Plazomicin Is Associated With Improved Survival and Safety Compared With Colistin in the Treatment of Serious Infections Due to Carbapenem-resistant Enterobacteriaceae: Results of the CARE Study

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• This drug is currently limited by law to investigational use, and no representation is made as to the safety or effectiveness for the purposes for which it is being investigated

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Combating Antibiotic-resistant Enterobacteriaceae (CARE)

A Phase 3 Study Evaluating the Efficacy and Safety of Plazomicin in the Treatment of Patients With Serious Infections due to Carbapenem-resistant Enterobacteriaceae (CRE)

Primary Objective
Evaluate the efficacy of plazomicin compared with colistin\(^a\) in the treatment of BSI or HABP/VABP due to CRE based on primary endpoint:

- Day 28 all-cause mortality or significant disease-related complications\(^b\)

\(^a\)Plazomicin or colistin in combination with adjunctive therapy of meropenem or tigecycline.

\(^b\)Within 7 days: New/worsening ARDS, new lung abscess or empyema, new-onset septic shock; persistence of bacteremia ≥5 days (BSI only); new-onset bacteremia (HABP/VABP only).

This trial is registered at ClinicalTrials.gov: NCT01970371.

ARDS, acute respiratory distress syndrome; BSI, bloodstream infection; CRE, carbapenem-resistant Enterobacteriaceae; HABP, hospital-acquired bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia.
CARE Study Design

**Screening**

Cohort 1:
BSI, HABP/VABP  
Randomization 1:1

Documented or presumed CRE infection

Cohort 2:
BSI, HABP/VABP, cUTI/AP

Documented or presumed CRE infection (with broader eligibility criteria)

**Treatment**

Plazomicin 15 mg/kg q24h as 30-minute infusion (with TDM)

Plus meropenem or tigecycline

Colistin 300-mg loading dose; 5 mg/kg/d divided q8h or q12h as 60-minute infusion

Plazomicin 15 mg/kg q24h as 30-minute infusion (with TDM)

Adjunctive therapy per investigator’s choice

**Follow-up**

TOC  
EOS  
LFU

TOC  
EOS  
LFU

Up to 96 hours
7-14 days IV study drug therapy
7 days from last dose IV study drug

Day 28  
Day 60

*Adjunctive therapy per investigator for BSI, HABP/VABP patients only; optional oral step-down after ≥4 days IV for cUTI/AP. AP, acute pyelonephritis; cUTI, complicated urinary tract infection; EOS, end of study; IV, intravenous; LFU, late follow up; q8h, every 8 hours; q12h, every 12 hours; q24h, every 24 hours; TDM, therapeutic drug management; TOC, test of cure.
Primary efficacy analysis population included patients with BSI or HABP/VABP due to CRE.
CRE = meropenem MIC of ≥4 µg/mL, or a meropenem MIC of 2 µg/mL and disk diffusion zone ≤19 mm on central laboratory testing.
ITT, intent-to-treat; MIC, minimum inhibitory concentration; mMITT, microbiological modified intent-to-treat.
CARE Baseline Characteristics
Well Balanced Across Treatment Groups Overall

<table>
<thead>
<tr>
<th>Baseline Characteristic (mMITT Population)</th>
<th>Plazomicin (N = 17)</th>
<th>Colistin (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD</td>
<td>66.7 ± 12</td>
<td>63.1 ± 19</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>12 (70.6)</td>
<td>10 (50.0)</td>
</tr>
<tr>
<td>APACHE II score, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 to 20</td>
<td>10 (58.8)</td>
<td>11 (55.0)</td>
</tr>
<tr>
<td>21 to 30</td>
<td>6 (35.3)</td>
<td>9 (45.0)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>1 (5.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Infection type, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSI</td>
<td>14 (82.4)</td>
<td>15 (75.0)</td>
</tr>
<tr>
<td>HABP/VABP</td>
<td>3 (17.6)</td>
<td>5 (25.0)</td>
</tr>
<tr>
<td>Baseline pathogens, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monomicrobial</td>
<td>14 (82.4)</td>
<td>17 (85.0)</td>
</tr>
<tr>
<td>Polymicrobial</td>
<td>3 (17.6)</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Creatinine clearance, n (%)a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;90 mL/min</td>
<td>4 (23.5)</td>
<td>10 (50.0)</td>
</tr>
<tr>
<td>≤90 mL/min CRRT</td>
<td>7 (41.2)</td>
<td>6 (30.0)</td>
</tr>
<tr>
<td></td>
<td>4 (23.5)</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Adjunctive therapy, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meropenem</td>
<td>6 (35.3)</td>
<td>9 (45.0)</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>11 (64.7)</td>
<td>11 (55.0)</td>
</tr>
</tbody>
</table>

aCockcroft-Gault estimation; baseline central laboratory data not available for subset of patients in each arm.

