12-Month Analysis of ILLUMINATE-A, a Phase 3 Study of Lumasiran: Sustained Oxalate Lowering and Kidney Stone Event Rates in Primary Hyperoxaluria Type 1

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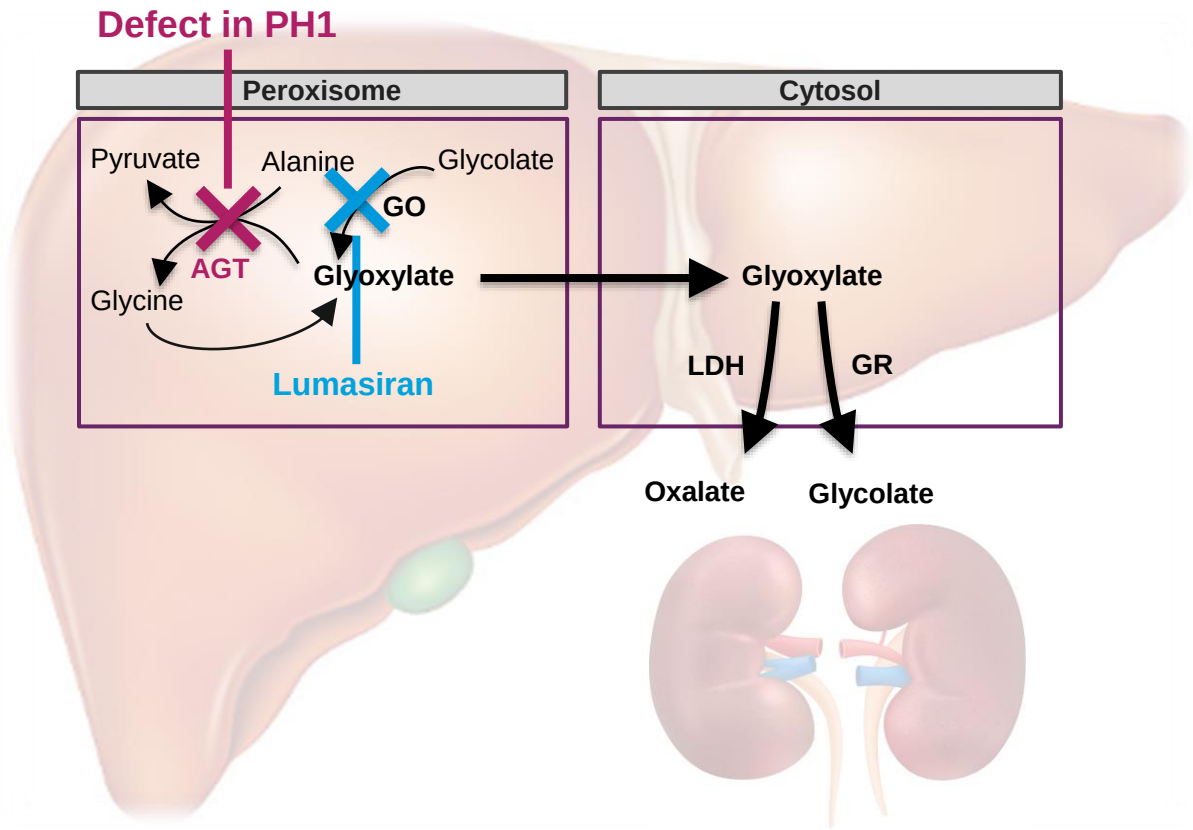
Primary Hyperoxaluria Type 1 and Lumasiran

- Patients with PH1 overproduce oxalate due to a deficiency in the hepatic peroxisomal enzyme AGT[1,2]
- Excess oxalate can lead to recurrent kidney stones, nephrocalcinosis, progressive kidney failure, and multiorgan damage from systemic oxalosis[1,2]
- Current management options are limited and there is an urgent need for new therapies that can reduce hepatic oxalate production
- Lumasiran is a subcutaneously administered investigational RNAi therapeutic that decreases hepatic oxalate production by inhibiting the production of GO[3]



Here, we present 12-month data from ILLUMINATE-A, a randomized, double-blind, placebo-controlled Phase 3 study designed to evaluate efficacy and safety of lumasiran in children and adults with PH1

