Plazomicin Versus Meropenem for the Treatment of Complicated Urinary Tract Infection and Acute Pyelonephritis: Results of the EPIC Study

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DJ Cloutier, AS Komirenko, DS Cebrik, KM Krause, TR Keepers, and LE Connolly are employees of and stockholders in Achaogen.

LG Miller has participated in advisory boards and received honoraria as a consultant for Achaogen and Tetraphase Pharmaceuticals and received research grants from Achaogen, Gilead Sciences, Merck, Abbott, and Cepheid.

FME Wagenlehner has participated in advisory boards and received honoraria as a consultant for Achaogen, Astellas, AstraZeneca, Bionorica, Cubist/MSD, Janssen, Leo-Pharma, Marpinion, MerLion, Pfizer, Vifor Pharma, Rempex, Rosen Pharma and received research grants from Deutsche Forschungsgemeinschaft (DFG) and Deutsches Zentrum für Infektionsforschung (DZIF).
Plazomicin Is a Next-generation Aminoglycoside for the Potential Treatment of MDR Enterobacteriaceae

- The structure of plazomicin protects it from most AMEs that inactivate existing aminoglycosides\(^1\)
  - AMEs co-travel with other resistance mechanisms, including \(\beta\)-lactamases and carbapenemases\(^1\)
- Inhibits bacterial protein synthesis and is rapidly bactericidal\(^2\)
- Potent in vitro activity against:
  - ESBL-producing Enterobacteriaceae\(^3\)
  - Carbapenem-resistant Enterobacteriaceae\(^3,4\)
  - Aminoglycoside-resistant Enterobacteriaceae\(^5\)
- IV, once-daily 30-minute infusion

AME, aminoglycoside-modifying enzyme; ESBL, extended-spectrum \(\beta\)-lactamase; MDR, multidrug resistant.
Evaluating Plazomicin in cUTI (EPIC)

A Phase 3, Randomized, Multicenter, Double-blind Study to Evaluate the Efficacy and Safety of Plazomicin Compared With Meropenem Followed by Optional Oral Therapy for the Treatment of Complicated Urinary Tract Infection (cUTI) and Acute Pyelonephritis (AP) in Adults

Primary Efficacy Endpoints for the EMA

Demonstrate noninferiority of plazomicin compared with meropenem based on the difference in microbiological eradication at the test-of-cure (TOC) visit in the microbiological modified intent-to-treat (mMITT) and microbiological evaluable (ME) populations

• 15% noninferiority margin (95% CI)

\(^a\)Registrational trial conducted in accordance with the EMA guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (15 December 2011) and addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (24 October 2013). This trial is registered at ClinicalTrials.gov: NCT02486627.

CI, confidence interval; EMA, European Medicines Agency.
Patients could receive levofloxacin or other approved oral therapy.

EOIV, end of intravenous therapy; IV, intravenous; LFU, late follow-up; PO, orally; q8h, every 8 hours; q24h, once every 24 hours.
**EPIC Baseline Characteristics**  
*Well Balanced Across Treatment Groups Overall*

<table>
<thead>
<tr>
<th>Baseline Characteristic (mMITT Population)</th>
<th>Plazomicin (n = 191)</th>
<th>Meropenem (n = 197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD</td>
<td>58.8 ± 18.0</td>
<td>60.0 ± 17.9</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>84 (44.0)</td>
<td>99 (50.3)</td>
</tr>
<tr>
<td>cUTI, n (%)</td>
<td>107 (56.0)</td>
<td>119 (60.4)</td>
</tr>
<tr>
<td>AP, n (%)</td>
<td>84 (44.0)</td>
<td>78 (39.6)</td>
</tr>
<tr>
<td>CrCl &gt;60-90 mL/min, n (%)</td>
<td>70 (36.6)</td>
<td>75 (38.1)</td>
</tr>
<tr>
<td>CrCl &gt;30-60 mL/min, n (%)</td>
<td>61 (31.9)</td>
<td>71 (36.0)</td>
</tr>
</tbody>
</table>

