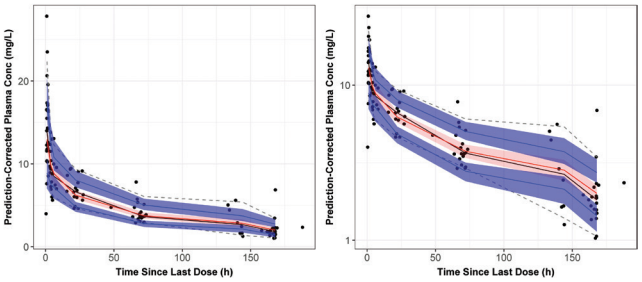


Figure 3. Prediction-corrected comparison of observed and simulated RZF plasma concentrations using additional STRIVE data



Disclosures. **E. A. Lakota**, Cidara Therapeutics: Research Contractor, Research support. **H. Ganesan**, Cidara Therapeutics: Research Contractor, Research support. **S. Flanagan**, Cidara Therapeutics: Employee and Shareholder, Salary and stock options. **V. Ong**, Cidara Therapeutics: Employee and Shareholder, Salary and Stock options. **T. Sandison**, Cidara Therapeutics: Employee and Shareholder, Salary and Stock options. **S. M. Bhavnani**, Cidara Therapeutics: Research Contractor, Research support. **C. M. Rubino**, Cidara Therapeutics: Research Contractor, Research support. **P. G. Ambrose**, Cidara Therapeutics: Research Contractor, Research support.

1391. Vancomycin Area Under the Curve (AUC) to Predict Nephrotoxicity: A Systematic Review and Meta-Analysis of Observational Studies

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Background. Recent studies have proposed monitoring vancomycin area under the curve (AUC) as a more precise method of attaining goal exposures compared with trough monitoring. Different dosing methods and different exposure-toxicity thresholds have been proposed. Therefore, we aimed to analyze the relationship between vancomycin AUC and nephrotoxicity reported across recent studies.

Methods. A systematic review of Pubmed, Medline, Scopus and compiled references was conducted. We included randomized, cohorts and case–control studies that reported vancomycin AUCs and risk of nephrotoxicity from (January 1, 1990 to January 31, 2018). The primary outcome was nephrotoxicity, defined as an increase in serum creatinine of ≥0.5 mg/L or a 50% increase from baseline on two or more consecutive measurements. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated. Subset analyses were conducted when possible on the impact of $AUC_{0\text{-}24\ hours}$ and $AUC_{24\text{-}48\ hours}$ exposures and AUC vs. trough guided dosing on the outcome of nephrotoxicity. AUC nephrotoxicity thresholds ranged between 550 and 700 mg hour/L. We grouped values according to lower (i.e., <650) or higher average AUC, with a threshold value of ≥650 mg hour/L defining higher AUC based on a recent prospective trial.

Results. We identified eight eligible observational studies with a total of 2,491 patients. Of those, five studies reported $AUC_{0\text{-}24}$ associated with nephrotoxicity, two studies reported $AUC_{24\text{-}48}$, and two studies reported nephrotoxicity associated with AUC vs. trough-guided dosing. No RCTs were identified. Lower $AUC_{0\text{-}24}$ values were associated with significantly reduced risk of nephrotoxicity (OR 0.36, 95% CI 0.23–0.56). In a sub-analysis of two studies, $AUC_{24\text{-}48}$ <650 mg hour/L was associated with significantly lower risk of nephrotoxicity (OR 0.45, 95% CI 0.27–0.75). Nephrotoxicity associated with AUC-guided dosing was significantly lower than trough-guided dosing (OR 0.68, 95% CI 0.46–0.99).

Conclusion. This meta-analysis suggests that $AUC_{0\text{-}24}$ lower than 650 mg hour/L may result in a decreased risk of nephrotoxicity. AUC-guided vancomycin dosing may result in less vancomycin-associated nephrotoxicity. Additional investigations into the benefit of AUC-guided dosing are warranted.

Figure 1. Forest Plot indicating the association between vancomycin $AUC_{0\text{-}24}$ and nephrotoxicity

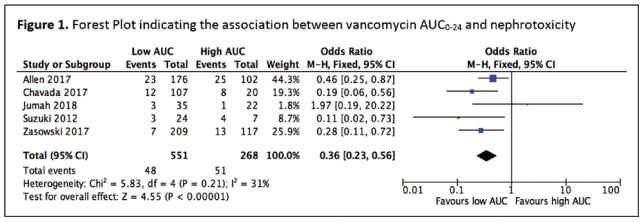


Figure 2. Forest Plot indicating the association between vancomycin $AUC_{24\text{-}48}$ and nephrotoxicity

