

Lumasiran for Patients With Primary Hyperoxaluria Type 1 With Impaired Kidney Function: Data From the 6-Month Analysis of the Phase 3 ILLUMINATE-C Trial

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R Singer: no disclosures to report.

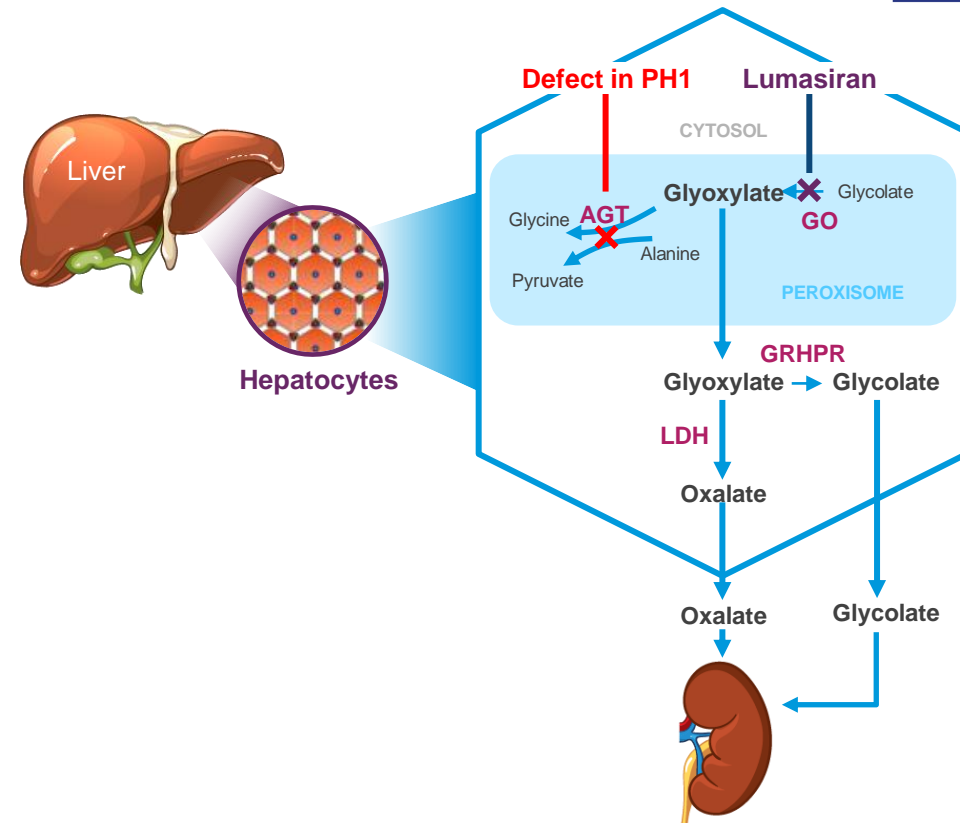
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Primary Hyperoxaluria Type 1 and Lumasiran

- PH1 is characterized by excessive hepatic oxalate production due to a deficiency in the hepatic peroxisomal enzyme AGT^{1,2}
- Patients with PH1 suffer from recurrent **kidney stones**, **nephrocalcinosis**, progressive kidney disease, and eventually **kidney failure in >70%**^{1,3}
- As kidney function declines, POx increases, leading to **systemic oxalosis and multi-organ damage**^{1,2}
- Lumasiran, an RNAi therapeutic that decreases hepatic oxalate production by **inhibiting the production of GO**,⁴⁻⁶ is approved for treatment of PH1 in all age groups⁵