- 98.5% of patients enrolled from Eastern Europe
EPIC Efficacy Results
Superior Eradication Rates With Plazomicin at TOC

Primary Endpoints

Difference (plazomicin minus meropenem) (95\% CI)

mMITT: 15.4 (7.5 to 23.2)$^a$

ME: 13.9 (6.3 to 21.7)$^a$

Microbiological eradication (%)

87.4\% 72.1\%

80
70
60
50
40
30
20
10
0

167/191 142/197

TOC (mMITT)

90.5\% 76.6\%

100
90
80
70
60
50
40
30
20
10
0

162/179 134/175

TOC (ME)

aLower bound of the CI exceeds zero.

Eradication defined as all baseline uropathogen(s) reduced to $<10^3$ CFU/mL. Patients with an indeterminate response at TOC were excluded from the ME population.

CFU, colony-forming unit.
EPIC Efficacy Results
Plazomicin Superior in cUTI and AP

Microbiological Eradication at TOC by Infection Type (mMITT Population)
Point estimate for difference (plazomicin minus meropenem) with 95% CI

Eradication defined as all baseline uropathogen(s) reduced to <10³ CFU/mL.

NI, noninferiority.
EPIC Efficacy Results: IV Only and IV Plus Oral Subgroups
No Evidence Oral Switch Contributed to Treatment Difference at TOC

Microbiological Eradication at TOC (mMITT Population)

Difference (plazomicin minus meropenem) (95% CI)

- IV only: 18.6 (-0.69 to 36.2)
- IV plus oral: 14.1 (5.5 to 22.9)

Microbiological eradication (%)

- Plazomicin: 83.8% (31/37)
- Meropenem: 65.2% (30/46)
- Plazomicin: 88.3% (136/154)
- Meropenem: 74.2% (112/151)

Oral therapy includes levofloxacin or other approved oral antibiotic. Eradication defined as all baseline uropathogen(s) reduced to <10³ CFU/mL.
## EPIC Efficacy Results

### Higher Per-pathogen Eradication at TOC in Resistant Subgroups

<table>
<thead>
<tr>
<th>Baseline Uropathogen (ME Population)</th>
<th>Plazomicin n/N (%)</th>
<th>Meropenem n/N (%)</th>
<th>% Difference (Plazomicin Minus Meropenem) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enterobacteriaceae</strong></td>
<td>167/185 (90.3)</td>
<td>141/182 (77.5)</td>
<td>12.8 (5.4 to 20.4)</td>
</tr>
<tr>
<td>ESBL(+)a</td>
<td>40/48 (83.3)</td>
<td>41/55 (74.5)</td>
<td>8.8 (-7.5 to 24.4)</td>
</tr>
<tr>
<td>Levofloxacin-nonsusceptibleb</td>
<td>60/72 (83.3)</td>
<td>60/83 (72.3)</td>
<td>11.0 (-2.3 to 23.9)</td>
</tr>
<tr>
<td>Aminoglycoside-nonsusceptiblec</td>
<td>42/52 (80.8)</td>
<td>35/51 (68.6)</td>
<td>12.1 (-4.8 to 28.7)</td>
</tr>
<tr>
<td><strong>Escherichia coli</strong></td>
<td>114/122 (93.4)</td>
<td>93/121 (76.9)</td>
<td>16.6 (8.0 to 25.7)</td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae</strong></td>
<td>25/29 (86.2)</td>
<td>31/40 (77.5)</td>
<td>8.7 (-11.2 to 26.7)</td>
</tr>
<tr>
<td><strong>Enterobacter cloacae</strong></td>
<td>12/15 (80.0)</td>
<td>2/2 (100)</td>
<td>-20.0 (-46.0 to 50.4)</td>
</tr>
<tr>
<td><strong>Proteus mirabilis</strong></td>
<td>9/11 (81.8)</td>
<td>4/7 (57.1)</td>
<td>24.7 (-18.1 to 63.1)</td>
</tr>
</tbody>
</table>

aESBL(+) defined as MIC of ≥2 µg/mL to aztreonam, ceftazidime, or ceftaxone. bLevofloxacin nonsusceptible per 2016 EUCAST criteria. cAminoglycoside nonsusceptible to amikacin, gentamicin, or tobramycin per 2016 EUCAST criteria.

