Dietary Oxalate Ingestion, Urinary Oxalate Levels, and Response to Reloxaliase in Three Phase II Studies

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Background

Enteric hyperoxaluria (EH) is a serious metabolic disorder that affects approximately 250,000 people in the United States. EH is characterized by excessive urinary oxalate (UOx) excretion that is a complication of increased oxalate absorption due to an underlying gastrointestinal (GI) condition associated with malabsorption (eg, ileal disease, short-bowel syndrome [SBS], inflammatory bowel disease [IBD]) (Figure 1).1

Chronically elevated UOx is a major risk factor for progression of kidney stone (KS) disease. KS and inflammation due to oxalate crystal deposition cause permanent damage to the renal parenchyma, which can lead to chronic kidney disease (CKD) and end-stage renal disease (ESRD).1

Methods

• A composite analysis of data from phase I studies of reloxaliase was performed, which included 18 subjects with EH (Table 1).2

• There were no pharmacological therapies for EH. Current management consists of recommendations to restrict dietary oxalate and increase calcium and fluid intake, but these may be difficult to sustain or may be of limited efficacy, especially in subjects with enteric disorders associated with malabsorption.

• Reloxaliase is an oral enzyme that degrades oxalate within the GI tract, aligns with the pathophysiology of EH.

• Reloxaliase appears well tolerated, with gastrointestinal complaints being the most commonly reported adverse event.

• There was a consistent reduction in EH subjects with higher baseline levels of UOx (Figure 2). A subgroup analysis of Studies 396, 206, and 713 evaluated UOx response in subjects with ≥50 mg/24 h dietary oxalate at baseline. (Note: ≥50 mg is the minimum UOx baseline and screening entry criterion for (D0X01). The results are presented in Figure 2.)

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• Subjects with hyperoxaluria and KS disease are at a higher risk of CKD. High UOx excretion is associated with the risk of CKD progression.3 Higher UOx levels are associated with increased risk of new-onset ESRD.4 After kidney transplant, oxalate deposition in renal allograft biopsies is associated with allograft dysfunction.5 Transplant recipients with biopsy-confirmed calcium oxalate crystal deposition had significantly higher risk of death or graft failure.6

We hypothesized that subjects with higher baseline levels of UOx may show increased responsiveness to reloxaliase therapy (ie, reloxaliase) that degrades dietary oxalate through the GI tract. Data from subjects with EH from these phase II studies were analyzed to examine this hypothesis.

Results

• Consistent reductions in UOx were observed in subjects with EH (Figure 2). A subgroup analysis of Studies 396, 206, and 713 evaluated UOx response in subjects with ≥50 mg/24 h dietary oxalate at baseline. (Note: ≥50 mg is the minimum UOx baseline and screening entry criterion for (D0X01).) The results are presented in Figure 2.

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Conclusions

• The mechanism of action of reloxaliase, to degrade oxalate within the GI tract, aligns with the pathophysiology of EH.

• With severe hyperoxaluria, subjects are at higher risk for kidney stone disease and CKD/ESRD; reloxaliase has the potential to address a significant unmet medical need by reducing UOx excretion in this high-risk population.

Table 1. Summary of Allenia Phase II Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Study Design</th>
<th>Reloxaliase Dose</th>
<th>Baseline v3 Disease</th>
<th>Subjects (N)</th>
<th>3-Month Baseline v3 UOx (mg/24 h)</th>
<th>Percent Change in UOx (% from Baseline to 3 Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 396 (4 Weeks)</td>
<td>Phase I</td>
<td>Randomized, open-label study</td>
<td>7,500 units Once daily (5 capsules)</td>
<td>≥40 mg/24 h</td>
<td>≥50 mg/24 h</td>
<td>-58 ± 20 g</td>
<td>-33% (n=10)</td>
</tr>
<tr>
<td>Study 206 (12 Weeks)</td>
<td>Phase I</td>
<td>Randomized, open-label study</td>
<td>7,500 units 3 per day</td>
<td>POx &gt;5 µmol/L</td>
<td>eGFR &lt;45 mL/min/1.73 m</td>
<td>-25 ± 8 mg/24 h</td>
<td>-5% (n=5)</td>
</tr>
<tr>
<td>Study 713 (4 Weeks)</td>
<td>Phase I</td>
<td>Randomized, open-label study</td>
<td>7,500 units Once daily (5 capsules)</td>
<td>≥36 mg/24 h</td>
<td>eGFR &gt;60 mL/min/1.73 m</td>
<td>-33 ± 11 mg/24 h</td>
<td>-12% (n=3)</td>
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Table 2. Demographic and Baseline Characteristics of EH Subjects from Three Phase II Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Phase</th>
<th>Gender (M/F)</th>
<th>Age (y)</th>
<th>BMI (kg/m²)</th>
<th>eGFR (mL/min/1.73 m²)</th>
<th>POx (µmol/L)</th>
<th>UOx (mg/24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 396</td>
<td>11</td>
<td>Phase I</td>
<td>6/5</td>
<td>48±10</td>
<td>27±3</td>
<td>-22±7</td>
<td>5±0</td>
<td>-25±7</td>
</tr>
<tr>
<td>Study 206</td>
<td>6</td>
<td>Phase I</td>
<td>3/3</td>
<td>47±12</td>
<td>26±3</td>
<td>-19±6</td>
<td>5±0</td>
<td>-21±6</td>
</tr>
<tr>
<td>Study 713</td>
<td>11</td>
<td>Phase I</td>
<td>5/6</td>
<td>48±10</td>
<td>27±3</td>
<td>-22±7</td>
<td>5±0</td>
<td>-25±7</td>
</tr>
</tbody>
</table>

References


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