AGT, alanine-glyoxylate aminotransferase; GO, glycolate oxidase; GR, glyoxylate reductase/hydroxypyruvate reductase; LDH, lactate dehydrogenase; PH1, primary hyperoxaluria type 1; RNAi, RNA interference

1. Cochat & Rumsby. *N Engl J Med* 2013;369:649–58; 2. Milliner et al. *GeneReviews*®. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1283/ (accessed September 08, 2020); 3. Liebow et al. *J Am Soc Nephrol* 2017;28:494–503

ILLUMINATE-A Phase 3 Study Design

PATIENT POPULATION (N=39)

- Adults and children ≥6 years
- Urinary oxalate excretion ≥0.7 mmol/24hr/1.73m^2
- Confirmed *AGXT* mutations
- eGFR ≥30 mL/min/1.73m^2

2:1 RANDOMIZATION

6-MONTH DOUBLE-BLIND TREATMENT PERIOD

Lumasiran
qM × 3 loading dose, then q3M[a]
3.0 mg/kg subcutaneously

Placebo
qM × 3 loading dose, then q3M subcutaneously

54-MONTH EXTENSION PERIOD

Lumasiran
q3M
3.0 mg/kg subcutaneously[b]

- **Treatment arms were stratified at randomization based upon mean 24hr urinary oxalate[c] from the first 2 valid samples collected during screening (≤1.70 mmol/24hr/1.73m^2 vs >1.70 mmol/24hr/1.73m^2)**
- **Oxalate was measured with a validated liquid chromatography-tandem mass spectrometry assay**

NCT03681184; EudraCT Number: 2018-001981-40; [a]Maintenance dose of 3.0 mg/kg (q3M) started 1 month after last loading dose. [b]Patients randomized to placebo received loading doses of 3.0 mg/kg lumasiran at Months 6, 7, and 8; patients randomized to lumasiran received a maintenance dose of 3.0 mg/kg lumasiran at Month 6, and placebo at Months 7 and 8. [c]1.70 mmol/24hr/1.73m^2 = 150 mg/24hr/1.73m^2 (1 mmol/24hr/1.73m^2 = 88 mg/24hr/1.73m^2)

AGXT, alanine-glyoxylate aminotransferase gene; eGFR, estimated glomerular filtration rate; hr, hour; min, minute; q3M, once every 3 months; qM, once monthly; qM × 3, once monthly for 3 consecutive months

ILLUMINATE-A: Baseline Demographic Characteristics

Baseline characteristic	Placebo (N=13)	Lumasiran (N=26)	Overall (N=39)
Age at informed consent, years, mean (range) Pediatric (6 to <18 years), n (%)	17.0 (6–60) 8 (61.5)	18.7 (6–47) 14 (53.8)	18.1 (6–60) 22 (56.4)
Sex, male, n (%)	8 (61.5)	18 (69.2)	26 (66.7)
Race, n (%) White Asian Other or >1 race	 9 (69.2) 3 (23.1) 1 (7.7)	 21 (80.8) 3 (11.5) 2 (7.7)	 30 (76.9) 6 (15.4) 3 (7.7)
Region, n (%) Europe North America Middle East	 8 (61.5) 2 (15.4) 3 (23.1)	 10 (38.5) 11 (42.3) 5 (19.2)	 18 (46.2) 13 (33.3) 8 (20.5)
24hr urinary oxalate excretion corrected for BSA[a], mean ± SD, mmol/24hr/1.73m^2	1.79 ± 0.68	1.84 ± 0.60	1.82 ± 0.62
eGFR, mean ± SD, mL/min/1.73m^2	78.9 ± 26.8	83.0 ± 25.5	81.6 ± 25.7
Pyridoxine (vitamin B6) use, n (%)	9 (69.2)	13 (50.0)	22 (56.4)
Nephrocalcinosis grade ≥1, n (%)[b]	12 (92.3)	17 (70.8)	29 (78.4)
Patients reporting history of renal stone events[c], n (%) Lifetime 12 months prior to consent	 10 (76.9) 4 (30.8)	 23 (88.5) 11 (42.3)	 33 (84.6) 15 (38.5)

