Establishing Safety and Efficacy of Reloxaliase in Patients With Enteric Hyperoxaluria (URIROX-2)

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KIDNEY WEEK 2020 REIMAGINED OCTOBER

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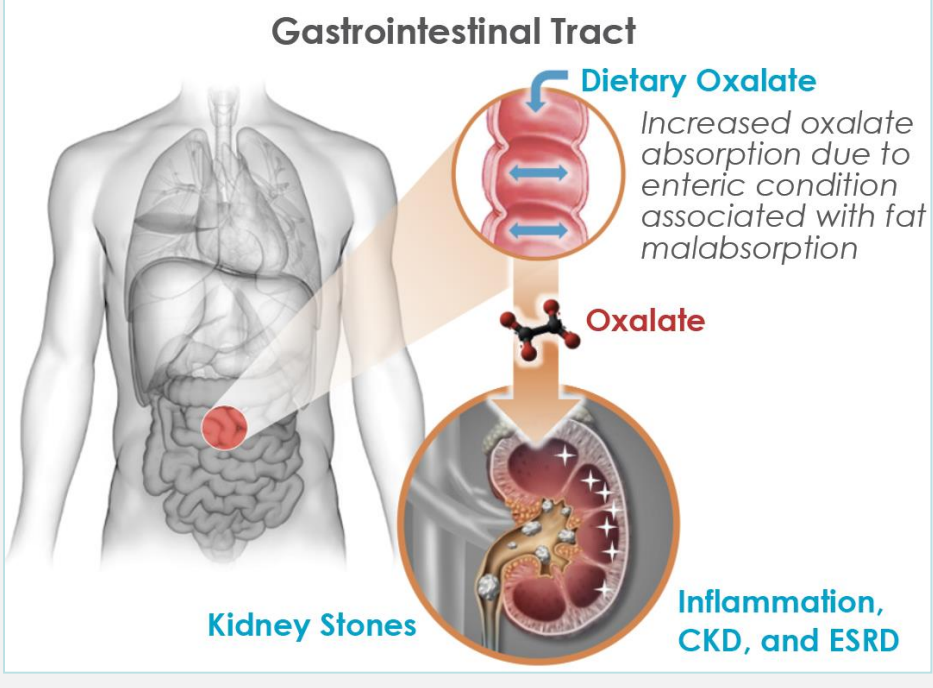
BACKGROUND

- Hyperoxaluria is a major risk factor for calcium oxalate kidney stones (KS) and can lead to chronic kidney disease (CKD), including end-stage renal disease (ESRD).[1,2]
- Enteric hyperoxaluria (EH) refers to increased urinary oxalate (UOx) excretion caused by fat malabsorption due to surgery or an underlying medical disorder (Figure 1).[1,3]

