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 in against Enterobacteriaceae.

**METHODS**

**Simulated Patient Populations**

- Using parameter estimates from the previously-developed population PK model[3] with a 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:
    - >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.

**RESULTS**

- 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 net bacterial stasis (B) among simulated patients by CLcr group are shown in Table 2. The scatter of average total-drug plasma AUC:MIC values on Days 1-2 among simulated patients by CLcr is shown in Figure 1.

**CONCLUSIONS**

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

**REFERENCES**


**ACKNOWLEDGMENTS**

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

<table>
<thead>
<tr>
<th>Baseline CLcr</th>
<th>Dose interval</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60 mL/min</td>
<td>q24h</td>
<td>15</td>
</tr>
<tr>
<td>&gt;30 to 60 mL/min</td>
<td>q24h</td>
<td>10</td>
</tr>
<tr>
<td>&gt;15 to 30 mL/min</td>
<td>q48h</td>
<td>10</td>
</tr>
</tbody>
</table>

**Figure 1** Scatterplot of average total-drug plasma AUC:MIC values on Days 1-2 among simulated patients by CLcr

**Figure 2** 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.

**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.