

**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.

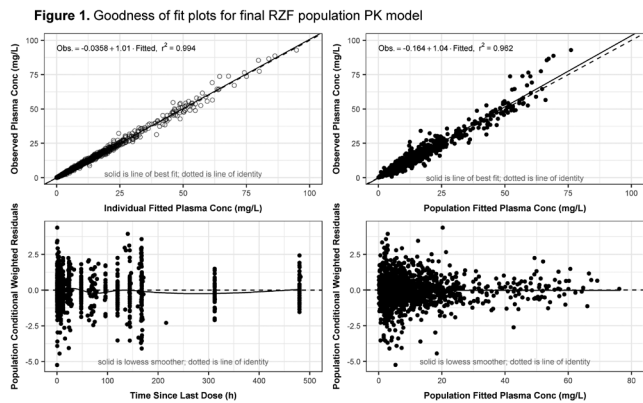


Figure 1. Goodness of fit plots for final RZF population PK model

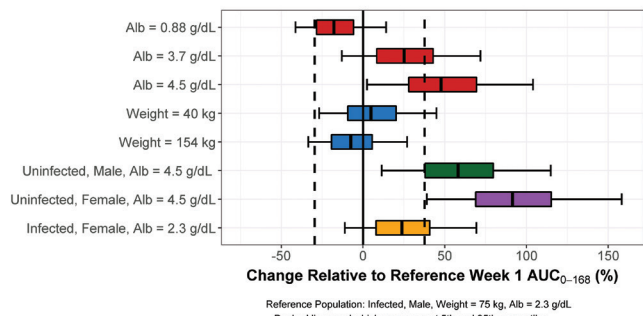
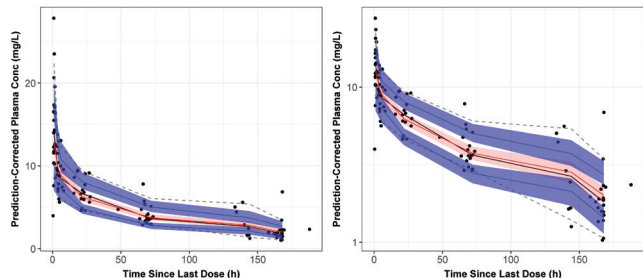


Figure 2. Forest plot of covariate effects on RZF Week 1 Plasma AUC



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

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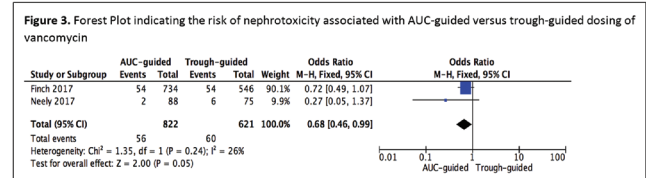
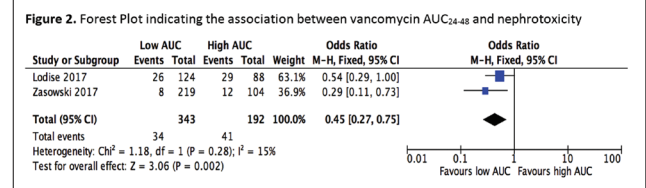
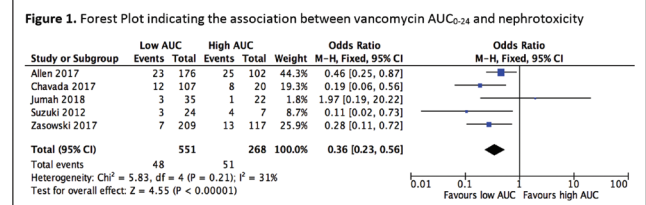
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**Background.** Recent studies have proposed monitoring vancomycin area under the curve (AUC) as a more precise method of attaining goal exposures compared with trough monitoring. Different dosing methods and different exposure-toxicity thresholds 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  $\geq 0.5$  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<sub>0-24 hours</sub> and AUC<sub>24-48 hours</sub> 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  $\geq 650$  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<sub>0-24</sub> associated with nephrotoxicity, two studies reported AUC<sub>24-48</sub> and two studies reported nephrotoxicity associated with AUC vs. trough-guided dosing. No RCTs were identified. Lower AUC<sub>0-24</sub> 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<sub>24-48</sub> <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<sub>0-24</sub> 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.



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

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

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