[a]ULN is 0.514 mmol/24hr/1.73m^2 = 45 mg/24hr/1.73m^2 (1 mmol/24hr/1.73m^2 = 88 mg/24hr/1.73m^2). [b]As assessed during screening, denominator includes all patients who had a graded renal ultrasound at baseline. [c]A renal stone event is defined as an event that includes at least one of the following: visit to healthcare provider because of a renal stone, medication for renal colic, stone passage, or macroscopic hematuria due to a renal stone

BSA, body surface area; SD, standard deviation; ULN, upper limit of normal

Percent Change in 24hr Urinary Oxalate

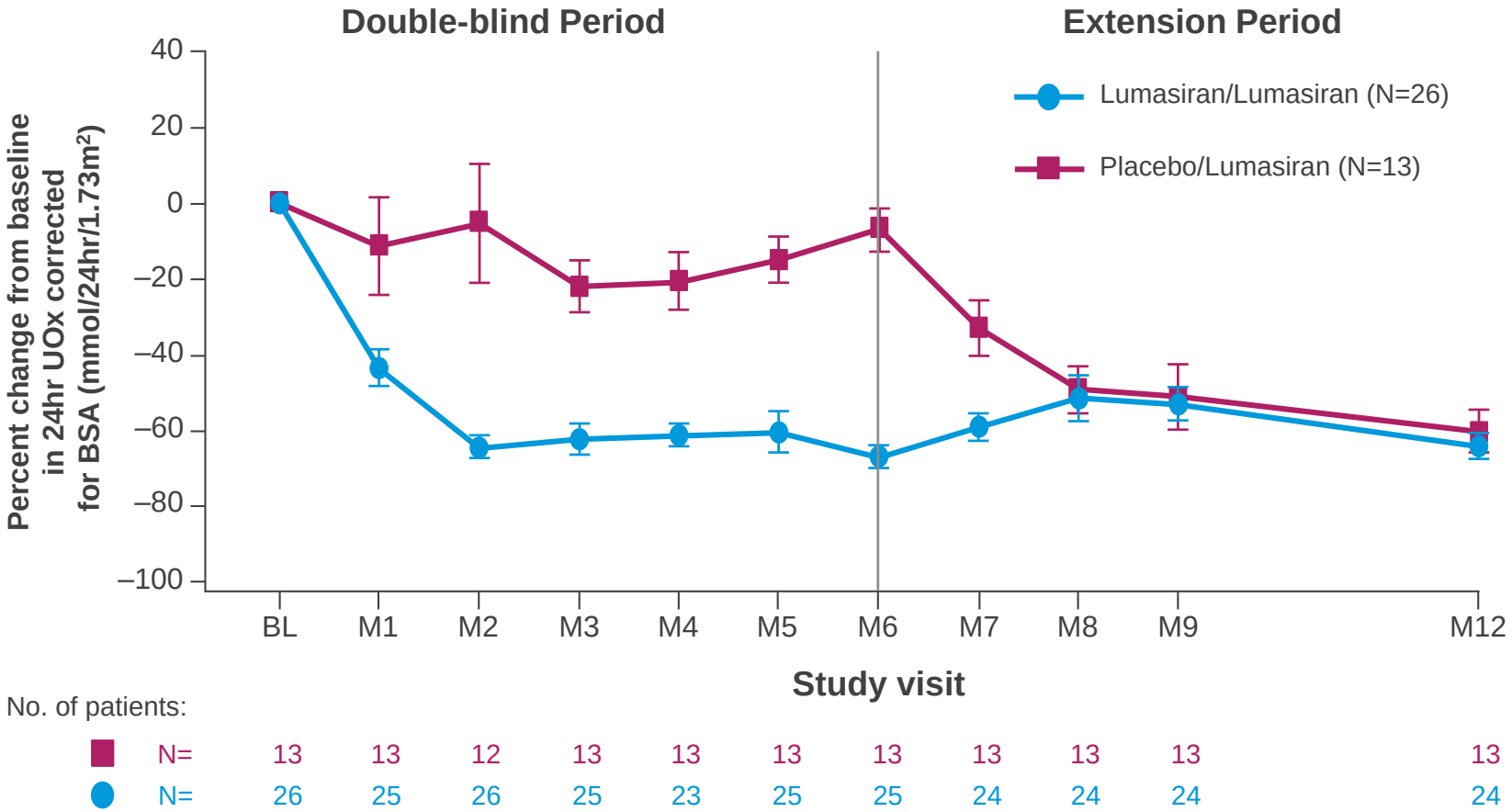
Reduction in 24hr UOx Was Replicated by the Placebo/Lumasiran Crossover Group in the Extension Period