APACHE, Acute Physiology and Chronic Health Evaluation; CRRT, continuous renal replacement therapy.
CARE Efficacy Results
Reduced Mortality at Day 28 for Plazomicin versus Colistin

BSI and HABP/VABP (mMITT Population)
Difference (colistin minus plazomicin) (90% CI)

26.5% (-0.7 to 51.2)
28.2% (0.7 to 52.5)

All-cause mortality at day 28 or significant complications

Plazomicin

Colistin

Two-sided 90% confidence interval (CI) calculated based on the unconditional exact method.
CARE Efficacy Results
Reduced Mortality at Day 28 for Plazomicin versus Colistin in BSI

BSI Subset (mMITT Population)
Difference (colistin minus plazomicin) (90% CI)

All-cause mortality at day 28 or significant complications

- Plazomicin: 14.3% (2/14)
- Colistin: 39.0% (8/15)

All-cause mortality at day 28

- Plazomicin: 7.1% (1/14)
- Colistin: 40.0% (6/15)

Two-sided 90% CI calculated based on the unconditional exact method.
CARE Kaplan-Meier Survival Curve

Sustained Survival Benefit in Plazomicin-treated Patients With BSI

60-day Survival in BSI Subset (mMITT Population)

HR for death (plazomicin:colistin) (90% CI)
0.37 (0.15-0.91)

Estimate of hazard ratio (HR) calculated as plazomicin:colistin based on Cox proportional hazards regression model.
**CARE Overall Summary of AEs and SAEs**

**Favorable Safety Profile for Plazomicin Versus Colistin**

<table>
<thead>
<tr>
<th>Adverse Event (Safety Population)</th>
<th>Plazomicin (N = 18) n (%)</th>
<th>Colistin (N = 21) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>16 (88.9)</td>
<td>21 (100.0)</td>
</tr>
<tr>
<td>Study drug-related</td>
<td>5 (27.8)</td>
<td>9 (42.9)</td>
</tr>
<tr>
<td>Led to discontinuation of study drug</td>
<td>2 (11.1)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Related to renal function</td>
<td>6 (33.3)</td>
<td>11 (52.4)</td>
</tr>
<tr>
<td>SAE</td>
<td>9 (50.0)</td>
<td>17 (81.0)</td>
</tr>
<tr>
<td>Study drug-related</td>
<td>1 (5.6)</td>
<td>4 (19.0)</td>
</tr>
<tr>
<td>Led to death (up to day 60)</td>
<td>8 (44.4)</td>
<td>13 (61.9)</td>
</tr>
<tr>
<td>Related to renal function</td>
<td>2 (11.1)</td>
<td>6 (28.6)</td>
</tr>
</tbody>
</table>

- Reduced drug-related AEs, SAEs, and AEs related to renal function in plazomicin arm
- No study drug-related deaths or events of ototoxicity reported

AE, adverse event; SAE, serious adverse event.
### CARE Laboratory Parameters Associated With Renal Function

**Notable Reduction in Serum Creatinine Elevations in Plazomicin Arm**

<table>
<thead>
<tr>
<th>Serum Creatinine (Safety Population)a</th>
<th>Plazomicin (N = 18) n/N1 (%)</th>
<th>Colistin (N = 21) n/N1 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.5 mg/dL increase any time on study (including on or post IV therapy)</td>
<td>2/12 (16.7)</td>
<td>8/16 (50.0)</td>
</tr>
<tr>
<td>≥0.5 mg/dL increase while on IV therapy</td>
<td>1/12 (8.3)</td>
<td>6/16 (37.5)</td>
</tr>
<tr>
<td>Full recovery or improvementb</td>
<td>1/1</td>
<td>3/6</td>
</tr>
</tbody>
</table>

*aPatients starting CRRT prior to baseline were excluded from the analysis, as were all post-baseline serum creatinine measurements collected after start of CRRT.*

**b**Full recovery defined as last post-baseline serum creatinine value <0.5 mg/dL above the baseline value. Improvement defined as last post-baseline serum creatinine value ≥0.3 mg/dL less than the peak serum creatinine but not <0.5 mg/dL above the baseline value.
CARE Conclusions

• Patients with serious CRE infections had significant mortality and disease-related complications

• Plazomicin treatment was associated with reduced all-cause mortality at day 28

• Survival benefit in plazomicin-treated BSI patients was sustained through day 60

• Favorable safety profile for plazomicin-treated patients compared with colistin when used as part of a combination regimen for the treatment of life-threatening infections due to CRE

• Data from the CARE study suggest that plazomicin could offer an important new treatment option for patients with serious infections due to CRE
Acknowledgments

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