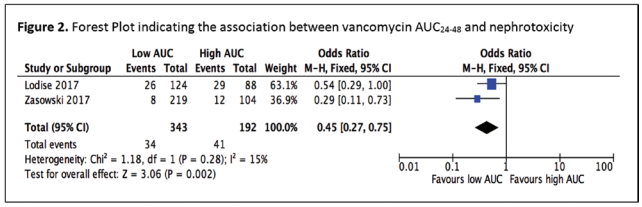
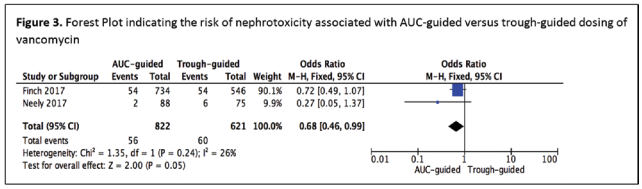


Figure 3. Forest Plot indicating the risk of nephrotoxicity associated with AUC-guided versus trough-guided dosing of vancomycin



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

1392. Pharmacokinetic-Pharmacodynamic (PK-PD) Target Attainment Analyses to Support Inhaled ME1100 Dose Selection

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Background. ME1100 (arbekacin inhalational solution) is an inhaled aminoglycoside being developed to treat patients with hospital-acquired and ventilator-associated bacterial pneumonia (HABP and VABP, respectively). PK-PD target attainment analyses were undertaken to evaluate ME1100 regimens for patients with HABP/VABP arising from *Klebsiella pneumoniae* (KP), *Pseudomonas aeruginosa* (PA) and *Staphylococcus aureus* (SA), including those with renal impairment.

Methods. Data used included a population pharmacokinetic (PPK) model developed using Phase 1 and post-marketing PK data, nonclinical PK-PD targets from one compartment *in vitro* and/or *in vivo* infection models, and MIC data. Using parameter estimates from the PPK model (four-compartment model with first-order elimination), total-drug epithelial lining fluid concentration-time profiles were generated for simulated patients with varying creatinine clearance (CLcr; mL/minute/1.73 m^2) and by CLcr group. Twice daily (BID) ME1100 regimens ranging from 300 to 900 mg were assessed in simulated patients with CLcr >80 to ≤120 mL/minute/1.73 m^2. Percent probabilities of PK-PD target attainment by MIC were determined based on total-drug ELF AUC:MIC ratio targets associated with 1- and 2-$\log_{10}$ CFU reductions from baseline for KP, PA and SA using Day 1 AUC. Regimens in simulated patients with renal impairment that best matched the BID regimen in the normal CLcr group with high percent probabilities of PK-PD target attainment and a low percent probability of C_{min} > 2 mg/L were identified.

Results. ME1100 600 mg BID in simulated patients with CLcr >80 to ≤120 mL/minute/1.73 m^2, with 600 mg once daily, 450 mg BID and 600 mg BID in simulated patients with CLcr of 0 to ≤30, >30 to ≤50 and >50 to ≤80 mL/minute/1.73 m^2, respectively, achieved high percent probabilities of PK-PD target attainment based on PK-PD targets for a 1-$\log_{10}$ CFU reduction from baseline at relevant MIC values for KP, PA and SA, and relatively lower C_{min} values. In simulated patients with varying CLcr who received these regimens, high percent probabilities of PK-PD target attainment were achieved for KP, PA and SA at the upper margins of the MIC distributions (Figures 1–3).

Conclusion. The data provide support for ME1100 dose selection for patients with HABP/VAPB.

Figure 1. Percent probabilities of PK-PD target attainment by MIC on Day 1 based on total-drug ELF AUC:MIC ratio targets for *K. pneumoniae* from an *in vitro* infection model among simulated patients after administration of inhaled ME1100 regimens, overlaid upon a *K. pneumoniae* MIC distribution

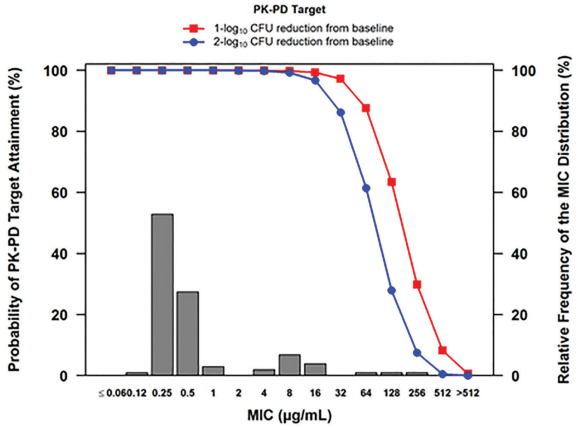


Figure 2. Percent probabilities of PK-PD target attainment by MIC on Day 1 based on total-drug ELF AUC:MIC ratio targets for *P. aeruginosa* from *in vitro* and *in vivo* infection models among simulated patients after administration of inhaled ME1100 regimens, overlaid upon a *P. aeruginosa* MIC distribution