Double-blind Period

- Patients treated with lumasiran had a significant reduction in 24hr UOx compared to placebo
- The least square mean change from baseline to Month 6[a] was −65.4% with lumasiran and −11.8% with placebo (LS mean difference: −53.5%; $p=1.7\times10^{-14}$)

Extension Period

- Patients initially randomized to lumasiran (Lumasiran/Lumasiran) had a sustained reduction in 24hr UOx through Month 12 (mean reduction from baseline 64.1%)
- Patients initially randomized to placebo who crossed over to lumasiran (Placebo/Lumasiran) demonstrated a similar time course and magnitude of 24hr UOx reduction (mean reduction 57.3% after 6 months of treatment)



[a]Average of Month 3 through Month 6

Data cut-off: 1 May 2020. Data in graph are mean ± SEM

SEM, standard error of mean; UOx, urinary oxalate

Proportion of Patients with 24hr Urinary Oxalate Level ≤1.5 × ULN

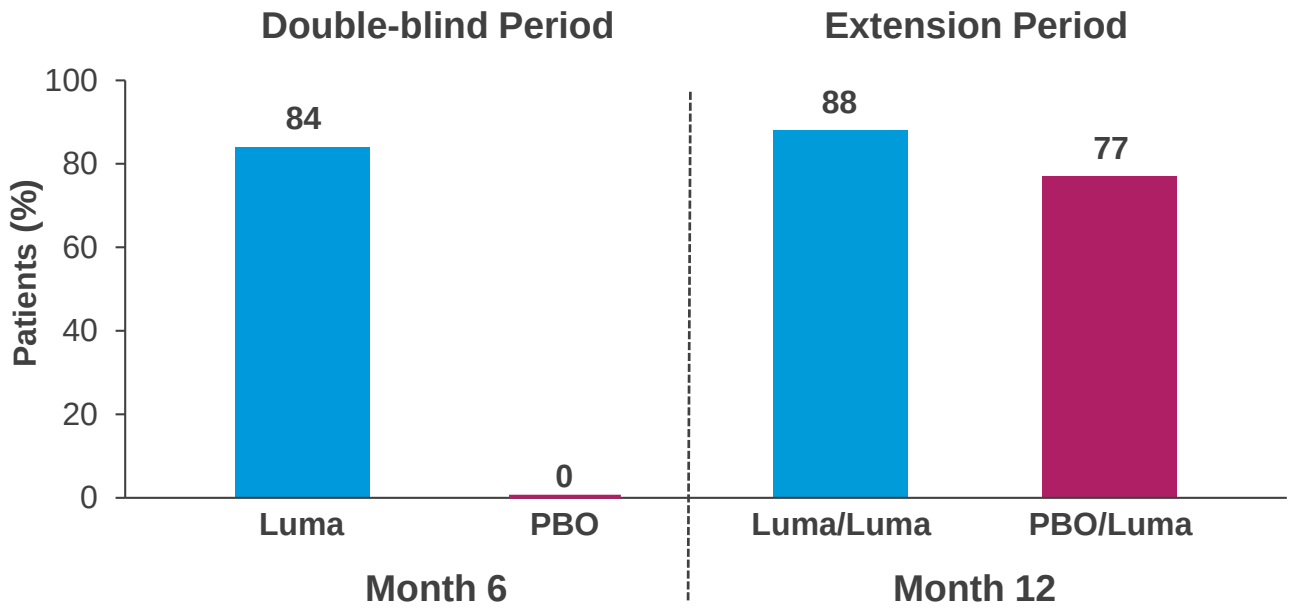
Comparable Proportion of Patients in the Placebo/Lumasiran Crossover Group Achieved Near Normalization or Normalization of 24hr UOx after 6 Months of Treatment

Double-blind Period

- 84% of lumasiran-treated patients achieved near normalization or normalization (≤1.5 × ULN) of 24hr UOx excretion at Month 6, compared to 0% of placebo-treated patients

