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 urinary oxalate (UOx) excretion that is a complication of increased oxalate absorption due to an underlying gastrointestinal (GI) condition associated with malabsorption (e.g., Crohn disease, 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 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 reabsorption in the GI tract, which results in less systemic oxalate absorption, thereby lowering UOx excretion.

Study Objectives

- **Primary Efficacy Endpoint**
  - URIROX-2 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 allow for modification in sample size and duration of treatment to support confirmation of clinical benefit.
  - **Primary Long-term Endpoint**
    - URIROX-2 will provide long-term efficacy and safety assessments to support and expand week 4 results reported in URIROX-1 (ClinicalTrials.gov NCT03456830)

- **Secondary Long-term Endpoints**
  - **Secondary Endpoints**

Study Design

| 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.
- **POST-APPROVAL CONFIRMATORY ENDPOINTS**
  - URIROX-2 will provide long-term efficacy and safety assessments to support and expand week 4 results reported in URIROX-1 (ClinicalTrials.gov NCT03456830)

Table 1. Eligibility Criteria

| Eligibility Criteria | 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.

Table 2. Study Endpoints

| Study Endpoints | 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.

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 a 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 or clinical302@allenapharma.com.

References


Methods

- **Methods**

  - 24-hour urine collections are performed at baseline, weekly for the first 4 weeks, every other week 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

  - **Proportion of participants with KS disease progression (composite outcome)** will be captured using RUS, KUB, and CT (Figure 3) at baseline, then serial imaging will be used to monitor for symptomatic stone growth

Figure 3. Imaging Modalities Used to Determine Kidney Stone Progression

Acknowledgments

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