LBA01-08
Kidney Stone Risk and Association with Urine Oxalate Levels in Enteric Hyperoxaluria
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Disclosures

- Allena Pharmaceutical – Scientific Study
- NIH/NIDDK – Scientific Study
- NCI – Scientific Study
The Pathophysiology of Enteric Hyperoxaluria

**Enteric Hyperoxaluria (EH)**

- **Definition**: Elevated urine oxalate excretion due to excess absorption of oxalate from the GI tract due to fat malabsorption

- **Mechanism**: Fatty acids bind calcium within the small bowel, resulting in unbound oxalate that is then free to be systemically absorbed in the colon, increasing renal oxalate excretion

- **Clinical Consequences**: Increased risk of CaOx nephrolithiasis and CaOx deposition within the renal interstitium leading to inflammation, CKD and even ESRD
Epidemiology of Enteric Hyperoxaluria

It is estimated that there are ~250,000 EH patients in the US: 40% have recurrent stones and 74% have CKD.

Risk of Kidney Stones Increases Progressively with Urine Oxalate Levels: A Recognized Phenomenon

Assuming a non-linear relation, pooled across the three datasets, the multivariate RR* per 20% higher oxalate:

\[ RR = 1.25 \ (1.14, 1.36); \ p<0.001 \]

*adjusted for age and other 24-hr urinary risk factors

HPFS = Health Professional Follow-up Study; NHS = Nurses Health Study
Reloxaliase: A First-in-class Therapeutic Candidate for EH

**Target Production Characteristics**

- Crystalline Oxalate-Specific Enzyme
- Oral Capsule Formulation
- Taken with Food
- Non-Absorbed/Non-Systemic
- Room Temperature Stability

**Mechanism of Action**

Oxalate Degradation in the Gastrointestinal Tract

- Reloxaliase
- By-Products for Excretion
Patients with Enteric Hyperoxaluria Have a High Burden of Kidney Stones: Data from Reloxaliase Program Phase 2

Study 713: Patient Examples

- Celiac disease
  - 3 stones in last 2 years
  - (4 stones visible by CT)

- Gastric Bypass
  - 8 stones in the last 5 years
  - (3 stones visible by CT)

- Whipple (Pancreatic Insufficiency)
  - 14 stones in last 5 years
  - (16 stones visible by CT)

• Very high baseline UOx, mean ~100 mg/24h
• On average, EH subjects had experienced 6 stones prior to enrollment
• On average, 3 kidney stones visible by routine CT scan at time of enrollment

Nigwekar, et al. Presented at the American Society of Nephrology Kidney Week 2018, San Diego, CA
URIROX-1: A Phase 3 Study Evaluating the Safety and Efficacy of Reloxaliase in Patients with Enteric Hyperoxaluria

**Primary Endpoint**
- Percent change from baseline in 24h UOx excretion during Weeks 1 to 4

**Key Secondary Endpoint**
- Proportion of subjects with a ≥ 20% reduction from baseline in 24h UOx excretion during Weeks 1 to 4