Figure 1: Schematic of Enteric Hyperoxaluria



Background

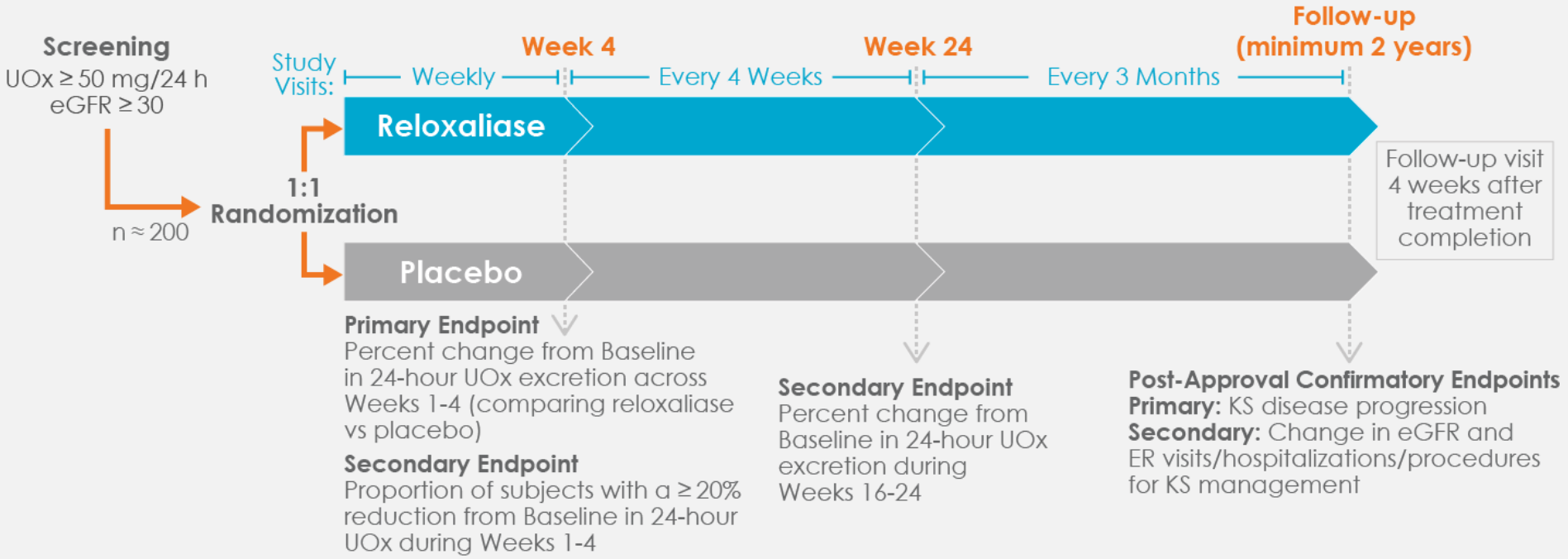
- EH affects approximately 250,000 people in the United States.[4]
- There are no approved pharmacological therapies for EH. Current management recommends restricting dietary oxalate and increasing calcium and fluid intake, which may be difficult to sustain or be of limited efficacy in subjects with enteric disorders associated with hyperoxaluria.
- Reloxaliase (oxalate decarboxylase) — a first-in-class oral enzyme therapy that decreases systemic oxalate absorption and in turn, UOx excretion by degrading oxalate within the GI tract — is in development to treat EH.
- Reloxaliase has consistently demonstrated a statistically significant reduction in 24-hour UOx in previously completed Phase 2 and 3 studies and is being developed to help address an unmet need in patients with EH.[5]

Study Design

- URIROX-2 (Clinicaltrials.gov NCT03847090) is a Phase 3 double-blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of reloxaliase in adults with EH (Figure 2).
- 200 subjects will be randomized 1:1 to either reloxaliase or placebo with stratification by bariatric surgery vs other enteric condition, presence vs absence of KS at Baseline, renal ultrasound (RUS)/kidney, ureter, bladder x-ray (KUB) vs computed topography scan (CT) for sequential imaging, and use of calcium supplements vs not.
- Dose regimen:
  - Oral 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
- Adaptive design elements are incorporated to maximize trial efficiency by ensuring the UOx primary endpoint is achieved and enabling optimal assessment of clinical benefit to support accelerated approval.

STUDY DESIGN

Figure 2: Study Design



Study Objectives

- URIROX-2 is being conducted to determine the long-term safety and efficacy of reloxaliase for decreasing 24-hour UOx excretion in subjects with EH; it expands on the recently completed four-week URIROX-1 study (ClincialTrials.gov NCT03456830) and will be the final study conducted to support a regulatory filing for drug approval. Other key study objectives are to:
  - 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

METHODS

- 24-hour urine collections are performed at Baseline, and Weeks 1, 4, 16, 20, and 24, then quarterly thereafter until end of study participation. Study participation continues until the last enrolled subject completes 24 months of treatment/follow-up.
- Following randomization, there are study visits at Weeks 1 and 4, and monthly thereafter during the first 24 weeks, then quarterly visits until end of study participation. A number of study visits may now be performed remotely (via telephone or videoconference and home visits by study nurse for processing of 24-hour urine collections), ensuring data capture continuity in accordance with current FDA guidance on conducting clinical trials during the COVID-19 pandemic.[6]
- KS disease progression will be assessed by obtaining serial imaging of the kidneys to monitor for asymptomatic stone growth; information on symptomatic / clinical events (KS passage, procedures for stone removal, etc.) will also be collected throughout the duration of the trial.

