Pharmacokinetic-Pharmacodynamic Target Attainment Analyses to Support Plazomicin Dose Selection and Recommendations for Interpretive Criteria for *In Vitro* Susceptibility Testing for Enterobacteriaceae

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INTRODUCTION

- Plazomicin is an aminoglycoside that was engineered to overcome aminoglycoside-modifying enzymes, the most common aminoglycoside-resistance mechanism in Enterobacteriaceae.
- Dose selection support for the plazomicin dosing regimens evaluated in the completed Phase 3 studies was based on a series of pharmacometric analyses undertaken early in drug development [1, 2].
- Refinement of a population pharmacokinetic (PK) model based on PK data from Phase 3 patients [3] allowed for the reassessment of initial plazomicin dosing regimen administered according to baseline creatinine clearance.
- As described herein, pharmacokinetic-pharmacodynamic (PK-PD) target attainment analyses were undertaken to evaluate initial plazomicin dosing regimens and interpretive criteria for the *in vitro* susceptibility testing for plazomicin against Enterobacteriaceae.

METHODS

Simulated Patient Populations

- Using parameter estimates from the previously-developed population PK model (3-compartment model with zero-order input and 1st-order elimination) [3], disease indicator parameters, and demographic variables, total-drug plasma concentration-time profiles were generated for three sets of simulated patients:
  - Simulated patients with complicated urinary tract infections (cUTI), including acute pyelonephritis (AP), and creatinine clearance (CLcr; mL/min) generated using two sets of ranges: >120 to ≤240, >90 to ≤120, >60 to ≤90, >50 to ≤60, >40 to ≤50, >30 to ≤40, ≥16 to ≤30 mL/min; and >60, >30 to ≤60, and >15 to ≤30 mL/min.
  - Simulated patients with cUTI or AP, bloodstream infection (BSI), or hospital-acquired bacterial pneumonia (HABP)/ventilator-associated bacterial pneumonia (VABP).
- Initial plazomicin dosing regimens were administered to simulated patients according to CLcr as described in **Table 1**.

Table 1. Initial plazomicin dosing regimens based on baseline renal function

Baseline CLcr[a]	Dose interval	Dose (mg/kg)[b]
CLcr >60 mL/min	q24h	15
CLcr >30 to 60 mL/min	q24h	10
CLcr >15 to 30 mL/min	q48h	10

a. Determined using the Cockcroft and Gault equation.
b. Adjusted body weight (ABW) was used in place of total body weight (TBW) if TBW was ≥ 25% higher than ideal body weight (IBW). ABW was calculated as follows: ABW (kg) = IBW + 0.4 • (TBW - IBW).

METHODS

- Total-drug epithelial lining fluid (ELF) AUC values were generated by multiplying total-drug plasma AUC by randomly assigned ELF penetration ratios from a distribution (median [min, max] of 0.60 [0.18, 1.06]) derived from a PK analysis for tobramycin that used data from patients with pneumonia to quantify ELF penetration [4].
- Average 24-hour total-drug plasma and ELF AUC (AUC_{0-24}) over Days 1-2 was calculated.

Pharmacokinetic-Pharmacodynamic Target Attainment Analyses

- Percent probabilities of PK-PD target attainment by MIC were determined using median or randomly assigned AUC:MIC ratio targets from the neutropenic infection models for plazomicin against Enterobacteriaceae described in **Table 2**.
  - AUC:MIC ratio target for a simulated patient was randomly assigned based on an estimated log normal distribution of targets associated with a given endpoint. The distribution was truncated at +/- 2 standard deviations on the log scale.
  - Focus was given by population to results based on AUC:MIC ratio targets associated with specific endpoints:
    - Simulated patients with cUTI or AP and BSI: net bacterial stasis from a neutropenic murine-thigh infection model.
    - Simulated patients with the HABP/VABP: a 1-log_{10} CFU reductions from baseline from a neutropenic murine-lung infection model.
- Percent probabilities of PK-PD target attainment were interpreted relative to *in vitro* surveillance data for 16,296 Enterobacteriaceae isolates collected worldwide between 2014 and 2016.

Table 2. PK-PD targets based on a neutropenic murine-thigh or murine-lung infection model

Statistic	Neutropenic murine-infection model			
	Thigh		Lung	
	Total-drug plasma AUC:MIC ratio		Total-drug ELF AUC:MIC ratio	
	Net bacterial stasis	1- log_{10} CFU	1- log_{10} CFU	2- log_{10} CFU
Mean	24.3	110.7	8.9	29.0
Median	23.6	85.0	5.5	19.8
Min	5.7	8.1	1.5	1.9
Max	49.4	518.3	26.2	82.6

a. Based on the evaluation of n=17 isolates for the neutropenic murine-thigh infection model and n=14 isolates for the neutropenic murine-lung model.

RESULTS

- As shown in **Figure 1**, the scatter of average total-drug plasma AUC_{0-24} values across the range of baseline CLcr values was reasonably consistent among simulated patients generated using seven baseline CLcr groups that were categorized by the three baseline CLcr groups for initial plazomicin dosing regimens shown in **Table 1**.
- As shown in **Figure 2**, percent probabilities of attaining the total-drug plasma AUC:MIC ratio target associated with net bacterial stasis at MIC values of 2 or 4 µg/mL approached or exceeded 90% among simulated patients generated using three baseline CLcr groups (>60, >30 to ≤60, and >15 to ≤30 mL/min).

