Omadacycline in female adults with acute pyelonephritis: Results from a randomized, double-blind, adaptive phase 2 study

Omadacycline demonstrated high clinical success rates despite not meeting noninferiority criteria versus levofloxacin in women with acute pyelonephritis

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Background

Acute pyelonephritis is a common infection of the kidney and renal pelvis. It occurs most often in young adult women (ages 15–29 years), and accounts for >150,000 hospitalizations per year in the US. Escherichia coli is the most common cause of infection, and current guidelines recommend outpatient treatment with oral fluoroquinolones.

Omadacycline has in vitro activity against most common uncomplicated urinary tract infection uropathogens, most notably E. coli and Staphylococcus saprophyticus.

Omadacycline is the first member of the aminomethylcycline class, and is currently approved in the US for community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections in adults.

Methods

In this randomized, double-blind, double-dummy, adaptive-designed phase 2 study, females aged ≥18 years with acute uncomplicated pyelonephritis were randomly assigned to one of four iv-bolus regimens: omadacycline (OMC) or a 1-second bolus of levofloxacin (LVX) in a 2:1 randomized allocation of the blinded treatment (study group: OMC 27–70%, LVX 75%). The planned duration of study therapy was 7–10 days (IV only, or IV + oral); subjects with bacteremia confirmed from local blood cultures drawn at screening were randomized up to 14 days of therapy. The randomization algorithm was subsequently adapted by the data monitoring committee following interim analyses of efficacy in the group treated with OMC.

Clinical success rates were high in both groups, although no OMC treatment group met criteria for noninferiority to LVX.

Primary and secondary efficacy were assessed for noninferiority according to:

• Based on interim analysis of the mITT population by the data monitoring committee (DMC), randomization into OMC Groups 2–4 was stopped because of lower response rates.

Clinical success rates for the intent-to-treat (ITT) population of OMC were high for all groups (OMC 83–94%, LVX 93%; Figure 1).

Clinical success rates at PTE were high for all groups (OMC 83–94%, LVX 93%; Table 1). Based on interim analysis of the mITT population by the DMC, randomization into OMC Groups 2–4 was stopped because of lower response rates.

Further evaluation of available pharmacokinetic data and knowledge pharmacodynamic drivers of efficacy for AP is warranted to determine an optimal dose–response relationship.

Results

(Total patients were randomized: OMC n=188, LVX n=76)

• Based on interim analysis of the mITT population by the data monitoring committee (DMC), randomization into OMC Groups 2–4 was stopped because of lower response rates.

Table 1. Study design and dosing groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Treat agent</th>
<th>Days Dose 1</th>
<th>Days Dose 2–10</th>
<th>Days 1–10</th>
<th>Days 1–20</th>
<th>Days 1–21</th>
<th>Days 1–28</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OMC 200 mg IV</td>
<td>100 mg PO</td>
<td>100 mg PO</td>
<td>100 mg PO</td>
<td>200 mg IV</td>
<td>200 mg IV</td>
<td>200 mg IV</td>
</tr>
<tr>
<td>2</td>
<td>OMC 300 mg PO</td>
<td>150 mg PO</td>
<td>150 mg PO</td>
<td>150 mg PO</td>
<td>300 mg PO</td>
<td>300 mg PO</td>
<td>300 mg PO</td>
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<tr>
<td>3</td>
<td>OMC 450 mg PO</td>
<td>225 mg PO</td>
<td>225 mg PO</td>
<td>225 mg PO</td>
<td>450 mg PO</td>
<td>450 mg PO</td>
<td>450 mg PO</td>
</tr>
<tr>
<td>4</td>
<td>OMC 600 mg PO</td>
<td>300 mg PO</td>
<td>300 mg PO</td>
<td>300 mg PO</td>
<td>600 mg PO</td>
<td>600 mg PO</td>
<td>600 mg PO</td>
</tr>
<tr>
<td>LVX</td>
<td>LVX 750 mg IV</td>
<td>LVX 750 mg IV</td>
<td>LVX 750 mg IV</td>
<td>LVX 750 mg IV</td>
<td>LVX 750 mg IV</td>
<td>LVX 750 mg IV</td>
<td>LVX 750 mg IV</td>
</tr>
</tbody>
</table>

Primary and secondary efficacy were assessed for noninferiority according to:

• Investigators’ assessment of clinical response (ACR) to the study drug at the end of therapy (EOT).

Secondary efficacy was assessed for noninferiority according to:

• Clinical success rates at post-therapy evaluation (PTE; Day 21) and end of therapy (EOT).

Clinical success rates at PTE were high for all groups (OMC 83–94%, LVX 93%); Table 1). Based on interim analysis of the mITT population by the DMC, randomization into OMC Groups 2–4 was stopped because of lower response rates.

Clinical success rates were high in both groups, although no OMC treatment group met criteria for noninferiority to LVX.

Clinic success rates at PTE were high for all groups (OMC 83–94%, LVX 93%; Table 1). Based on interim analysis of the mITT population by the DMC, randomization into OMC Groups 2–4 was stopped because of lower response rates.

Further evaluation of available pharmacokinetic data and knowledge pharmacodynamic drivers of efficacy for AP is warranted to determine an optimal dose–response relationship.