Dietary Oxalate Ingestion, Urinary Oxalate Levels, and Response to Reloxaliase in Three Phase II Studies

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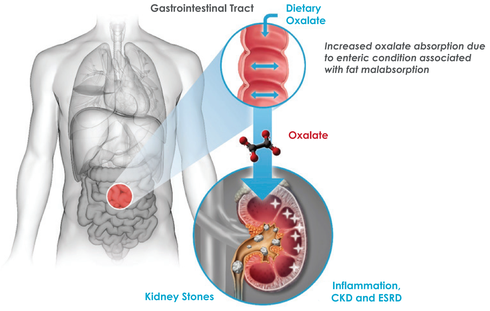
Background

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 consists of recommendations to restrict dietary oxalate and increase calcium and fluid intake, but these may be difficult to sustain or may be of limited efficacy, especially in subjects with enteric disorders associated with EH.

Reloxaliase is an oral enzyme that degrades oxalate within the GI tract, resulting in less oxalate absorption and lower UOx excretion.

KS disease in subjects with EH is a sign of on-going crystal deposition and is associated with higher UOx levels.[1] Urinary stone events are predicted by UOx excretion in EH.[4]

Subjects with hyperoxaluria and KS disease are at a higher risk of CKD. High UOx excretion is associated with the risk of CKD progression.[5] Higher UOx levels are associated with increased risk of new-onset ESRD.[6] After kidney transplant, oxalate deposition in renal allograft biopsies is associated with allograft dysfunction.[7] Renal transplant subjects with biopsy-confirmed calcium oxalate crystal deposition had significantly higher risk of death or graft failure.[8]

We hypothesized that subjects with higher baseline levels of UOx may show increased responsiveness to therapy (ie, reloxaliase) that degrades dietary oxalate through the GI tract.

Data of subjects with EH from three phase II studies were analyzed to examine this hypothesis.

Methods

- A composite analysis of data from phase II studies of reloxaliase was performed, which included 18 subjects with EH (**Table 1**)

Table 1. Summary of Allena Phase II Studies

Study	Phase II Study Design	Reloxaliase Dose	EH Inclusion Criteria	Enrolled & Treated (N)	Subjects with EH (n)
396 (NCT02289755)	Open-label, single-arm	7,500 units (5 capsules) x 3 per day for 4 days	• Mean 24 h UOx ≥36 mg/24 h • eGFR >60 mL/min/1.73 m^2	16	5
713 (NCT02547805)	Randomized, double-blind, placebo-controlled	7,500 units (5 capsules) x 3 per day for 28 days	• Mean 24 h UOx ≥50 mg/24 h • eGFR >45 mL/min/1.73 m^2	67	11
206 (NCT03391804)	Open-label, single-arm, PH and EH	7,500 units (2 capsules) x 5 per day for 3 months	• Mean 24 h UOx ≥40 mg/24 h and POx >5 µmol/L • eGFR <45 mL/min/1.73 m^2	Ongoing	2

eGFR, estimated glomerular filtration rate; PH, primary hyperoxaluria; POx, plasma oxalate

- Oxalate intake was assessed via dietary recall in Studies 396 and 713. UOx levels were assessed serially as part of the respective protocols
- Demographic and baseline characteristics of subjects with EH treated with reloxaliase from each of the 3 studies is presented in **Table 2**

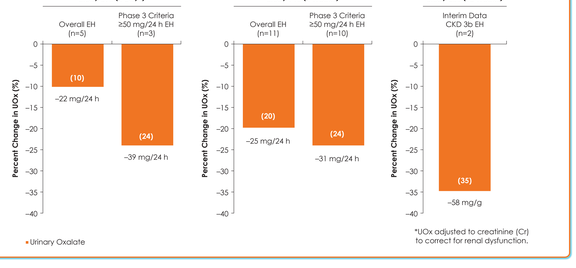
Table 2. Demographic and Baseline Characteristics of EH Subjects from Three Phase II Studies

Variable*	Study 396 (n=5)	Study 713 (n=11)	Study 206 (n=2)
Age (years), mean (SD)	57.0 (11.7)	63.3 (12.0)	74.0 (2.8)
Female, N (%)	3 (60)	4 (36.4)	1 (50)
BMI (kg/m^2), mean (SD)	36.3 (11.2)	32.6 (8.0)	21.4 (2.4)
eGFR, N (%)			
≥60 mL/min/1.73 m^2	5 (100)	10 (91)	–
30-59 mL/min/1.73 m^2	–	1 (9)	2 (100)
Underlying enteric disorder, N (%)			
Bariatric surgery	5 (100)	7 (63.6)	–
IBD	–	3 (27.3)	–
Pancreatic insufficiency	–	1 (9.1)	–
Fat malabsorption	–	–	1 (50)
Short bowel syndrome	–	–	1 (50)
Dietary oxalate from recall (mg/24 h), mean (SD)	147.3 (73.5)	273.4 (220.3)	n/a

BMI, body mass index
*Values reported as mean (SD) or N (%) where indicated

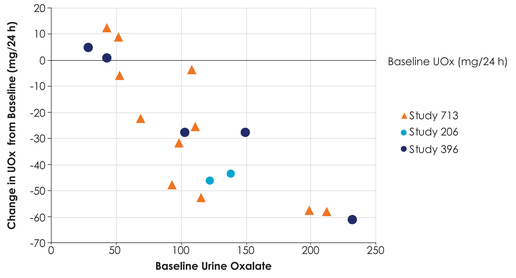
- Consistent reductions in UOx were observed in subjects with EH (**Figure 2**). A subgroup analysis of Studies 396, 206, and 713 evaluated UOx response in subjects with ≥50 mg/24 h dietary oxalate at baseline. (Note: ≥50 mg is the minimum UOx baseline and screening entry criterion for URIROX-1). The results are presented in **Figure 2**
- Reloxaliase appears well tolerated, with gastrointestinal complaints being the most commonly reported adverse event

Figure 2. Urine Oxalate Response to Reloxaliase Treatment



- There was a consistent reduction in EH subjects with higher baseline (≥50 mg/24 h) UOx levels across 3 phase II clinical studies
- On average, subjects who had a ≥50 mg/24 h baseline UOx demonstrated a ≥24% reduction in UOx across all studies (**Figure 3**)

Figure 3. Change in Urine Oxalate Compared to Baseline



Conclusions

- The mechanism of action of reloxaliase, to degrade oxalate within the GI tract, aligns with the pathophysiology of EH
- With severe hyperoxaluria, subjects are at higher risk for kidney stone disease and CKD/ESRD; reloxaliase has the potential to address a significant unmet medical need by reducing UOx excretion in this high-risk population

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