Evaluating Once-daily Plazomicin Versus Meropenem for the Treatment of Complicated Urinary Tract Infection and Acute Pyelonephritis: Results From a Phase 3 Study (EPIC)

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Plazomicin Is a Next-generation Aminoglycoside for the Potential Treatment of MDR Enterobacteriaceae

- Structure protects it from most AMEs that inactivate other aminoglycosides
  - AMEs co-travel with other resistance mechanisms, including β-lactamases and carbapenemases
- Inhibits bacterial protein synthesis and is rapidly bactericidal
- Potent in vitro activity against:
  - ESBL-producing Enterobacteriaceae
  - Carbapenem-resistant Enterobacteriaceae
  - Aminoglycoside-resistant Enterobacteriaceae
- IV, once-daily 30-minute infusion

AME, aminoglycoside-modifying enzyme; ESBL, extended-spectrum β-lactamase; IV, intravenous; MDR, multidrug resistant.
Evaluating Plazomicin in cUTI (EPIC) Study

Co-Primary Efficacy Objectives for the FDA

Demonstrate noninferiority of plazomicin versus meropenem based on composite cure endpoint (achieve both microbiological eradication and clinical cure) in the microbiological modified intent-to-treat (mMITT) population:

• Composite cure at Day 5 visit
• Composite cure at Test-of-Cure (TOC; Day 15-19) visit
• 15% noninferiority margin (95% CI)

This trial is registered at ClinicalTrials.gov: NCT02486627.
CI, confidence interval; FDA, US Food and Drug Administration.
EPIC Study Design

**Screening**
- Randomization 1:1
- N = 609

**Signs/ symptoms of cUTI or AP**
- Within 36 hours before 1st dose IV study drug

**Treatment**
- **Plazomicin IV**
  - 15 mg/kg q24h
- **EOIV**
- ± **Levofloxacin PO**
  - 500 mg q24h

*4-7 days IV therapy, followed by optional oral therapy\(^a\) for a total of 7-10 days of therapy*

- **Meropenem IV**
  - 1 g q8h
- **EOIV**
- ± **Levofloxacin PO**
  - 500 mg q24h

**Follow-up**
- **TOC**
- **LFU**

- **Study days 1-4** (IV study drug)
- **Study days 5 to ≤10** (IV study drug >4 days and/or oral switch)
- **15-19 days from 1st dose IV study drug**
- **24-32 days from 1st dose IV study drug**

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\(^a\)Patients could receive levofloxacin or other approved oral therapy.

EOIV, end of intravenous therapy; LFU, late follow-up; PO, orally; q8h, every 8 hours; q24h, once every 24 hours.
EPIC Patient Disposition
Primary Reason for Exclusion From mMITT Was Lack of Study-qualifying Uropathogen

N = 609
ITT

n = 306 (100%)
Plazomicin

n = 303 (99.0%)
Safety

n = 191 (62.4%)
mMITT

All randomized patients

n = 303 (100%)
Meropenem

n = 301 (99.3%)
Safety

n = 197 (65.0%)
mMITT

Patients who received any amount of IV study drug

Patients who had ≥1 uropathogen in a qualifying baseline urine culture that was susceptible to both IV study drugs

ITT, intent-to-treat; mMITT, microbiological modified intent-to-treat.
### EPIC Baseline Characteristics

*Well Balanced Across Treatment Groups Overall*

<table>
<thead>
<tr>
<th>Baseline Characteristic (mMITT Population)a</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>70/188 (37.2)</td>
<td>75/194 (38.7)</td>
</tr>
<tr>
<td>CrCl &gt;30-60 mL/min, n (%)</td>
<td>61/188 (32.4)</td>
<td>71/194 (36.6)</td>
</tr>
<tr>
<td>Urosepsisb</td>
<td>39 (20.4)</td>
<td>34 (17.3)</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>25 (13.1)</td>
<td>23 (11.7)</td>
</tr>
</tbody>
</table>

*aPercentages are calculated as n/N unless stated otherwise. bDefined according to SIRS criteria.*

