A Phase 3, Randomized, Placebo-Controlled Trial of Reloxaliase in Enteric Hyperoxaluria (URIROX-1): Clinical Characteristics and Burden of Illness

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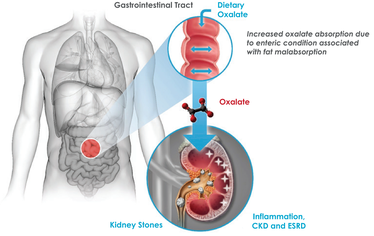
Background

Enteric hyperoxaluria (EH) is a serious metabolic disorder that affects approximately 250,000 people in the United States.

EH is characterized by excessive urine oxalate (UOx) excretion that is a complication of increased oxalate absorption due to an underlying gastrointestinal (GI) condition associated with fat malabsorption (eg. bariatric surgery, short-bowel syndrome [SBS], inflammatory bowel disease [IBD]) (**Figure 1**).[1,2]

Chronically elevated UOx is a major risk factor for progression of kidney stone (KS) disease.[1] 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).[1,3]

Figure 1. Schematic of Enteric Hyperoxaluria



There are no approved pharmacological therapies for EH. Current recommendations are to restrict dietary oxalate intake and increase calcium and fluid intake, but these are of limited efficacy and may be difficult to sustain, especially in EH.[4]

The clinical literature suggests that a 20% reduction in 24-hour UOx would translate to a 25%-50% reduction in the risk of KS.[5,6]

Reloxaliase (ALLN-177) is a first-in-class oral enzyme therapy that specifically targets oxalate and achieves its therapeutic effect by degrading oxalate within the GI tract, resulting in less systemic oxalate absorption and thereby lowering UOx excretion.[7,8]

Phase 2 trials in patients with secondary hyperoxaluria (HOx) showed reduction in 24-hour UOx with reloxaliase, particularly in EH.

Methods

Key Study Objectives

- Determine the efficacy of reloxaliase in reducing UOx excretion in patients with EH
- Evaluate the safety of reloxaliase in patients with EH

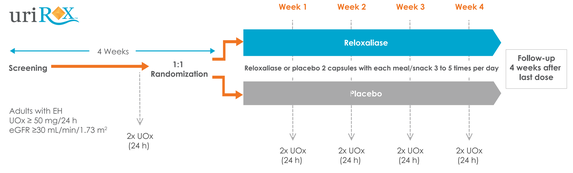
Study Design Elements (Figure 2)

- Phase 3, multi-center, randomized, double-blind, placebo-controlled study
- Planned enrollment: 124 subjects (to allow for 10% drop-out); key eligibility criteria are shown in **Table 1**
- Randomized 1:1 to receive reloxaliase (7,500 units) or placebo 3 to 5 times per day for 4 weeks
- Randomization was stratified by:
  1. Bariatric surgery vs other enteric condition
  2. Baseline UOx <90 vs ≥90 mg/24 h
  3. Use of proton pump inhibitors (PPI)/H_2 blockers vs not

Table 1. Eligibility Criteria

Key Inclusion Criteria
• ≥18 years of age • History of HOx, secondary to a known underlying enteric disorder associated with malabsorption • Adequate 24-hour urine collection at screening (UOx ≥50 mg/24 h) • Two adequate 24-hour urine collections at baseline (UOx ≥50 mg/24 h; neither <40 mg/24 h) • If on concomitant medication for management of KS risk factor, dose regimen stable for ≥8 weeks
Key Exclusion Criteria
• Unable or unwilling to discontinue vitamin C supplementation • Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 at screening • Active autoimmune disorder or other condition requiring systemic steroids or intensification of other immunosuppressant therapy • Prior receipt of clinical study drug or recent participation in other drug/device clinical trial

Figure 2. Study Design



Study Endpoints

Primary Efficacy Endpoint

- Percent change from baseline in 24-hour UOx excretion during Weeks 1-4

Secondary Efficacy Endpoints

- Proportion of subjects with a ≥20% reduction from baseline in 24-hour UOx excretion during Weeks 1-4
- Primary and secondary efficacy endpoints in bariatric surgery subgroup vs other enteric condition

Safety Assessments

- Treatment-emergent adverse events (TEAEs)
- Adverse events of special interest (KS passage; procedures, hospitalizations, or emergency room visits related to KS)
- Subgroup analyses of TEAEs and other selected safety parameters by underlying condition

Results

- Of 222 subjects screened, 115 were randomized and 114 completed the study; 1 subject from the placebo group discontinued prematurely
- Subjects' mean age was 59 years and 48% were female; demographic and baseline characteristics are summarized in **Table 2**
- The most common underlying enteric condition was bariatric surgery (68%) followed by IBD (17%). The distribution of underlying enteric conditions and CKD status are shown in **Table 2** and **Figure 4**.
- Overall, the mean (SD) UOx at baseline was 89.2 (35.7) mg/day, and 39% had UOx ≥90 mg/day
- The mean and median number of kidney stones historically reported by subjects in the past 5 years was 11.4 and 3.0, respectively; during the study, 19 subjects reported 32 KS events
- Overall treatment compliance was 97%

Table 2. Baseline Demographics and Characteristics

Category / Statistic	Reloxaliase (N=58)	Placebo (N=57)
Age (years), mean (SD)	58.7 (10.09)	58.6 (10.18)
Gender, n (%) Female	28 (48.3)	27 (47.4)
Race, n (%)		
Caucasian	56 (96.6)	54 (94.7)
Black or African American	0	3 (5.3)
American Indian or Alaska Native	1 (1.7)	0
Other	1 (1.7)	0
Enteric condition, n (%)		
Bariatric surgery [Roux-en-Y gastric bypass]	40 (69.0) [27 (46.6)]	38 (66.7) [27 (47.4)]
IBD	10 (17.2)	10 (17.5)
SBS	3 (5.2)	8 (14.0)
Pancreatic insufficiency	3 (5.2)	0
Other	2 (3.4)	1 (1.8)
Baseline UOx (mg/24 h), mean (SD)	87.3 (28.87)	91.1 (41.64)
Baseline UOx ≥90 mg/24 h, n (%)	22 (37.9)	23 (40.4)
eGFR (mL/min/1.73 m^2), mean (SD)	76.4 (22.71)	80.5 (24.60)
CKD stage 3, n (%)	16 (27.6)	14 (24.6)

SD, standard deviation.

Efficacy Results

- Subjects treated with reloxaliase for 4 weeks had a reduction in 24-hour UOx from a baseline of 87.3 to 71.2 mg/24 h across Weeks 1-4, representing a 22.6% reduction; subjects on placebo had a reduction from 91.1 to 84.6 mg/24 h, representing a 9.7% reduction. The treatment difference of −14.3% was highly statistically significant (p=0.0040). Refer to **Figure 3** and **Table 3**
- The proportion of subjects with a ≥20% reduction in 24-hour UOx was 48.3% in the reloxaliase group, compared with 31.6% in the placebo group (p=0.0605)
- In the bariatric surgery subgroup, subjects on reloxaliase had a 21.2% reduction in 24-hour UOx, compared with a 6.0% reduction on placebo; the treatment difference was −16.2% (p=0.0103)

Figure 3. Statistically Significant Reduction of UOx

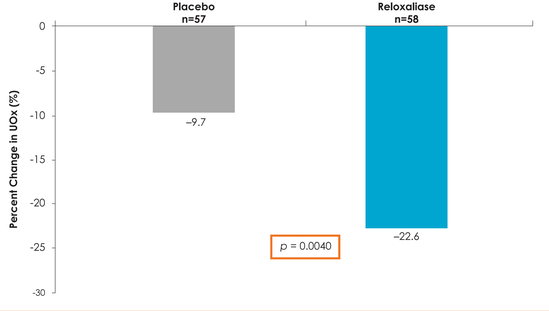


Table 3. Primary and Secondary Endpoints

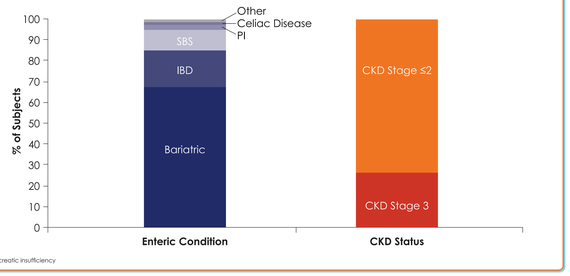
	Reloxaliase (N=58)	Placebo (N=57)
Primary Endpoint – Percent Change in 24-h UOx From Baseline During Weeks 1-4		
Baseline,[a] mean (SD)	87.3 (28.87)	91.1 (41.64)
Percent change from baseline, LS mean (log scale SE)	−22.6 (0.04)	−9.7 (0.04)
Comparison between treatments in percent change from baseline[b]	−14.329 (-22.806, -4.922)	
LS mean relative ratio, (95% CI) p-value	p=0.0040	
Secondary Endpoint – Proportion With ≥20% Reduction in 24-h UOx From Baseline During Weeks 1-4		
n/N* (%)	28/58 (48.3)	18/57 (31.6)
Comparison between treatments[c]	2.141 (0.967, 4.743)	
Odds ratio (95% CI), p-value	p=0.0605	

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]Odd ratio, confidence interval, and p-value are from a stratified logistic regression model.

Safety Results

- Reloxaliase was generally well tolerated. TEAEs were reported in 69% of reloxaliase-treated subjects compared with 53% of placebo subjects
- TEAEs were considered of mild or moderate intensity, except 1 severe TEAE, which was unrelated to reloxaliase
- No deaths and no related serious adverse events were reported. GI events reported by >2 subjects included, in reloxaliase and placebo, respectively: abdominal distension 8.6% and 3.5%, diarrhea 3.4% and 10.5%, dyspepsia 5.2% and 1.8%, flatulence 6.9% and 1.8%, and nausea 3.4% and 5.3%

Figure 4. Enteric Condition and CKD Status – Enrolled Subjects



PI, pancreatic insufficiency

Summary

- This phase 3 randomized, placebo-controlled trial (URIROX-1) demonstrated that reloxaliase significantly reduced 24-hour UOx over a 4-week treatment period by −22.6%, compared to placebo −9.7%. The treatment difference was −14.3% (p=0.004)
- Compliance with the study drug was very high (97%), with no difference between treatment groups
- Reloxaliase was well tolerated. There was a higher proportion of subjects on reloxaliase reporting AEs compared with placebo; these were mainly GI in nature
- The burden of KS disease and CKD is significant in this population, with the majority of subjects having multiple KS episodes in the previous 5 years; 16.5% had a KS episode during the study, and 26% had CKD

Conclusions

- Subjects were referred to the URIROX-1 study by nephrologists and urologists because of persistent HOx and recurrent KS, illustrating the limitations of existing therapeutic approaches and the opportunity for a novel therapy to reduce the kidney oxalate burden
- A confirmatory, randomized, placebo-controlled trial (URIROX-2) is currently under way. URIROX-2 is designed to establish the effect of reloxaliase on 24-hour UOx excretion and KS disease progression, as well as kidney function

References

1. Nazzal L, et al. Enteric hyperoxaluria: an important cause of end-stage kidney disease. *Nephrol Dial Transplant*. 2016;31(3):375-82.
2. Lieske JC, et al. Kidney stones are common after bariatric surgery. *Kidney Int*. 2015;87(4):839-45.
3. Zhao F, et al. Predictors of incident ESRD among patients with primary hyperoxaluria presenting prior to kidney failure. *Clin J Am Soc Nephrol*. 2016;11(1):119-26.
4. Nigwekar SU, et al. Unmet need in enteric hyperoxaluria: clinical characteristics and stone burden in patients from ALLN-177 studies. Paper presented at: American Society of Nephrology Kidney Week; October 23-28, 2018; San Diego, CA.
5. Curhan GC, et al. 24-h uric acid excretion and the risk of kidney stones. *Kidney Int*. 2008 Feb;73(4):489-96. Epub 2007 Dec 5.
6. Borghi L, et al. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. *N Engl J Med*. 2002 Jan 20;346(2):77-84.
7. Knauf F, et al. Study ALLN-177-206: case series of first four subjects with EH and advanced CKD treated with reloxaliase. Paper presented at: OHF International Hyperoxaluria Workshop; June 21-22, 2019; Boston, MA.
8. Nigwekar SU, et al. Results of a phase 2 randomized controlled trial of ALLN-177 in patients with secondary hyperoxaluria. Paper presented at: American Society of Nephrology Kidney Week; November 2, 2017; New Orleans, LA.

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Trial Information

Sponsor: Allena Pharmaceuticals
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For Information about recruitment and participating research centers:
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