Safety and Efficacy of Reloxaliase in Enteric Hyperoxaluria (EH): an Aggregate Review of Completed Studies

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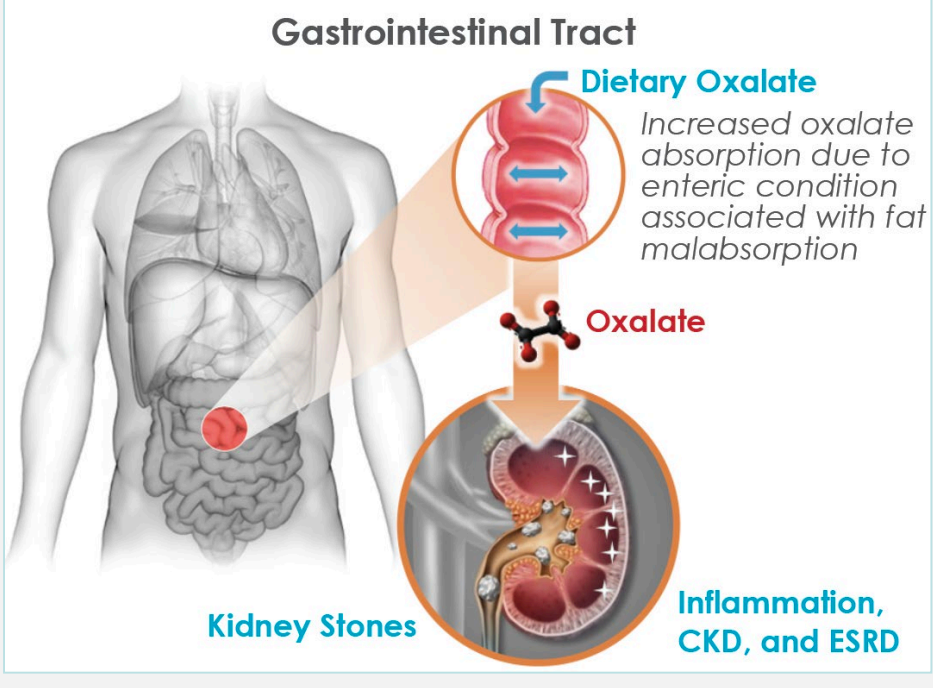
BACKGROUND

- Enteric Hyperoxaluria is a serious metabolic disorder that affects approximately 250,000 people in the United States.[1]
- EH is characterized by excessive urine oxalate (UOx) excretion that is due to increased oxalate absorption resulting from an underlying gastrointestinal (GI) condition associated with fat malabsorption (eg, malabsorptive bariatric surgery, short-bowel syndrome, inflammatory bowel disease (Figure 1).[2,3]

Figure 1: Schematic of Enteric Hyperoxaluria



Background

- Chronically elevated UOx is a major risk factor for development of kidney stone disease[1], and is also associated with kidney failure. Kidney stones and inflammation due to oxalate crystal deposition may cause permanent damage to the renal parenchyma, which can lead to chronic kidney disease (CKD), including end-stage renal disease (ESRD).[1,4] The potential for kidney failure in EH is highlighted by the report from one institution that 3% of patients presenting for kidney transplant evaluation had EH.[5]
- The risk of kidney stone events can be predicted by 24-hour UOx excretion in EH. An analysis from the Mayo Clinic suggested that lowering 24-hour UOx by 10%, 20%, and 30% may reduce the risk of kidney stones by approximately 13%, 25%, and 37%, respectively.[6]

Background

- There are no approved therapies for EH. Current management recommendations are to restrict dietary oxalate and increase calcium and fluid intake. However, these recommendations are difficult to sustain or may be of limited efficacy in patients with the types of enteric disorders associated with hyperoxaluria.
- Reloxaliase is a first-in-class oral enzyme therapy that degrades oxalate within the GI tract, resulting in less oxalate being systemically absorbed and thus, lower UOx excretion. Degradation products include carbon dioxide and formate (formic acid) in a 1:1 ratio.
- To date, a total of 4 clinical trials with reloxaliase have enrolled subjects with EH and provide data for this aggregate safety and efficacy assessment in the EH population: 2 single-arm open-label studies and 2 randomized controlled trials.

METHODS

- The 4 clinical trials of reloxaliase had a total of 148 subjects with EH (84 reloxaliase-treated and 64 placebo-treated), most with malabsorptive bariatric surgery as the underlying enteric disorder.
- The clinical trial designs, including entry criteria, treatment regimen and duration, and the number of subjects with EH, are summarized in Table 1.
- Demographic and baseline characteristics of subjects with EH from each of the 4 studies are presented in Table 2.

METHODS

Table 1: Summary of EH Subjects in Allena Phase 2 and 3 Clinical Studies

Protocol Number Study Phase & Design	Study Population	Study Drug* Dose Regimen Duration	Subjects (N) Reloxaliase/Placebo
396 (NCT02289755) Phase 2 open-label, single-arm	UOx ≥36 mg/24h eGFR ≥60 mL/min/1.73 m^2	Reloxaliase 3x/day with meals 4 days	5
713 (NCT02547805) Phase 2 randomized, double-blind, placebo-controlled	UOx ≥50 mg/24h eGFR ≥45 mL/min/1.73 m^2	Reloxaliase or Placebo 3x/day with meals 28 days	11 / 7
206 (NCT03391804) Phase 2 open-label, single-arm	UOx ≥40 mg/24h eGFR <45 mL/min/1.73 m^2	Reloxaliase 5x/day with meals/snacks 12 weeks	10
301 (NCT03456830) Phase 3 randomized, double-blind, placebo-controlled (URIROX-1)	UOx ≥50 mg/24h eGFR ≥30 mL/min/1.73 m^2	Reloxaliase or Placebo 3-5x/day with meals/snacks 28 days	58 / 57

*Reloxaliase dose: 7,500 units

METHODS

Table 2: Demographic and Baseline Characteristics of EH Subjects from Phase 2 and 3 Clinical Studies

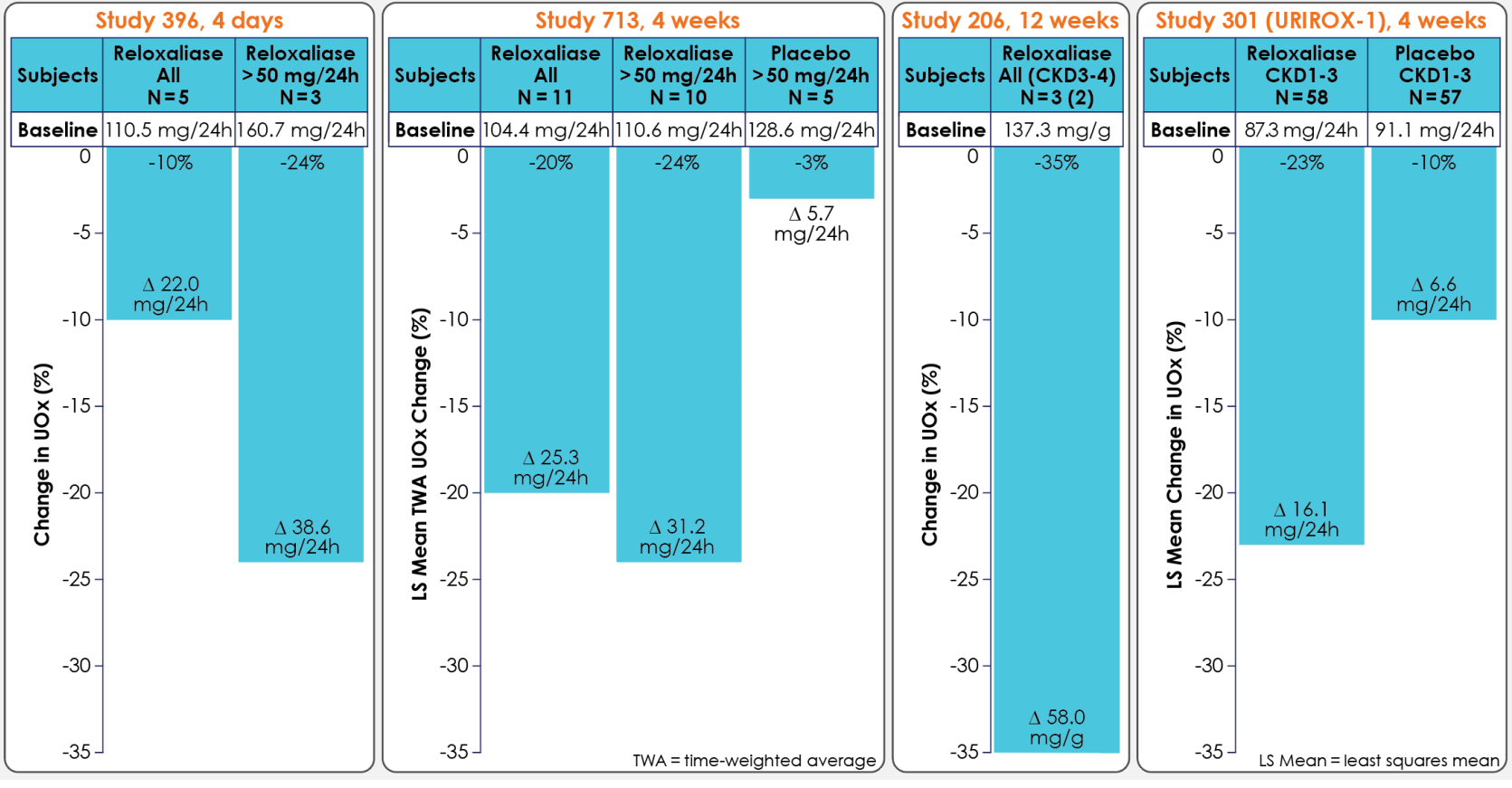
Variable	Study 396 (N = 5)	Study 713 (N = 18)	Study 206 (N = 10)	Study 301 (N = 115)
Age (years), mean (SD)	57.0 (11.7)	63.9 (9.9)	63.7 (9.1)	58.7 (10.1)
Female, n (%)	3 (60.0)	10 (55.6)	3 (30.0)	55 (47.9)
Body Mass Index (kg/m^2), mean (SD)	36.3 (11.2)	34.5 (7.6)	25.0 (6.6)	31.8 (7.7)
eGFR (mL/min/1.73 m^2) Mean (SD) Median Min, Max	 99.2 (12.5) 95.0 85, 118	 73.8 (14.2) 71.8 48, 97	 37.7 (0.6)* 38.0 37, 38	 78.4 (23.6) 82.0 33, 127
Underlying enteric disorder, n (%) Bariatric surgery Inflammatory bowel disease Pancreatic insufficiency Fat malabsorption Short bowel syndrome	 5 (100) – – – –	 13 (72.2) 3 (27.3) 2 (11.1) – –	 4 (40) 3 (30) 1 (10) 1 (10) 1 (10)	 78 (67.9) 20 (17.4) 3 (2.6) 3 (2.6) 11 (9.5)

*CKD Stage 3-4 subjects

EFFICACY

- The efficacy parameter assessed in all trials was change in 24-hour UOx excretion (for Study 206, which had subjects with advanced CKD, it is presented as oxalate:creatinine ratio in mg/g).
- For this aggregate analysis, change from baseline was calculated using the average of all UOx values obtained during treatment in all subjects, and also for the subgroup with baseline UOx ≥ 50 mg/d in Studies 396 and 713 (the Phase 3 target population). Figure 2 shows the percent change, and the absolute change is also provided (Δ within the bars).
- Across these clinical trials, reloxaliase meaningfully decreased 24-hour UOx excretion compared with placebo in subjects with EH, including in subjects with CKD Stage 3 (eGFR ranged from normal to as low as 33 mL/min/1.73m^2).
- In subjects with severe hyperoxaluria (baseline UOx ≥ 50 mg/d), reloxaliase consistently reduced 24-hour UOx excretion, with mean reductions ranging from 23 to 35% across these studies that examined different dosing frequencies and durations of treatment (Figure 2). In the Phase 3 (URIROX-1) study, reloxaliase demonstrated a significant treatment difference vs. placebo (P = 0.004).
- URIROX-2, a currently enrolling Phase 3 trial that will examine the impact of reloxaliase on 24-hour UOx as well as kidney stones and kidney function (see poster #INFO-06[7]), shares common enrollment criteria and a primary endpoint with URIROX-1.

Figure 2: Efficacy Results in EH Subjects in Allena Phase 2 and 3 Clinical Studies



SAFETY

- There were 168 subjects with EH across all completed reloxaliase studies. Treatment-emergent adverse events (TEAEs) were reported in 67% of subjects treated with reloxaliase compared with 51.4% of subjects on placebo (Table 3).

Table 3: Overview of Treatment-Emergent Adverse Events (TEAEs)

	Other Completed Phase 2 Studies*		Study 206**	Study 301 (URIROX-1)		Overall	
	Reloxaliase (N = 26)	Placebo (N = 17)	Reloxaliase (N = 10)	Reloxaliase (N = 58)	Placebo (N = 57)	Reloxaliase (N = 94)	Placebo (N = 74)
Any TEAE, n (%)	13 (50.0)	8 (47.1)	10 (100.0)	40 (69.0)	30 (52.6)	63 (67.0)	38 (51.4)
Related TEAE, n (%)	2 (7.7)	2 (11.8)	2 (20.0)	17 (29.3)	11 (19.3)	21 (22.3)	13 (17.6)
Serious TEAE, n (%)	0	0	3 (30)	1 (1.7)	0	4 (4.3)	0
Related Serious TEAE, n (%)	0	0	0	0	0	0	0
Death, n (%)	0	0	0	0	0	0	0

*Includes safety data from additional EH subjects that received reloxaliase or placebo in a separate Phase 2 dosing study.

**Study 206 had a longer treatment duration (3 months) in a more severe subject population vs other completed Phase 2 studies

SAFETY

- The incidence of TEAEs related to study drug was 22.3% in reloxaliase-treated subjects compared to 17.6% in placebo-treated subjects.
- Four subjects treated with reloxaliase reported serious TEAEs, all were considered unrelated to study drug. Two subjects reported TEAEs that led to study drug discontinuation, one on placebo (leading to early study termination) and one on reloxaliase.
- No deaths have occurred in the reloxaliase development program.
- Adverse events associated with GI disorders were the most frequently reported TEAEs in reloxaliase-treated (36%) and placebo-treated (27%) EH subjects. Most were of mild to moderate severity and did not lead to study drug discontinuation in either group (Table 4).
- The analysis of serum samples in Study 206, in which subjects received reloxaliase 5 times/day for 12 weeks, demonstrated no evidence of reloxaliase (oxalate decarboxylase) absorption or formate accumulation (a by-product of oxalate degradation).

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Table 4: Summary of Most Frequent GI-related TEAEs Reported by ≤ 2 EH Subjects Across All Studies

GI TEAEs	Reloxaliase Tx (%)	Placebo Tx (%)
Abdominal Distention	8.5	4.1
Diarrhea	8.5	10.8
Flatulence	8.5	5.3
Nausea	5.3	4.1
Abdominal Discomfort	3.2	–
Abdominal Pain	2.1	–
Dyspepsia	–	2.7
Toothache	–	2.7

CONCLUSIONS

- Reloxaliase reduces 24-hour UOx excretion in patients with EH with reductions of 23 to 35% observed in Phase 2 and 3 studies.
- Reloxaliase was well-tolerated in EH subjects independent of eGFR, dosing frequency, or duration of treatment.
- The URIROX-2 Phase 3 trial, which is currently recruiting, will assess the long-term benefits of reloxaliase and its potential to decrease kidney stone events and preserve kidney function (See information poster INFO-06).

References

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