- 98.5% of patients enrolled from Eastern Europe

**AP**, acute pyelonephritis; **cUTI**, complicated urinary tract infection; **CrCl**, creatinine clearance; **SIRS**, systemic inflammatory response syndrome.
EPIC Efficacy Results

Plazomicin Successfully Achieved Primary Efficacy Objectives

*Co-Primary Endpoints

Composite Cure (mMITT)
Difference plazomicin minus meropenem (95% CI)

-3.4 (-10.0 to 3.1)
-1.2 (-6.5 to 4.0)
11.6 (2.7 to 20.3)a

Composite Cure (%)

Plazomicin: 88.0%, 93.7%, 81.7%
Meropenem: 91.4%, 94.9%, 70.1%

Day 5* 168/191 179/191 156/191
EOIV 180/197 187/197 138/197
TOC* 11.6 (2.7 to 20.3)a

aLower bound of the CI exceeds zero. Composite cure: achieve both microbiological eradication (reduction in all baseline uropathogens to <10⁴ CFU/mL in urine culture) and clinical cure (significant improvement [Day 5 and EOIV] or complete resolution [TOC] in all signs and symptoms of the infection).

CFU, colony-forming units; EOIV, end of IV therapy 4-8 days from 1st dose IV study drug; TOC, test of cure 15-19 days from 1st dose of IV study drug.
EPIC Efficacy Results: cUTI and AP Subgroups

Higher Composite Cure Rates With Plazomicin in Both cUTI and AP

Composite Cure at TOC (mMITT)

Difference plazomicin minus meropenem (95% CI)

- 9.6 (-2.6 to 21.3)
- 13.9 (0.4 to 27.1)\(^a\)

Composite cure (%)

84/107 Plazomicin 82/119 Meropenem
85.7% Plazomicin 71.8% Meropenem

68.9% Plazomicin 72/84 Plazomicin 56/78 Meropenem
71.8% Meropenem

\(^a\)Lower bound of the CI exceeds zero. Percentages are calculated as n (number of patients in specified category)/N1 (number of patients in the specified subgroup [cUTI or AP]).
EPIC Efficacy Results: Bacteremia Subgroup
Favorable Composite Cure Rates With Plazomicin at TOC in Patients With Bacteremia

Composite Cure at TOC (mMITT)

Difference plazomicin minus meropenem (95% CI)

72.0% 18/25
56.5% 13/23

Percentages are calculated as n (number of patients in specified category)/N1 (number of patients in the specified subgroup [bacteremia]).
EPIC Efficacy Results: IV Only and IV Plus Oral Subgroups

No Evidence Oral Switch Contributed to Treatment Difference at TOC

Composite Cure at TOC (mMITT)

Difference plazomicin minus meropenem (95% CI)

17.5 (-4.3 to 36.6)

9.6 (-0.2 to 19.3)

**Oral therapy includes levofloxacin or other approved oral antibiotic.**

Percentages are calculated as n (number of patients in specified category)/N1 (number of patients in the specified subgroup [IV only or IV plus oral]).
EPIC Efficacy Results

Significantly Higher Eradication Rates With Plazomicin at TOC and LFU

Eradication Rates (mMITT)

Difference plazomicin minus meropenem (95% CI)

- TOC: 14.9 (7.0 to 22.7)^a
- LFU: 19.3 (10.4 to 27.9)^a

Microbiological eradication (%)

<table>
<thead>
<tr>
<th>Study</th>
<th>Plazomicin</th>
<th>Meropenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOC</td>
<td>89.5%</td>
<td>74.6%</td>
</tr>
<tr>
<td>LFU</td>
<td>84.3%</td>
<td>65.0%</td>
</tr>
<tr>
<td>Count</td>
<td>171/191</td>
<td>147/197</td>
</tr>
<tr>
<td></td>
<td>161/191</td>
<td>128/197</td>
</tr>
</tbody>
</table>

^aLower bound of the CI exceeds zero. Microbiological eradication defined as baseline uropathogen reduced to <10^4 CFU/mL.