METHODS

- RUS, KUB and CT (Figure 3) will be obtained at Baseline, and either RUS/KUB or CT will be sequentially obtained at defined timepoints (RUS/KUB every 6 months for the first 24 months, then annually thereafter; CT every 12 months), with a CT in all subjects at the end of the treatment period. Determination of KS disease progression will be based on comparison of serial images performed utilizing the same imaging modality by blinded readers at the central imaging lab. Imaging performed for clinical assessment of KS events will also be obtained and centrally read.

Figure 3: Imaging Modalities Used to Determine Kidney Stone Progression

Recruitment and Sample Size

- A minimum of 200 subjects will be randomized and treated.
- Two sample size reassessments (SSRs) are planned, which may result in an increase in sample size and/or treatment duration:
  - The first SSR will examine the blinded KS event rate and the conditional probability for achieving the UOx endpoint
  - The second SSR will examine the conditional probability for achieving the KS disease progression endpoint to confirm clinical benefit

Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• ≥18 years of age at Screening • Enteric disorder associated with malabsorption with known or suspected history of hyperoxaluria (e.g., history of KS or oxalate nephropathy) • UOx ≥50 mg/24h for both the Screening collection and the average of 2 Baseline collections (with neither <40 mg/24h) • ≥1 KS within 2 years prior to Screening* • Stable dose regimen of any medication for management of KS risk factors for >8 weeks prior to Screening, and with no changes in dosing anticipated during the first 24 weeks of the study Treatment Period	• >30% variability in the ratio of creatinine to body weight (mg/kg) among the three 24-hour urine collections prior to randomization (1 at Screening, 2 at Baseline) • Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 at Screening • Cannot establish Baseline KS burden via study-required imaging • Has a known genetic, congenital, or other cause of KS • Cannot discontinue vitamin C supplementation >200 mg daily

*Spontaneous KS passage, intervention for KS removal or new or enlarged KS on imaging

Key Study Endpoints

Efficacy Endpoints

Primary

- Percent change from Baseline in 24-hour UOx excretion (Weeks 1-4)

Secondary

- Percent change from Baseline in 24-hour UOx excretion (Weeks 16-24)
- ≥20% reduction from Baseline in 24-hour UOx excretion (Weeks 1-4)
- Percent change from Baseline in 24-hour UOx excretion (Weeks 1-4 & 16-24) in the bariatric surgery subgroup

Primary Long-Term

- KS disease progression, defined as a composite of symptomatic KS or finding of new or enlarged KS on imaging (KUB/RUS and CT)

Secondary Long-Term

- Hospitalizations or emergency room visits or procedures for KS management
- Change in eGFR from Baseline

Safety Assessments

- Treatment-emergent adverse events (TEAEs)
- Subgroup analyses of TEAEs and other selected safety parameters by enteric condition

Exploratory Endpoints

- Change in total kidney calcification burden (nephrocalcinosis and KS as quantified by CT)
- 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

- Reloxaliase is being developed as a potential first-in-class, non-absorbed, orally administered enzyme for the treatment of EH.
- URIROX-2, the largest randomized controlled trial to date in EH, is designed to establish the safety of long-term use of reloxaliase and demonstrate the effect of reloxaliase on 24-hour UOx, KS disease progression, and kidney function in long-term follow-up. This is the final planned study to support a regulatory filing for drug approval.
- The study will also provide valuable information regarding the natural history of EH, and its impact on quality of life and healthcare resource utilization.

Trial Information: Currently Enrolling

For information about recruitment or becoming a clinical trial site, contact us at: 617-467-4577 x398 or clinical302@allenapharma.com

- **ClinicalTrials.gov Identifier:** NCT03847090
- **Eudra-CT Number:** 2018-000921-29

- **Sponsor:**
  Allena Pharmaceuticals
  www.allenapharma.com
- **Contract Research Organization:**
  Medpace, 5375 Medpace Way
  Cincinnati, OH 45227

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