Eradication defined as baseline uropathogen(s) reduced to <10³ CFU/mL.

**EUCAST**, European Committee on Antimicrobial Susceptibility Testing; **MIC**, minimum inhibitory concentration.
**EPIC Efficacy Results**

*Lower Relapse Rate at Late Follow-up in Plazomicin-treated Patients*

Clinical relapse defined as worsening relative to baseline, any new symptom relative to baseline, or no return to pre-morbid status of any core symptoms of cUTI. Late follow-up (LFU) visit 24-32 days from 1st dose of IV study drug. Asymptomatic bacteriuria at TOC defined as clinical cure at TOC together with microbiological persistence at TOC (baseline uropathogen(s) ≥10³ CFU/mL).

**Clinical Relapse at LFU in Patients Who Were Clinical Cures at TOC**

(mMITT Population)

- **Plazomicin**: 1.8% relapse rate (3/170)
- **Meropenem**: 7.9% relapse rate (14/178)

19.5% clinical relapse rate with meropenem in subgroup of patients with asymptomatic bacteriuria at TOC.
# EPIC Summary of Most Common AEs

*Similar Safety Profile in Both Treatment Groups*

Most AEs were mild or moderate in severity

- Ototoxicity: single mild and reversible event in each treatment arm

<table>
<thead>
<tr>
<th>AEs in &gt;1% of Patients in Either Arm (Safety Population)</th>
<th>Plazomicin (N = 303) n (%)</th>
<th>Meropenem (N = 301) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>7 (2.3)</td>
<td>5 (1.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (2.3)</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (1.3)</td>
<td>9 (3.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (1.3)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (1.3)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (0.3)</td>
<td>4 (1.3)</td>
</tr>
</tbody>
</table>

Note: Patients reporting a particular AE (Preferred Term) more than once are counted only once by Preferred Term.
### EPIC Laboratory Parameters Associated With Renal Function

**Comparable Incidence of Serum Creatinine Increase on Treatment**

<table>
<thead>
<tr>
<th>Serum Creatinine (Safety Population)</th>
<th>Plazomicin n/N (%)</th>
<th>Meropenem n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.5 mg/dL increase any time on study (including on and/or post IV therapy)</td>
<td>21/300 (7.0)</td>
<td>12/297 (4.0)</td>
</tr>
<tr>
<td>≥0.5 mg/dL increase while on IV therapy</td>
<td>11/300 (3.7)</td>
<td>9/297 (3.0)</td>
</tr>
<tr>
<td>Full recovery at EOIV</td>
<td>6/11</td>
<td>4/9</td>
</tr>
<tr>
<td>Full recovery at last follow-up visit</td>
<td>9/11</td>
<td>9/9</td>
</tr>
</tbody>
</table>

Full recovery defined as serum creatinine value <0.5 mg/dL above the baseline value at the EOIV visit or last post-baseline measurement.
• Plazomicin demonstrated superiority for the primary endpoints of microbiological response at TOC in both the mMITT and ME populations

• Consistent with the primary results, plazomicin demonstrated higher microbiological eradication rates than meropenem at TOC in key subgroups, including patients with cUTI or AP and patients with resistant infections

• Higher incidence of clinical relapse at late follow-up was observed in the meropenem group, with the majority of relapses occurring in patients with asymptomatic bacteriuria at TOC

• Overall, plazomicin was well tolerated

• The incidence of serum creatinine increase while on IV therapy was similar between treatment groups, and slightly greater in plazomicin-treated patients at any time on study

• The results support plazomicin as a potential new treatment option for cUTI and AP, which could provide an alternative to carbapenems in the setting of suspected or documented resistance
Acknowledgments

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