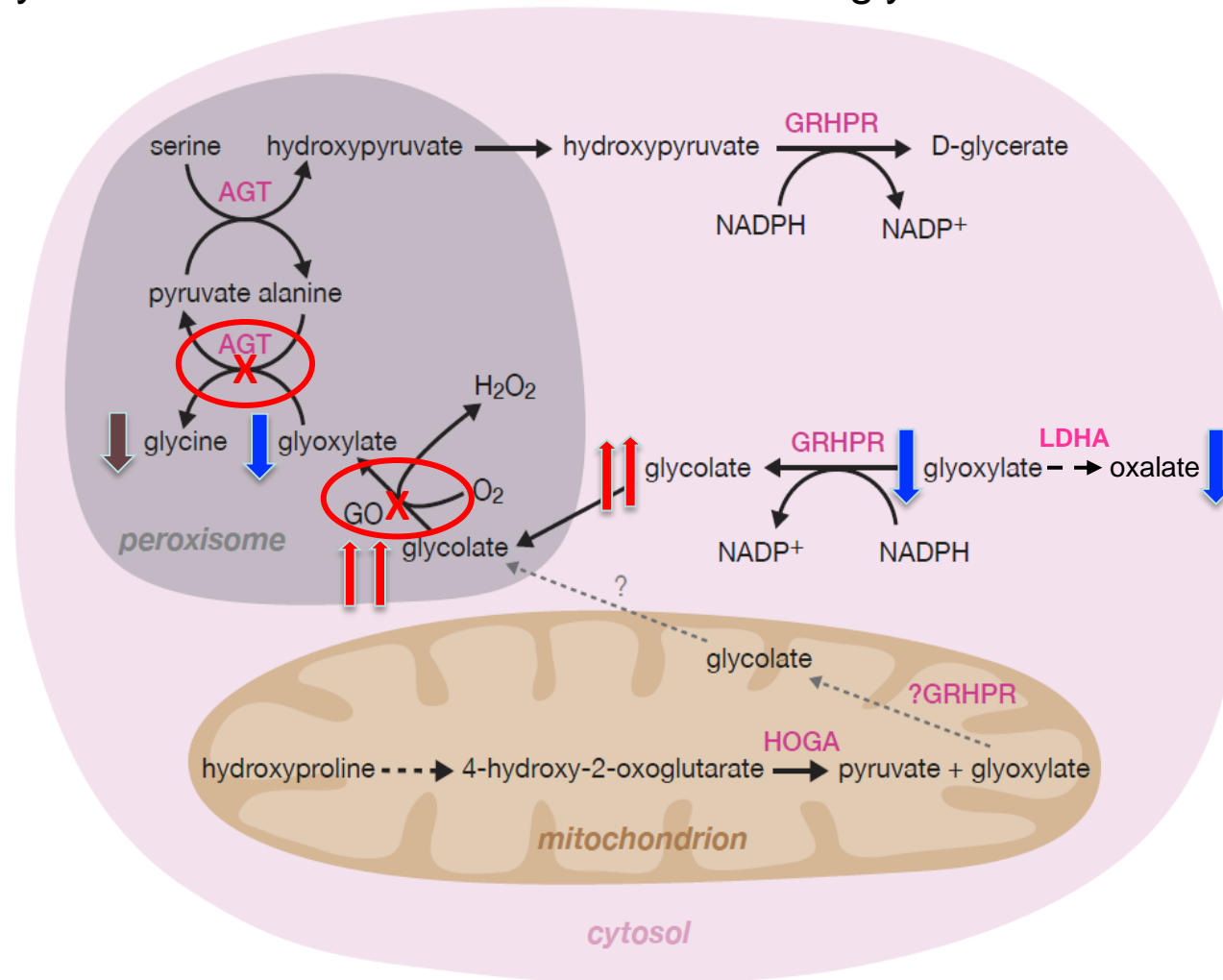


AGT, alanine-glyoxylate aminotransferase; GO, glycolate oxidase; GRHPR, glyoxylate reductase/hydroxypyruvate reductase; LDH, lactate dehydrogenase; PH1, primary hyperoxaluria type 1; POx, plasma oxalate; RNAi, ribonucleic acid interference; UOx, urinary oxalate.

1. Cochat P, Rumsby G. *N Engl J Med*. 2013;369:649-58. 2. Danpure CJ. *The Online Metabolic and Molecular Bases of Inherited Disease*. New York, NY: The McGraw-Hill Companies, Inc.; 2019. 3. Lieske JC, et al. *Am J Nephrol*. 2005;25:290-6. 4. Oxumo [package insert]. Cambridge, MA: Alnylam Pharmaceuticals; 2020. 5. Oxumo [summary of product characteristics]. Amsterdam, the Netherlands: Alnylam Netherlands; 2020. 6. Liebow A, et al. *J Am Soc Nephrol*. 2017;28:494-503.

