LBA01-08

Kidney Stone Risk and Association with Urine Oxalate Levels in Enteric Hyperoxaluria

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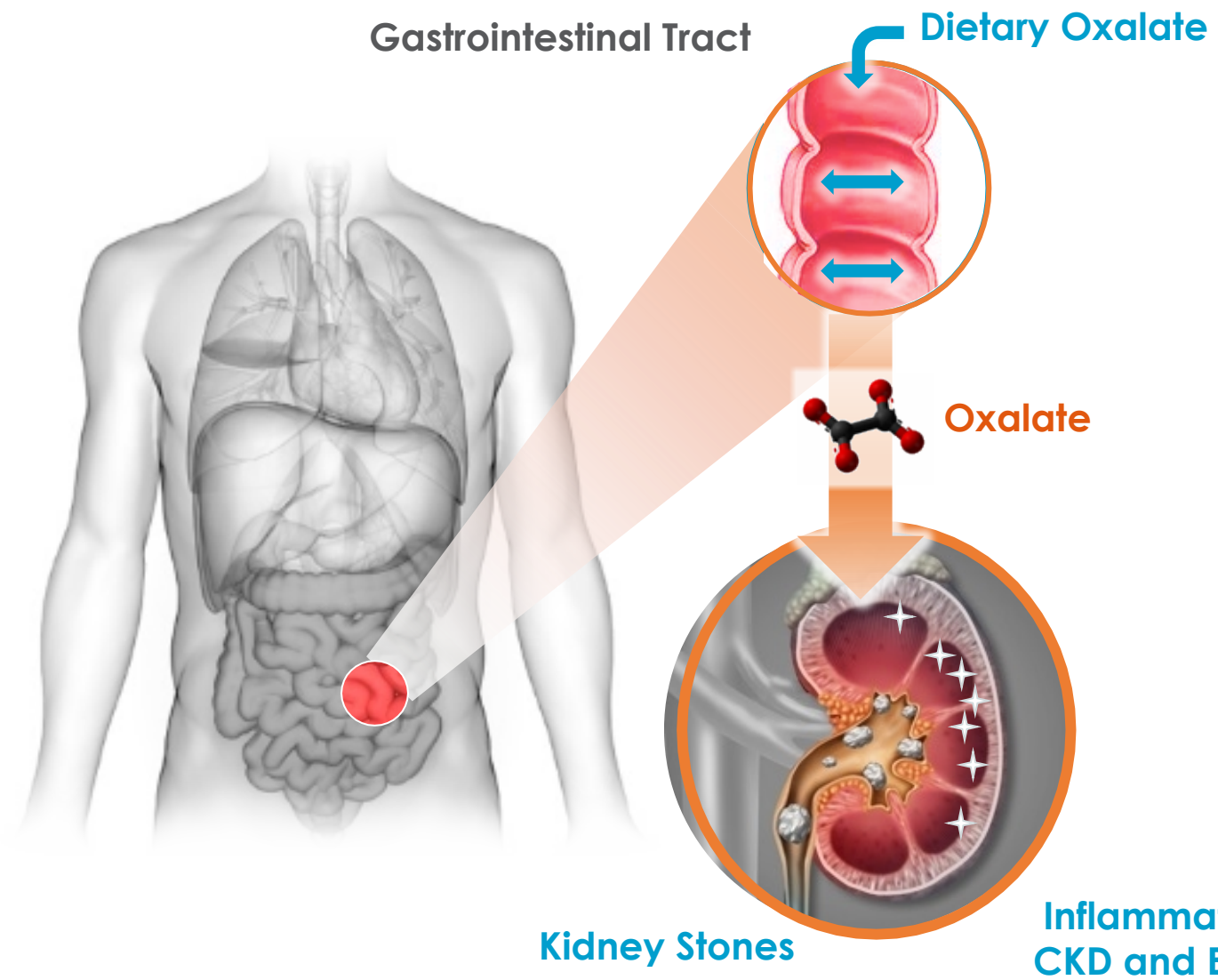
Disclosures

- Allena Pharmaceutical – Scientific Study
- NIH/NIDDK – Scientific Study
- NCI – Scientific Study

The Pathophysiology of Enteric Hyperoxaluria

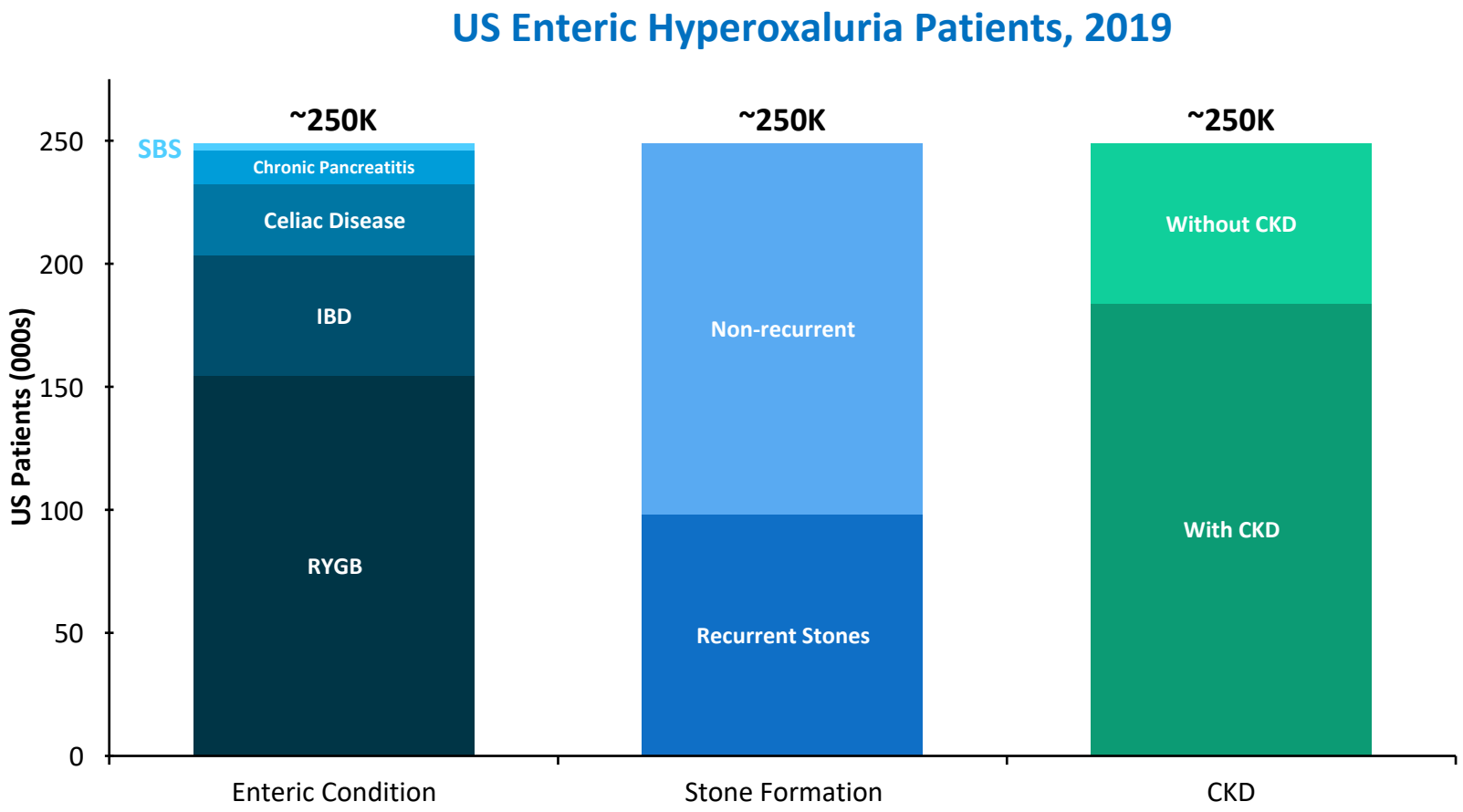


Enteric Hyperoxaluria (EH)

- **Definition**: Elevated urine oxalate excretion due to excess absorption of oxalate from the GI tract due to fat malabsorption
- **Mechanism**: Fatty acids bind calcium within the small bowel, resulting in unbound oxalate that is then free to be systemically absorbed in the colon, increasing renal oxalate excretion
- **Clinical Consequences:** Increased risk of CaOx nephrolithiasis and CaOx deposition within the renal interstitium leading to inflammation, CKD and even ESRD

Epidemiology of Enteric Hyperoxaluria

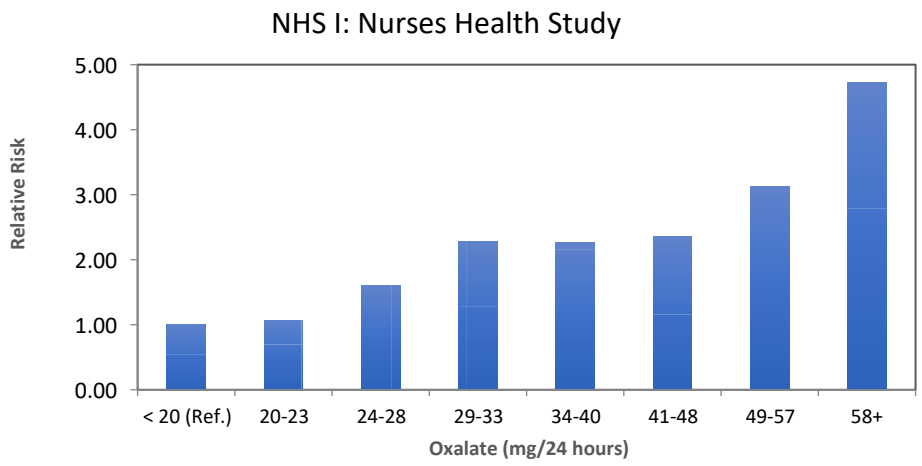
It is estimated that there are ~250,000 EH patients in the US: 40% have recurrent stones and 74% have CKD

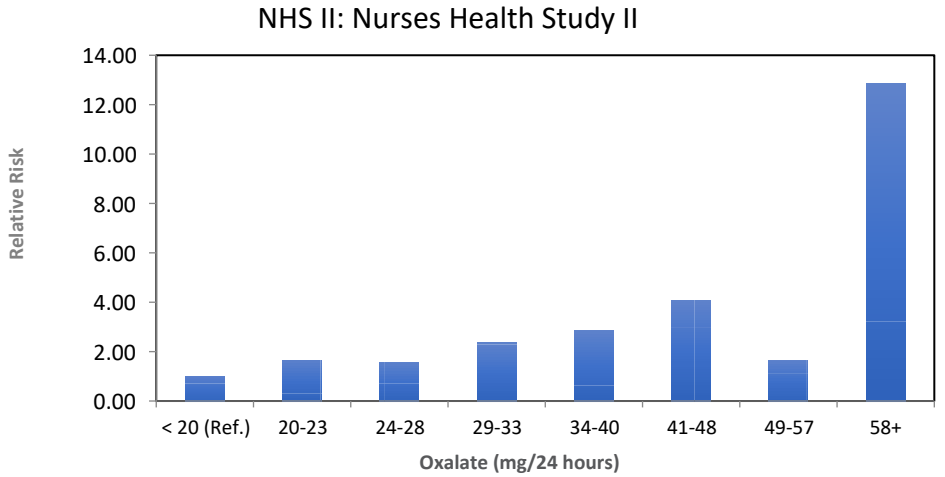


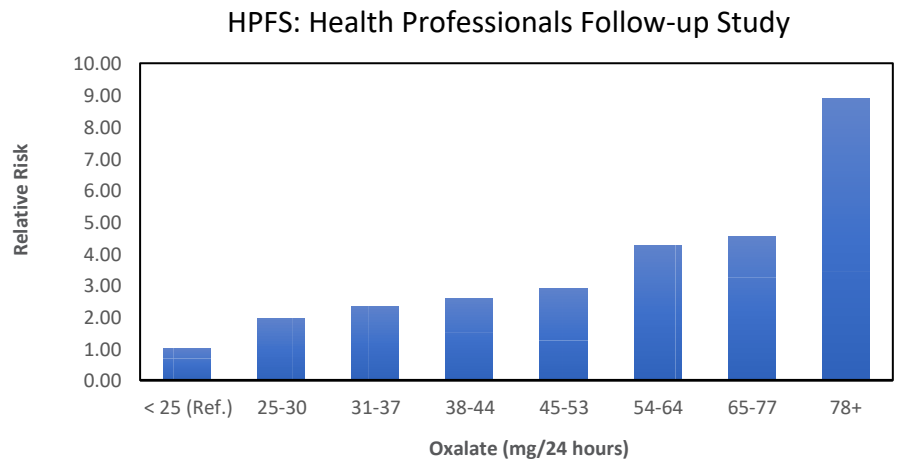
SBS=Short Bowel Syndrome

Tasian, et al. Presented at the 2019 American Society of Nephrology Meeting, Washington D.C.

Risk of Kidney Stones Increases Progressively with Urine Oxalate Levels: A Recognized Phenomenon







Assuming a non-linear relation, pooled across the three datasets, the multivariate RR* per 20% higher oxalate:

RR = 1.25 (1.14, 1.36); p<0.001

*adjusted for age and other 24-hr urinary risk factors

HPFS = Health Professional Follow-up Study; NHS = Nurses Health Study

GC Curhan and EN Taylor. 24-h uric acid excretion and the risk of kidney stones. Kidney Int 2008; 73:489; GC Curhan, et al. Absolute Compared with Percentage Differences in 24-Hour Urine Oxalate and Likelihood of Being a Kidney Stone Former Session Information . ASN kidney week, 2017

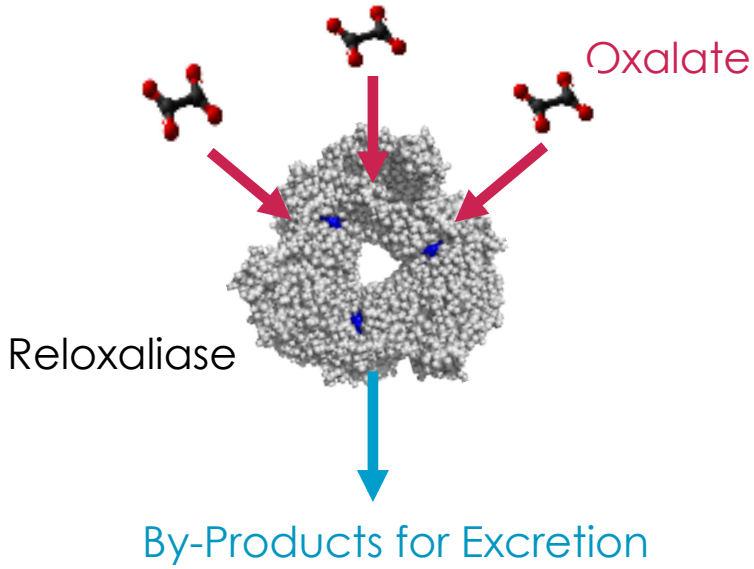
Reloxaliase: A First-in-class Therapeutic Candidate for EH

Target Production Characteristics

- Crystalline Oxalate-Specific Enzyme
- Oral Capsule Formulation
- Taken with Food
- Non-Absorbed/Non-Systemic
- Room Temperature Stability

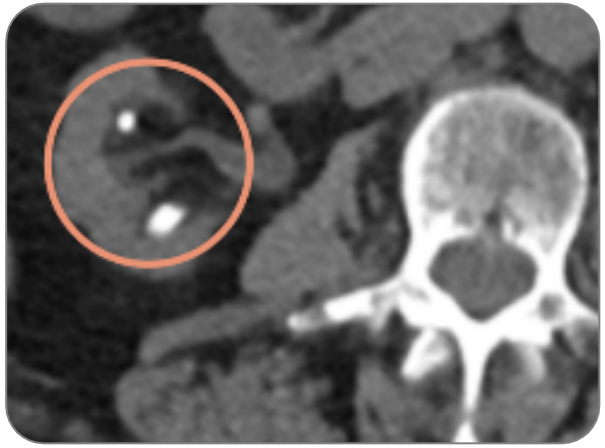
Mechanism of Action

Oxalate Degradation in the Gastrointestinal Tract

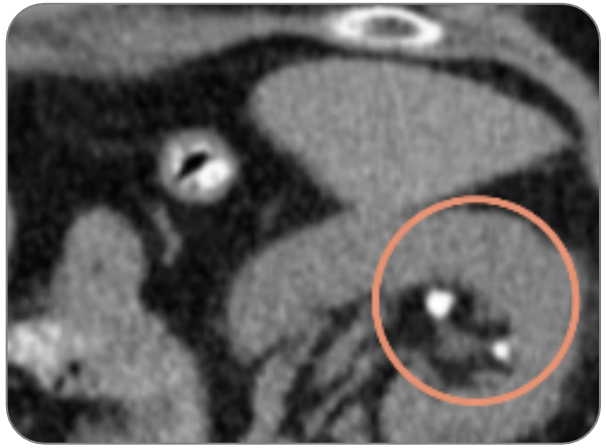


Patients with Enteric Hyperoxaluria Have a High Burden of Kidney Stones: Data from Reloxaliase Program Phase 2

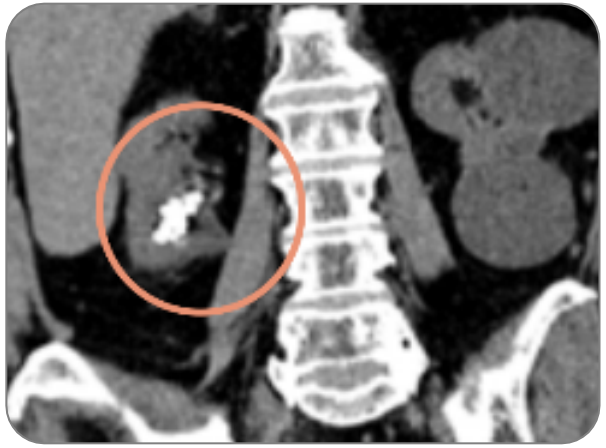
Study 713: Patient Examples



Celiac disease
3 stones in last 2 years
(4 stones visible by CT)



Gastric Bypass
8 stones in the last 5 years
(3 stones visible by CT)

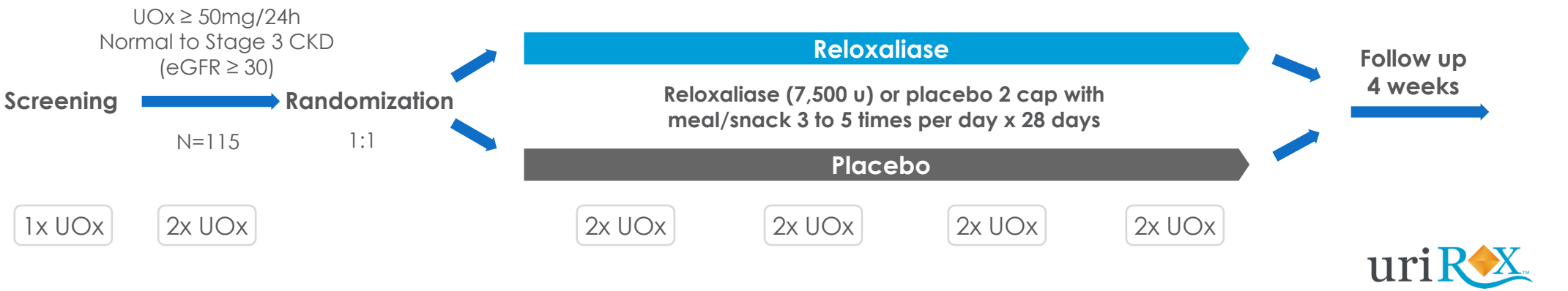


Whipple
(Pancreatic Insufficiency)
14 stones in last 5 years
(16 stones visible by CT)

- Very high baseline UOx, mean ~100 mg/24h
- On average, EH subjects had experienced 6 stones prior to enrollment
- On average, 3 kidney stones visible by routine CT scan at time of enrollment

Nigwekar, et al. Presented at the American Society of Nephrology Kidney Week 2018, San Diego, CA

URIROX-1: A Phase 3 Study Evaluating the Safety and Efficacy of Reloxaliase in Patients with Enteric Hyperoxaluria



Primary Endpoint

- Percent change from baseline in 24h UOx excretion during Weeks 1 to 4

Key Secondary Endpoint

- Proportion of subjects with a ≥ 20% reduction from baseline in 24h UOx excretion during Weeks 1 to 4

Pre-Specified, Stratified Analysis

- Subset analysis of the primary and lead secondary endpoint in subjects with a history of bariatric surgery

URIROX-1: Patient Demographics and Baseline Characteristics

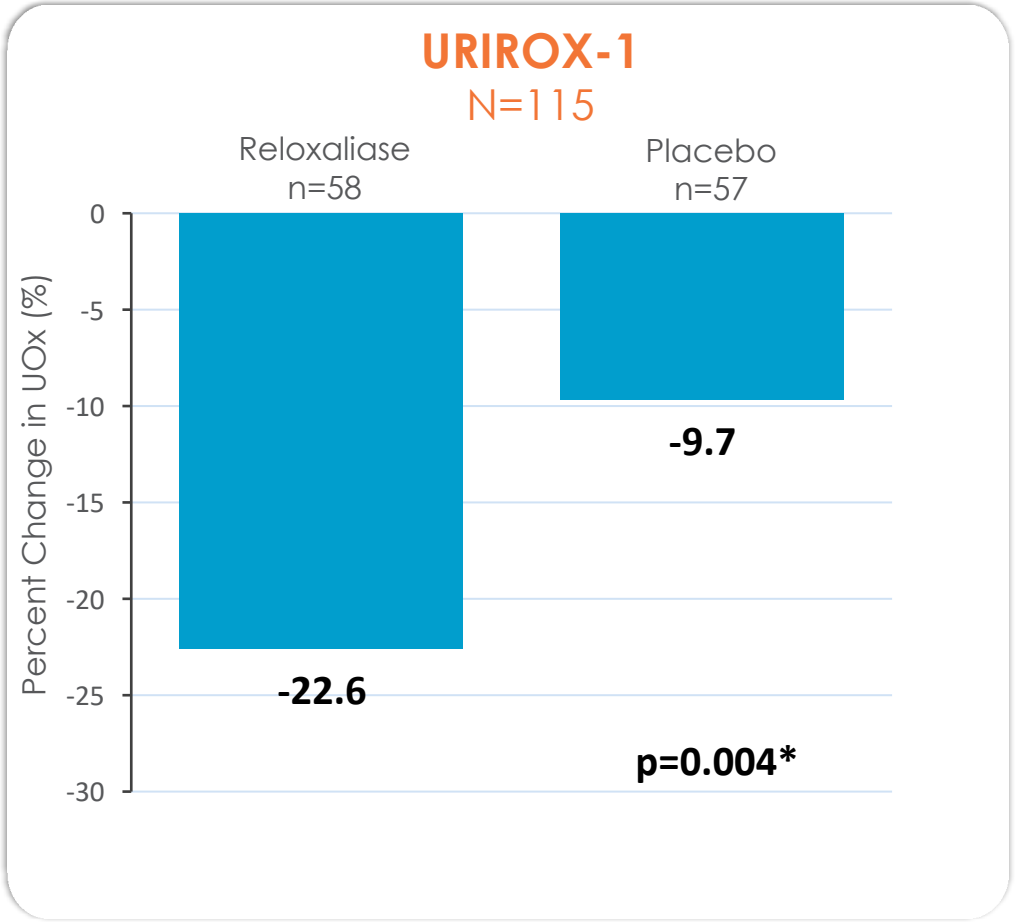
Category / Statistic	Reloxaliase (N=58)	Placebo (N=57)
Age (years) – Mean (SD)	58.7 (10.09)	58.6 (10.18)
Gender, n (%) Female	28 (48.3)	27 (47.4)
Enteric condition, n (%) Bariatric surgery [Roux-en-Y gastric bypass] Inflammatory bowel disease Short bowel syndrome Pancreatic insufficiency Other	 40 (69.0) [27 (46.6)] 10 (17.2) 3 (5.2) 3 5.2) 2 (3.4)	 38 (66.7) [27 (47.4)] 10 (17.5) 8 (14.0) 0 1 (1.8)
Baseline UOx (mg/24h) – Mean (SD)	87.3 (28.87)	91.1 (41.64)
Baseline UOx ≥ 90 mg/24h, n (%)	22 (37.9)	23 (40.4)
Number of kidney stone episodes in past 5 years- Mean (SD)	8.8 (27.49)	14.2 (43.23)
eGFR (mL/min/1.73m^2) - Mean (SD)	76.4 (22.71)	80.5 (24.60)
CKD Stage 3, n (%)	16 (27.6)	14 (24.6)

High Burden of Disease

- Baseline UOx of 89.2 mg/day
- Average 11 stone events in last 5 years
- 16.5% reported an adverse event associated with KS during study[1]
- 26% CKD Stage 3

1. Kidney stone events during the study period were approximately equally distributed between treatment and placebo groups

URIROX-1 Primary Endpoint: Statistically Significant Reduction of UOx

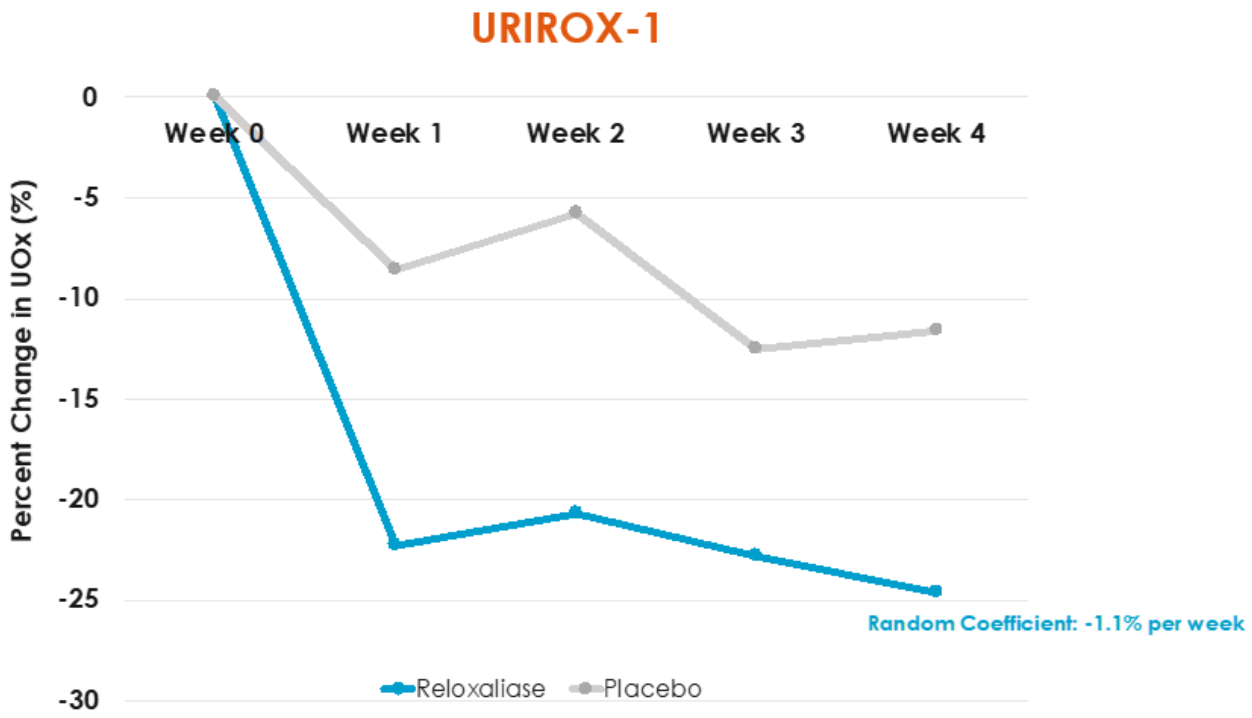


- Achieved primary endpoint
- Highly statistically significant response vs. placebo (P=0.004)
- 22.6% reduction in UOx from baseline (LS mean)
- -14.3% LS mean treatment difference

**Percent change from Baseline in 24-hour UOx excretion during Weeks 1 to 4*

URIROX-1: Primary Endpoint Sustained Over Time

Reloxaliase Demonstrates Sustained Reductions in UOx Across Weeks 1-4



URIROX-1: Summary of Efficacy Results

	Overall Population		Pre-Specified Sub-Population Analysis	
	Reloxaliase (N=58)	Placebo (N=57)	Bariatric Reloxaliase (N=40)	Bariatric Placebo (N=38)
PRIMARY ENDPOINT: Percent change in 24h UOx from Baseline during Weeks 1-4				
Comparison in percent change from baseline[a]				
LS mean relative ratio (95% CI)[b]	-14.329 (-22.81, -4.92)		-16.190 (-26.68, -4.20)	
P-value	**0.004**		**0.010**	
SECONDARY ENDPOINT: Proportion with ≥20% Reduction in 24h UOx from Baseline during Weeks 1-4				
n/N (%)	28/58 (48.3)	18/57 (31.6)	20/40 (50.0)	11/38 (28.9)
Comparison between treatments[c]				
Odds ratio (95% CI)	2.141 (0.97, 4.74)		2.891 (1.07, 7.82)	
P-value	**0.061**		**0.036**	

CI, confidence interval; LS, least squares; MMRM, mixed model repeated measures; N, number of subjects dosed; SE, standard error
[a]Baseline is defined as the average of the UOx values derived from the two baseline 24-hour urine collections prior to randomization.
[b]LS means, CIs, and p-values are based on an MMRM model.
[c]Odds ratio, confidence interval, and p-value are from a stratified logistic regression model.

URIROX-1 Safety Results

Reloxaliase continues to be well tolerated throughout clinical trials

	Reloxaliase (n=58)	Placebo (n=57)
	n (%)	n (%)
TEAE[1]	40 (69.0%)	30 (52.6%)
Severe TEAE	1 (1.7%)[2]	0
Related TEAE	17 (29.3%)	11 (19.3%)
Serious TEAE (TESAE)	1 (1.7%)[2]	0
Related TEAEs	0	0
TEAEs Leading to Study Drug Withdrawal	0	1 (1.8%)
TEAEs leading to Death	0	0

1 TEAE=Treatment Emergent Adverse Event are AEs with an onset or worsening at the time of or following the 1 st dose of study drug through 7 days after the last dose

2 Sacral Radiculopathy that was unrelated to reloxaliase

URIROX-1 Confirms that High Urine Oxalate is Associated with Increased KS Burden

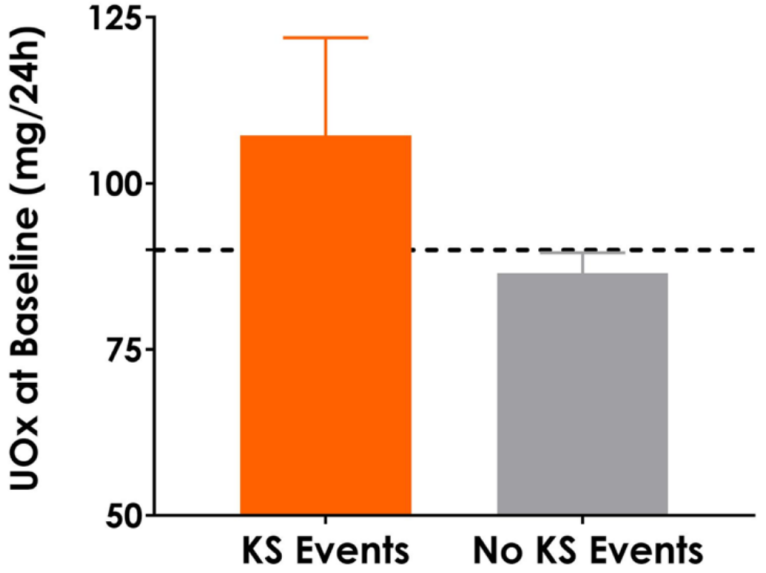
Historic KS Burden
URIROX-1 Population

UOx at Baseline (mg/24h)	<90	>90
n	66	43
KS mean (SE)	8.6 (3.4)	14.7 (6.9)

Available kidney stone history data within 5 years prior to enrollment

Higher UOx was associated with an increased rate of kidney stones both historically and during URIROX-1

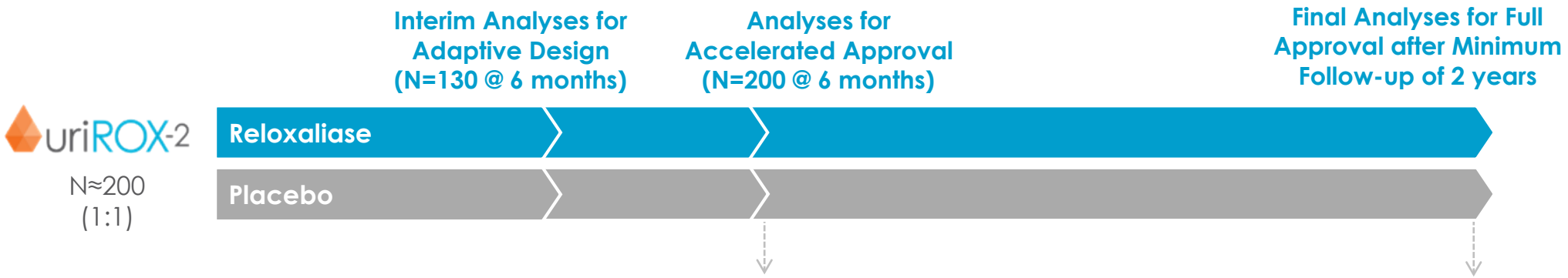
Baseline UOx for Patients With or Without a KS Event During URIROX-1



Patients	15*	100
Baseline UOx, mean (SE)	107.2 (14.7)	86.5 (3.1)

** Subjects reporting kidney stone passage*

URIROX-2 Phase 3 Adaptive Design RCT:
Efficient Assessment of Long-term Efficacy of Reloxaliase for Reducing UOx and Kidney Stone Disease Progression in EH



Key Study Design Elements

N=200

Enteric hyperoxaluria, 24-hr UOx ≥50 mg/d, prior history of KS, and eGFR ≥ 30 mL/min/1.73m^2

Treatment: reloxaliase or placebo, 3-5x/d with meals/snacks for minimum 2 years

Assessments: 24-hour urine collections, imaging for kidney stones

Adaptive design: Two sample size reassessments to ensure sufficient KS events in long-term follow-up

Key Endpoints for Accelerated Approval

Primary : Percent change from baseline in 24h UOx excretion during Wks 1-4

Secondary:

- Percent change from baseline in 24h UOx excretion during Wks 16-24
- Bariatric surgery subgroup analyses

Long-term Efficacy Endpoints

Primary: Kidney stone disease progression*

Secondary:

- Hospitalizations, ER visits, procedures for KS
- Change in eGFR

*Composite of clinical stone events and asymptomatic stone growth on imaging

Conclusions

- Phase 3 URIROX-1 Study represents an important first step in addressing an unmet need for an effective therapeutic for patients with enteric hyperoxaluria (EH)
  - Confirms high KS burden in EH, and relationship between higher UOx and KS
  - Reloxaliase meaningfully reduces 24-hour UOx excretion and is well tolerated
- Measurement of 24-hour UOx is a clinically meaningful marker to assess kidney stone risk in patients with EH
- URIROX-2, the ongoing Phase 3 trial designed to confirm the clinical benefit of reloxaliase with respect to kidney stone disease progression and kidney function, will advance the care of patients with EH
  - Adaptive Design will support FDA filing using UOx for approval, to most efficiently address the unmet need for new therapeutics to treat hyperoxaluria in patients with EH