**Pre-Specified, Stratified Analysis**
- Subset analysis of the primary and lead secondary endpoint in subjects with a history of bariatric surgery
## URIROX-1: Patient Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Category / Statistic</th>
<th>Reloxaliase (N=58)</th>
<th>Placebo (N=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) – Mean (SD)</td>
<td>58.7 (10.09)</td>
<td>58.6 (10.18)</td>
</tr>
<tr>
<td>Gender, n (%) Female</td>
<td>28 (48.3)</td>
<td>27 (47.4)</td>
</tr>
<tr>
<td>Enteric condition, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bariatric surgery [Roux-en-Y gastric bypass]</td>
<td>40 (69.0) [27 (46.6)]</td>
<td>38 (66.7) [27 (47.4)]</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>10 (17.2)</td>
<td>10 (17.5)</td>
</tr>
<tr>
<td>Short bowel syndrome</td>
<td>3 (5.2)</td>
<td>8 (14.0)</td>
</tr>
<tr>
<td>Pancreatic insufficiency</td>
<td>3 (5.2)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>2 (3.4)</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Baseline UOx (mg/24h) – Mean (SD)</td>
<td>87.3 (28.87)</td>
<td>91.1 (41.64)</td>
</tr>
<tr>
<td>Baseline UOx ≥ 90 mg/24h, n (%)</td>
<td>22 (37.9)</td>
<td>23 (40.4)</td>
</tr>
<tr>
<td>Number of kidney stone episodes in past 5 years- Mean (SD)</td>
<td>8.8 (27.49)</td>
<td>14.2 (43.23)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²) - Mean (SD)</td>
<td>76.4 (22.71)</td>
<td>80.5 (24.60)</td>
</tr>
<tr>
<td>CKD Stage 3, n (%)</td>
<td>16 (27.6)</td>
<td>14 (24.6)</td>
</tr>
</tbody>
</table>

### High Burden of Disease

- Baseline UOx of 89.2 mg/day
- Average 11 stone events in last 5 years
- 16.5% reported an adverse event associated with KS during study
- 26% CKD Stage 3

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1. Kidney stone events during the study period were approximately equally distributed between treatment and placebo groups.
URIROX-1 Primary Endpoint: Statistically Significant Reduction of UOx

- Achieved primary endpoint
- Highly statistically significant response vs. placebo (P=0.004)
- 22.6% reduction in UOx from baseline (LS mean)
- -14.3% LS mean treatment difference

*Percent change from Baseline in 24-hour UOx excretion during Weeks 1 to 4
URIROX-1: Primary Endpoint Sustained Over Time

Reloxaliase Demonstrates Sustained Reductions in UOx Across Weeks 1-4

URIROX-1

Week 0 Week 1 Week 2 Week 3 Week 4

Percent Change in UOx (%)

Random Coefficient: -1.1% per week

Reloxaliase Placebo
URIROX-1: Summary of Efficacy Results

<table>
<thead>
<tr>
<th></th>
<th>Overall Population</th>
<th>Pre-Specified Sub-Population Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reloxaliase (N=58)</td>
<td>Placebo (N=57)</td>
</tr>
<tr>
<td></td>
<td>Bariatric Reloxaliase (N=40)</td>
<td>Bariatric Placebo (N=38)</td>
</tr>
</tbody>
</table>

**PRIMARY ENDPOINT: Percent change in 24h UOx from Baseline during Weeks 1-4**

Comparison in percent change from baseline\(^a\)

<table>
<thead>
<tr>
<th>LS mean relative ratio (95% CI)(^b)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>-14.329 (-22.81, -4.92)</td>
<td>0.004</td>
</tr>
<tr>
<td>-16.190 (-26.68, -4.20)</td>
<td>0.010</td>
</tr>
</tbody>
</table>

**SECONDARY ENDPOINT: Proportion with ≥20% Reduction in 24h UOx from Baseline during Weeks 1-4**

<table>
<thead>
<tr>
<th>n/N (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>28/58 (48.3)</td>
<td>18/57 (31.6)</td>
</tr>
<tr>
<td>20/40 (50.0)</td>
<td>11/38 (28.9)</td>
</tr>
</tbody>
</table>

Comparison between treatments\(^c\)

<table>
<thead>
<tr>
<th>Odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.141 (0.97, 4.74)</td>
<td>0.061</td>
</tr>
<tr>
<td>2.891 (1.07, 7.82)</td>
<td>0.036</td>
</tr>
</tbody>
</table>

CI, confidence interval; LS, least squares; MMRM, mixed model repeated measures; N, number of subjects dosed; SE, standard error

\(^a\)Baseline is defined as the average of the UOx values derived from the two baseline 24-hour urine collections prior to randomization.

\(^b\)LS means, CIs, and p-values are based on an MMRM model.