TOC, test of cure 15-19 days from 1st dose IV study drug; LFU, late follow-up 24-32 days from 1st dose IV study drug.
Clinical Relapse at LFU in Patients Who Were Clinical Cures at TOC (mMITT)

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) ≥10^4 CFU/mL).
## EPIC Efficacy Results
### Higher Per-pathogen Eradication at TOC in Resistant Subgroups

<table>
<thead>
<tr>
<th>Baseline Uropathogen (mMITT Population)</th>
<th>Plazomicin (N = 191) n/N1 (%)</th>
<th>Meropenem (N = 197) n/N1 (%)</th>
<th>Difference (Plazomicin Minus Meropenem) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td>177/198 (89.4)</td>
<td>157/208 (75.5)</td>
<td>13.9 (6.2 to 21.5)</td>
</tr>
<tr>
<td>ESBL(+)a</td>
<td>42/51 (82.4)</td>
<td>45/60 (75.0)</td>
<td>7.4 (-9.6 to 23.1)</td>
</tr>
<tr>
<td>Aminoglycoside-nonsusceptibleb</td>
<td>41/52 (78.8)</td>
<td>35/51 (68.6)</td>
<td>10.2 (-8.1 to 27.8)</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>120/128 (93.8)</td>
<td>106/142 (74.6)</td>
<td>19.1 (10.0 to 27.9)</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>27/33 (81.8)</td>
<td>32/43 (74.4)</td>
<td>7.4 (-13.9 to 26.5)</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>9/11 (81.8)</td>
<td>4/7 (57.1)</td>
<td>24.7 (-21.4 to 64.5)</td>
</tr>
<tr>
<td><em>Enterobacter cloacae</em></td>
<td>13/16 (81.3)</td>
<td>3/3 (100)</td>
<td>-18.8 (-46.3 to 51.6)</td>
</tr>
</tbody>
</table>

aESBL(+) defined as MIC of ≥2 μg/mL to aztreonam, ceftazidime, or ceftriaxone. bAminoglycoside not susceptible to amikacin, gentamicin, or tobramycin per 2016 CLSI criteria.

Microbiological eradication defined as baseline uropathogen reduced to <10^4 CFU/mL.

CLSI, Clinical Laboratory Standards Institute; ESBL, extended-spectrum β-lactamase; MIC, minimum inhibitory concentration.
EPIC Summary of Most Common AEs
Similar Safety Profile in Both Treatment Groups

**AEs in >1% of Patients in Either Treatment Group (Safety Population)**

<table>
<thead>
<tr>
<th>AEs</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.

- Most AEs were mild or moderate in severity
- Ototoxicity: single mild and reversible event in each treatment group
- 1 death in the plazomicin group due to preexisting cancer, considered unrelated to study drug

AE, adverse event.
<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 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>
<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>
</tbody>
</table>

Full recovery defined as serum creatinine value <0.5 mg/dL above the baseline value at the EOIV visit or last postbaseline measurement.
**EPIC Laboratory Parameters Associated With Renal Function**

*Higher Incidence of Serum Creatinine Increase Post IV Therapy*

<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 post IV therapy only</td>
<td>10/300 (3.3)</td>
<td>3/297 (1.0)</td>
</tr>
</tbody>
</table>

- Majority of plazomicin-treated patients with post IV therapy increases had moderate renal impairment (CrCl 30-60 mL/min) at baseline (9/10 patients), and serum creatinine increases <1.0 mg/dL (8/10 patients)

- Among 4 patients with follow-up assessments, 3 patients met the criteria for full recovery\(^a\)

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\(^a\)Full recovery defined as serum creatinine value <0.5 mg/dL above the baseline value at the last postbaseline measurement.
EPIC Conclusions

- Plazomicin successfully met the primary objective of noninferiority, while demonstrating a significantly higher composite cure rate than meropenem at TOC.

- Consistent with the primary results, plazomicin demonstrated higher composite cure rates than meropenem at TOC in key subgroups, including patients with cUTI or AP and patients with bacteremia.

- Plazomicin was associated with higher microbiological eradication rates at TOC overall and in patients with ESBL(+) and aminoglycoside-resistant infections.

- Higher incidence of clinical relapse at LFU 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 post IV therapy.

- 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.
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