Extension Period

- Lumasiran/Lumasiran patients sustained near normalization or normalization through Month 12
- 77% of Placebo/Lumasiran crossover patients achieved near normalization or normalization (≤1.5 × ULN) of 24hr UOx after 6 months of treatment



Additional Results

- Reduction in plasma oxalate was replicated by Placebo/Lumasiran crossover patients after 6 months of treatment: POx mean percent reduction 48.9%[a] (in the Double-blind Period, the least square mean treatment difference in POx for lumasiran compared to placebo was –39.5%; $p=2.9\times10^{-8}$)
- eGFR remained stable in both groups through Month 12

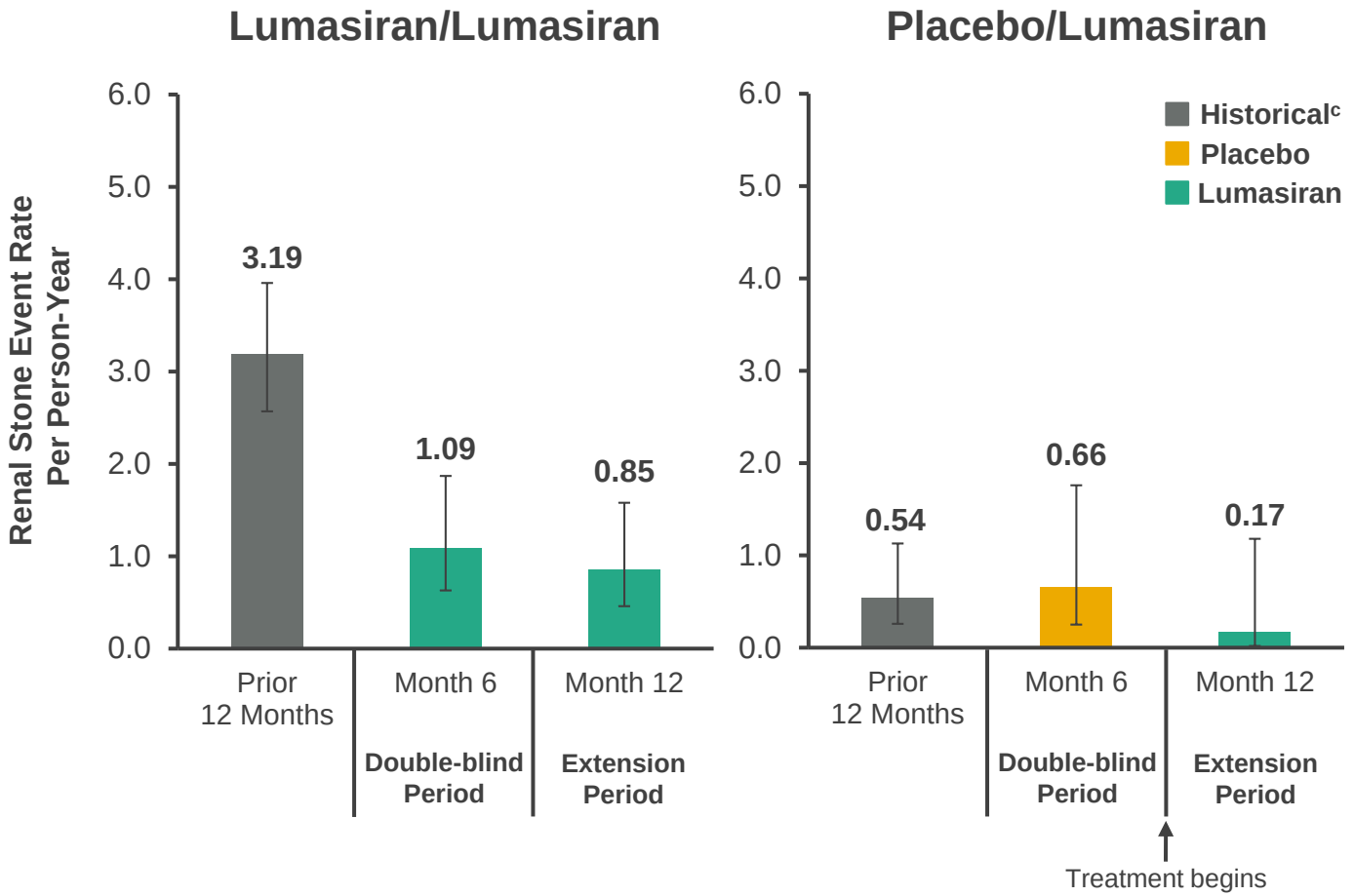
[a]The plasma oxalate analysis set was defined as those patients who had a baseline plasma oxalate level ≥1.5 × LLOQ (LLOQ is 5.55 µmol/liter)