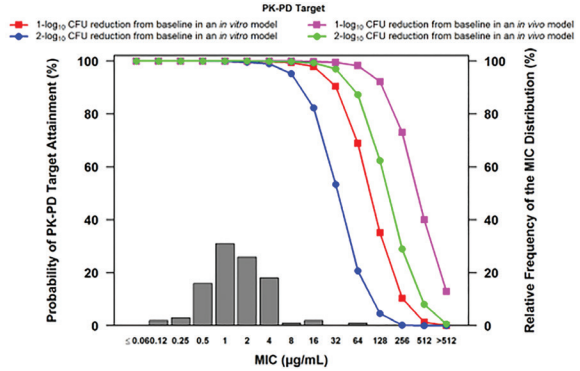
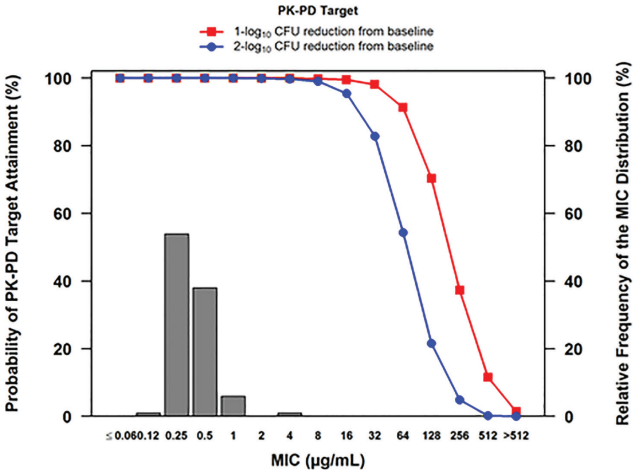


Figure 3. Percent probabilities of PK-PD target attainment by MIC on Day 1 based on total-drug ELF AUC:MIC ratio targets for *S. aureus* from an *in vitro* infection model among simulated patients after administration of inhaled ME1100 regimens, overlaid upon a *S. aureus* MIC distribution



Disclosures. **S. M. Bhavnani**, Meiji Seika Pharma Co. Ltd.: Research Contractor, Research support. **J. P. Hammel**, Meiji Seika Pharma Co. Ltd.: Research Contractor, Research support. **E. A. Lakota**, Meiji Seika Pharma Co. Ltd.: Research Contractor, Research support. **B. D. VanScoy**, Meiji Seika Pharma Co. Ltd.: Research Contractor, Research support. **Y. Nagira**, Meiji Seika Pharma Co. Ltd.: Employee, Salary. **C. M. Rubino**, Meiji Seika Pharma Co. Ltd.: Research Contractor, Research support. **N. Sato**, Meiji Seika Pharma Co. Ltd.: Employee, Salary. **T. Koresawa**, Meiji Seika Pharma Co. Ltd.: Employee, Salary. **K. Kondo**, Meiji Seika Pharma Co. Ltd.: Employee, Salary. **P. G. Ambrose**, Meiji Seika Pharma Co. Ltd.: Research Contractor, Research support.

1393. A Phase 1, Randomized, Open-Label, Crossover Study in Healthy Subjects Under Fasting Conditions of Orally Administered Sulopenem Etzadroxil Alone or with Probenecid to Determine the Pharmacokinetics of Sulopenem

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Background. Antimicrobial resistance to available oral antibiotics is becoming progressively more common, precipitating the need for additional treatment options as step-down from initial intravenous (IV) therapy as well as for treatment of infections in the community. Sulopenem (CP-70,429) is a thiopenem antibiotic active against quinolone non-susceptible and ESBL-producing Enterobacteriaceae. As the key pharmacokinetic-pharmacodynamic variable correlating with efficacy for penem antibiotics is time above minimum inhibitory concentration (T > MIC), we examined the utility of probenecid, an OAT-1 inhibitor of β-lactam excretion, on the pharmacokinetic (PK) parameters for the oral prodrug of sulopenem, sulopenem etzadroxil

Methods. Twelve healthy males and females received a single oral dose of 500 mg sulopenem etzadroxil as powder in bottle either alone or co-administered with a single oral dose of probenecid 500 mg in a crossover design with a washout period of 6 days. All doses were administered under fasting conditions. Blood samples for plasma PK analysis were collected and PK parameters for sulopenem, the parent compound of sulopenem etzadroxil, were determined.

Results. Treatment

		Sulopenem Parameter (Day 1; Mean)			
Treatment	*N*	Cmax (ng/mL)	AUC0-INF (hour ng/mL)	*T* > MIC (0.5 µg/mL) [hour]	*T* > MIC (0.5 µg/mL) [%, 12 hour Interval]
500 mg sulopenem etzadroxil	10	1,928	3,871	2.8	23.3
500 mg sulopenem etzadroxil + 500 mg probenecid	11	1,929	4,964	3.6	30.2

Conclusion. Probenecid increases the AUC of sulopenem by 28% in the fasted state and extends the mean time over MIC.

Disclosures. **M. Dunne**, Iterum Therapeutics: Employee and Shareholder, Salary. **S. Aronin**, Iterum Therapeutics: Employee and Shareholder, Salary. **E. Dunzo**, Parexel: