Establishing the Safety and Efficacy of Reloxaliase in Patients With Enteric Hyperoxaluria (URIROX-2): A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study

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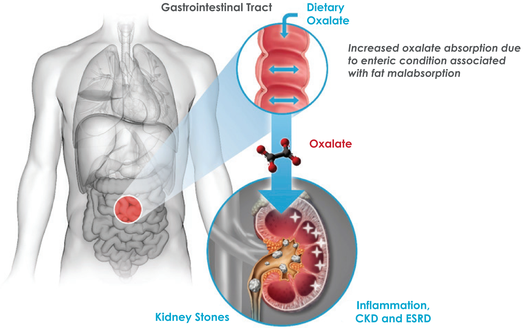
Background

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 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 management recommends restricting dietary oxalate and increasing calcium and fluid intake. These recommendations may be difficult to sustain or be of limited efficacy in subjects with enteric disorders associated with hyperoxaluria.

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

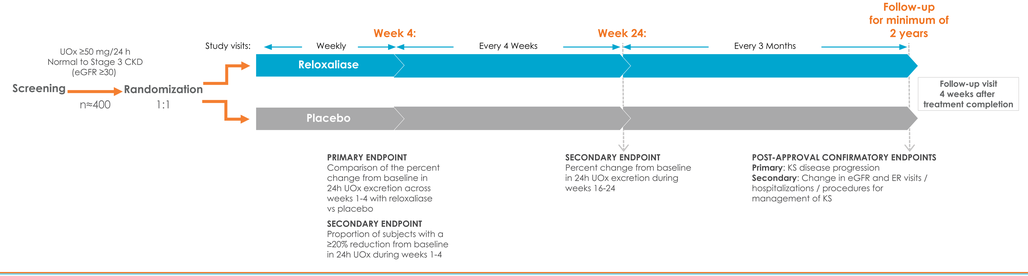
Study Objectives

- Determine the efficacy and long-term safety of reloxaliase in subjects with EH
- Evaluate the long-term effect of treatment with reloxaliase on KS disease progression and kidney function
- Assess the impact of treatment with reloxaliase on burden of illness (KS–associated healthcare resource utilization)
- Evaluate the long-term effect of reloxaliase on total kidney calcification burden
- Assess the effect of treatment with reloxaliase on patient-reported outcomes and quality of life (QoL)

Study Design

- URIROX-2 (Clinicaltrials.gov NCT03847090) is a phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of reloxaliase in subjects with EH (**Figure 2**). The study incorporates adaptive design elements that will, if necessary, allow for modification in sample size and duration of treatment to support confirmation of clinical benefit
- 400 subjects are being randomized 1:1 to either reloxaliase or placebo with stratification by: bariatric surgery vs other enteric condition, presence vs absence of KS(s) at baseline, renal ultrasound (RUS)/kidney, ureter, bladder x-ray (KUB) vs computed topography scan (CT) for sequential imaging, and use of proton pump inhibitors/H_2 blockers vs not
- Dose regimen:
  – Reloxaliase (284 mg or equivalent to 7,500 units) or matching placebo
  – 3-5 times per day with each meal/snack for a minimum of 2 years and up to 5 years
- URIROX-2 will provide long-term efficacy and safety assessments to support and expand week 4 results reported in URIROX-1 (ClincialTrials.gov NCT03456830)

Figure 2. Study Design



Methods

- 24-hour urine collections are performed at baseline, weekly for the first 4 weeks, every 4 weeks until week 24, then quarterly thereafter
- KS disease progression will be determined by RUS, KUB, and CT (**Figure 3**) at baseline, then serial imaging will be used to monitor for asymptomatic stone growth
- Symptomatic KS events will be captured. Imaging obtained for KS assessment will be centrally read

Figure 3. Imaging Modalities Used to Determine Kidney Stone Progression

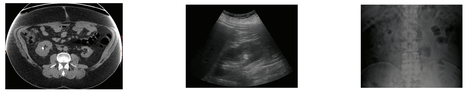


Table 1. Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• ≥18 years of age • Enteric disorder associated with malabsorption • UOx ≥50 mg/24 h at screening • Average 24-hour urine collections at baseline ≥50 mg/24 h (and neither <40 mg/24 h) • ≥1 KS within 2 years prior to screening • Stable doses of medications for management of KS risk factors (eg, thiazides, calcium supplements, alkali therapy, allopurinol) for ≥8 weeks prior to screening; no anticipated change during first 24 weeks of treatment	• Cannot discontinue vitamin C supplementation • eGFR <30 mL/min/1.73 m^2 at screening • Active autoimmune disorder or other condition requiring high doses of systemic steroids (ie, >10 mg/day prednisone or equivalent) or intensification of other immunosuppressant therapy

Table 2. Study Endpoints

Primary Efficacy Endpoint	Key Secondary Endpoints
• Percent change from baseline in 24-hour UOx excretion during weeks 1-4 **Primary Long-term Endpoint** • Proportion of participants with KS disease progression (composite of symptomatic stone(s) or finding of new or enlarged stone(s) on imaging)	• ≥20% reduction from baseline in 24-hour UOx excretion during weeks 1-4 • Percent change from baseline in 24-hour UOx excretion during weeks 16-24 • Percent change from baseline in 24-hour UOx excretion during weeks 1-4 and weeks 16-24 in the bariatric surgery subgroup **Secondary Long-term Endpoints** • Hospitalizations or emergency room visits or procedures for the management of KS • Change in estimated glomerular filtration rate (eGFR) from baseline
Safety Assessments	**Exploratory Endpoints**
• Treatment-emergent adverse events (TEAEs) • Subgroup analyses of TEAEs and other selected safety parameters by enteric condition	• Change in total kidney calcification burden (nephrocalcinosis and kidney stones) • Time to KS disease progression • Change from baseline in Wisconsin Stone Quality-of-Life (WisQoL) and Medical Outcomes Study Questionnaire Short-Form 36 Health Survey (SF-36) scores

Summary

- This randomized, placebo-controlled trial in EH is designed to establish the effect of reloxaliase on 24-hour UOx excretion and KS disease progression in long-term follow-up
- The study will provide valuable information regarding the natural history of disease on the basis of clinical, biological, radiographic, and QoL endpoints
- This international trial is registered on ClinicalTrials.gov (NCT03847090) and is currently enrolling subjects
- Information on becoming a clinical trial site can be obtained by calling (617) 467-4577, x398, or by email: clinical302@allenapharma.com

References

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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):19-26.

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Trial Information

Sponsor: Allena Pharmaceuticals
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For information about recruitment and participating research centers:
(617) 467-4577 or clinical302@allenapharma.com
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