LLOQ, lower limit of quantification; Luma, lumasiran; PBO, placebo; POx, plasma oxalate

Renal Stone Events[a]

Lower Renal Stone Event Rates Were Seen after 6–12 Months of Treatment[b]

- In the Lumasiran/Lumasiran group, renal stone event rates decreased with lumasiran treatment through Month 12
- In the Placebo/Lumasiran crossover group, renal stone event rates decreased after 6 months of treatment with lumasiran
- Renal stone event rate data will continue to be collected in the Extension Period of ILLUMINATE-A



[a]A renal stone event is defined as an event that includes at least one of the following: visit to healthcare provider because of a renal stone, medication for renal colic, stone passage, or macroscopic hematuria due to a renal stone. [b]Randomization was not stratified by renal stone events at baseline. [c]Patient reported history of renal stone events

Error bars represent 95% confidence interval

Safety of Lumasiran in PH1 Patients with Ongoing Dosing

Safety Profile Remained Consistent

- Overall mean exposure: 9.9 months (range 2.8–15.1 months) with 233 doses given
  - 35 patients treated for ≥6 months and 10 patients for ≥12 months
- Majority of AEs were mild in severity
- Most common related AEs (≥10%) were injection-site reactions, which were mild and transient
  - Erythema, pain, pruritus, or swelling at the injection site most common
- 1 patient with serious AE of urosepsis (severe), considered not related to study drug
- No treatment interruptions or discontinuations related to lumasiran; no deaths
- No clinically relevant changes in laboratory measures (including LFTs), vital signs, and electrocardiograms were observed

Event, n (%)	Placebo/ Lumasiran (N=13)	Lumasiran/ Lumasiran (N=26)	All Lumasiran (N=39)
AEs	9 (69)	24 (92)	33 (85)
Serious AE[a]	0	1 (4)	1 (3)
Severe AE[a]	0	1 (4)	1 (3)
AE leading to discontinuation of study treatment[b]	0	1 (4)	1 (3)
AEs occurring in ≥10% of patients			
Injection-site reactions[c]	5 (39)	11 (42)	16 (41)
Abdominal pain	1 (8)	6 (23)	7 (18)
Headache	0	4 (15)	4 (10)
Rhinitis	2 (15)	2 (8)	4 (10)
Upper respiratory infection	1 (8)	3 (12)	4 (10)
Death	0	0	0

Safety data from first dose of lumasiran to data cut-off date: 1 May 2020.

[a]Urosepsis, considered not related to study drug by the Investigator. [b]Fatigue and disturbance in attention, considered not related to lumasiran by the Investigator. [c]Includes adverse events of injection-site reaction, injection-site pain, injection-site erythema, and injection-site discomfort

AE, adverse event; LFT, liver function test; PH1, primary hyperoxaluria type 1

Summary

- PH1 is a rare devastating disease, with high morbidity and mortality in all age groups
- Current management options for PH1 are limited and there is an urgent need for new therapies that can reduce the production of hepatic oxalate, the key toxic metabolite in PH1
- Substantial reduction in urinary oxalate is expected to confer clinical benefit in patients with PH1[1]
- The reduction in urinary oxalate and plasma oxalate seen with lumasiran treatment in the 6-month Double-blind Period was replicated in Placebo/Lumasiran crossover patients in the Extension Period, confirming the robustness of the results
- Patients initially randomized to lumasiran maintained their reduction in 24hr urinary oxalate excretion through Month 12
- Lower renal stone event rates were seen after 6–12 months of treatment
- Lumasiran demonstrated an acceptable safety profile
  - Most common adverse events related to lumasiran were injection-site reactions, all of which were mild and transient

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1. Milliner et al. *Clin J Am Soc Nephrol* 2020;15:1056–65