

**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 regimen 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, a compartment model with zero-order input and 1st-order elimination [3], disease indicator parameters, and demographic variables, total-dose plasma concentration-time profiles were generated for three sets of simulated patients:
  1. Simulated patients with complicated urinary tract infections (cUTI), including acute pyelonephritis (AP), and creatinine clearance (CLcr; mL/min) generated using two sets of ranges: >0 to <20, >20 to ≤50, >50, >30 to ≤40, >40 to ≤60, >60, >30 to ≤30 mL/min; and >60 mL/min.
  2. Simulated patients with cUTI or AP, bloodstream infection (BSI), or hospital-acquired bacterial pneumonia (HABP)/ventilator-associated bacterial pneumonia (VABP).
  3. Initial plazomicin dosing regimens were administered to simulated patients according to CLcr as described in Table 1.

**RESULTS**

As shown in Figure 1, the scatterplot of average total-dose plasma AUC(MIC) values on Days 1-2 among simulated patients by baseline CLcr

As shown in Figures 2 and 3, percent probabilities of attaining the total-dose 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, BSI, or HABP/VABP (C) based on total-dose plasma or ELF AUC(MIC) ratio targets for net bacterial stasis (A) and MIC-targeted (B) among simulated patients by CLcr group.

**CONCLUSIONS**

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

**REFERENCES**


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