\(^c\)Odds ratio, confidence interval, and p-value are from a stratified logistic regression model.
## URIROX-1 Safety Results
Reloxaliase continues to be well tolerated throughout clinical trials

<table>
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<th></th>
<th>Reloxaliase (n=58)</th>
<th>Placebo (n=57)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>TEAE(^1)</td>
<td>40 (69.0%)</td>
<td>30 (52.6%)</td>
</tr>
<tr>
<td>Severe TEAE</td>
<td>1 (1.7%)(^2)</td>
<td>0</td>
</tr>
<tr>
<td>Related TEAE</td>
<td>17 (29.3%)</td>
<td>11 (19.3%)</td>
</tr>
<tr>
<td>Serious TEAE (TESAE)</td>
<td>1 (1.7%)(^2)</td>
<td>0</td>
</tr>
<tr>
<td>Related TEAEs</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TEAEs Leading to Study Drug Withdrawal</td>
<td>0</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>TEAEs leading to Death</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

1  TEAE=Treatment Emergent Adverse Event are AEs with an onset or worsening at the time of or following the 1st dose of study drug through 7 days after the last dose
2  Sacral Radiculopathy that was unrelated to reloxaliase
URIROX-1 Confirms that High Urine Oxalate is Associated with Increased KS Burden

<table>
<thead>
<tr>
<th>UOx at Baseline (mg/24h)</th>
<th>&lt;90</th>
<th>&gt;90</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>66</td>
<td>43</td>
</tr>
<tr>
<td>KS mean (SE)</td>
<td>8.6 (3.4)</td>
<td>14.7 (6.9)</td>
</tr>
</tbody>
</table>

Available kidney stone history data within 5 years prior to enrollment

Higher UOx was associated with an increased rate of kidney stones both historically and during URIROX-1

Baseline UOx for Patients With or Without a KS Event During URIROX-1

<table>
<thead>
<tr>
<th>Patients</th>
<th>15*</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline UOx, mean (SE)</td>
<td>107.2 (14.7)</td>
<td>86.5 (3.1)</td>
</tr>
</tbody>
</table>

*Subjects reporting kidney stone passage
URIROX-2 Phase 3 Adaptive Design RCT: Efficient Assessment of Long-term Efficacy of Reloxaliase for Reducing UOx and Kidney Stone Disease Progression in EH

Key Study Design Elements
N=200
Enteric hyperoxaluria, 24-hr UOx ≥50 mg/d, prior history of KS, and eGFR ≥ 30 mL/min/1.73m²
Treatment: reloxaliase or placebo, 3-5x/d with meals/snacks for minimum 2 years
Assessments: 24-hour urine collections, imaging for kidney stones
Adaptive design: Two sample size reassessments to ensure sufficient KS events in long-term follow-up

Key Endpoints for Accelerated Approval
Primary: Percent change from baseline in 24h UOx excretion during Wks 1-4
Secondary:
  • Percent change from baseline in 24h UOx excretion during Wks 16-24
  • Bariatric surgery subgroup analyses

Long-term Efficacy Endpoints
Primary: Kidney stone disease progression*
Secondary:
  • Hospitalizations, ER visits, procedures for KS
  • Change in eGFR

*Composite of clinical stone events and asymptomatic stone growth on imaging
Conclusions

- Phase 3 URIROX-1 Study represents an important first step in addressing an unmet need for an effective therapeutic for patients with enteric hyperoxaluria (EH).
  - Confirms high KS burden in EH, and relationship between higher UOx and KS.
  - Reloxaliase meaningfully reduces 24-hour UOx excretion and is well tolerated.

- Measurement of 24-hour UOx is a clinically meaningful marker to assess kidney stone risk in patients with EH.

- URIROX-2, the ongoing Phase 3 trial designed to confirm the clinical benefit of reloxaliase with respect to kidney stone disease progression and kidney function, will advance the care of patients with EH.
  - Adaptive Design will support FDA filing using UOx for approval, to most efficiently address the unmet need for new therapeutics to treat hyperoxaluria in patients with EH.