RESULTS

Figure 1. Scatterplot of average total-drug plasma AUC_{0-24} values on Days 1-2 among simulated patients by baseline CLcr

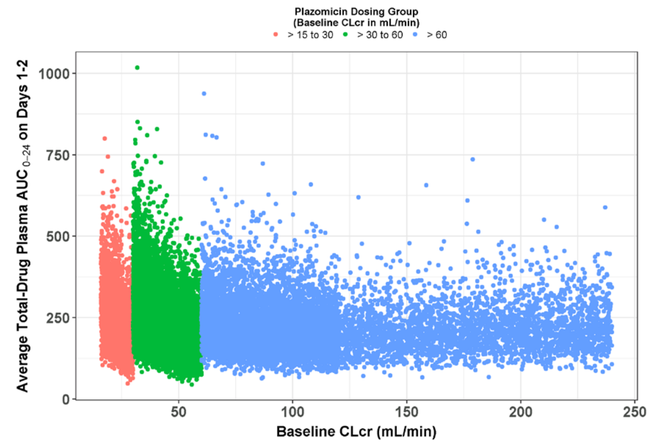


Figure 2. Percent probabilities of PK-PD target attainment by MIC based on the median total-drug plasma AUC:MIC ratio target for net bacterial stasis (A) and randomly assigned total-drug plasma AUC:MIC ratio target for net bacterial stasis (B) among simulated patients by CLcr group

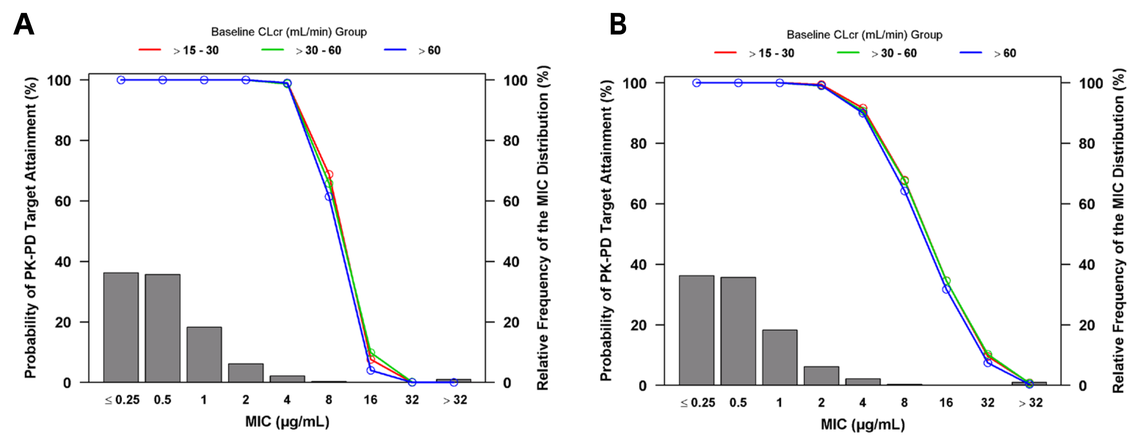
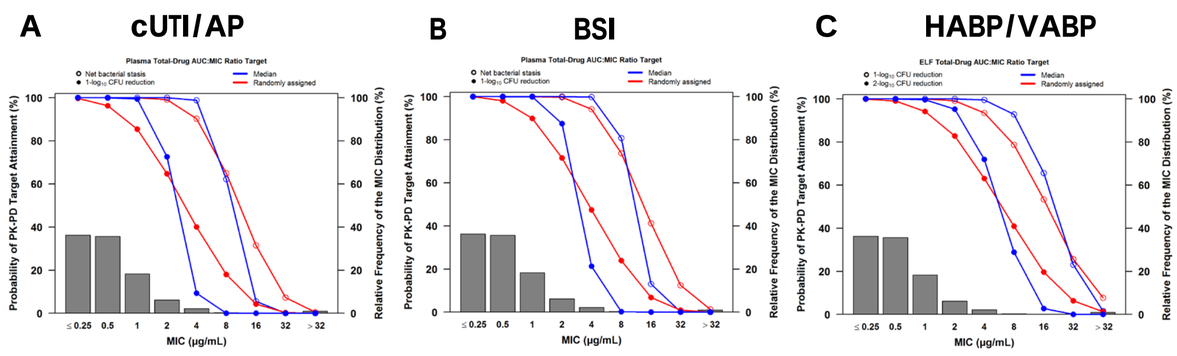


Figure 3. Percent probabilities of PK-PD target attainment by MIC for initial plazomicin dosing regimens among simulated patients, cUTI/AP(A), BSI (B), or HABP/VABP (C) based on total-drug plasma or ELF AUC:MIC ratio targets for plazomicin against Enterobacteriaceae



- As shown in **Figures 3A** and **3B**, percent probabilities of attaining the total-drug plasma AUC:MIC ratio target associated with net bacterial stasis at MIC values of 2 or 4 µg/mL approached or exceeded 90% among simulated patients with cUTI, AP, or BSI. At a MIC value of 2 µg/mL, percent probabilities of PK-PD target attainment for the total-drug plasma AUC:MIC ratio target associated with a 1- log_{10} CFU reduction from baseline ranged from 64.7 to 87.5%.
- As shown in **Figure 3C**, percent probabilities of attaining the total-drug ELF AUC:MIC ratio target associated with a 1-log_{10} CFU reduction from baseline at MIC values of 2 or 4 µg/mL ranged from 93.5 to 100% among simulated patients with HABP/VABP.

CONCLUSIONS

- These data provide support for proposed plazomicin dosing regimens and the evaluation of plazomicin susceptibility breakpoints against Enterobacteriaceae.

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