PH1 and GO Blockade by Lumasiran

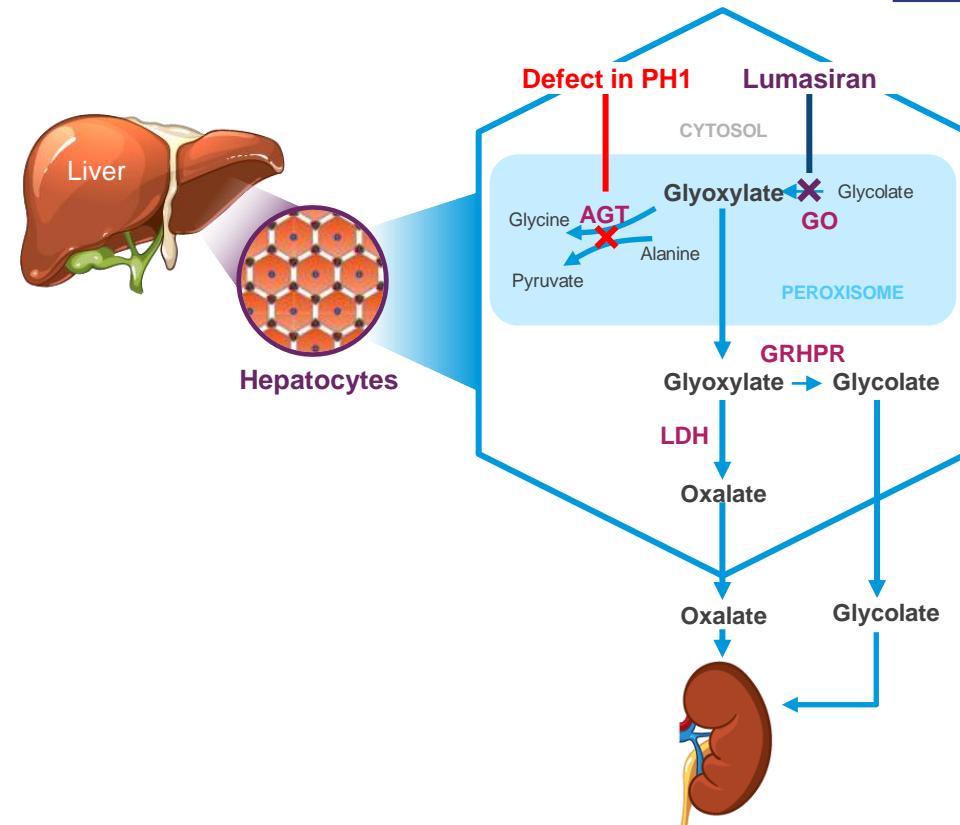
- Decrease in glyoxylate and oxalate and further increase in glycolate



HOGA, 4-hydroxy-2-oxoglutarate aldolase; LDHA, lactate dehydrogenase A; NADP⁺, nicotinamide adenine dinucleotide phosphate; NADPH, reduced nicotinamide adenine dinucleotide phosphate.

Primary Hyperoxaluria Type 1 and Lumasiran

- Reductions in UOx were observed in patients with PH1 in ILLUMINATE-A (age ≥ 6 years and eGFR ≥ 30 mL/min/1.73m²)¹ and ILLUMINATE-B (age < 6 years and eGFR > 45 mL/min/1.73m² [≥ 12 months] or normal serum creatinine [< 12 months])²
- In ILLUMINATE-A through 24 months and ILLUMINATE-B through 12 months, the most common AEs related to lumasiran were injection-site reactions
- In PH1 patients with CKD stage 3b–5 (eGFR < 45 mL/min/1.73m²), elevated POx is directly related to the pathophysiology of oxalosis, making reduction of POx a suitable clinical target in this population³

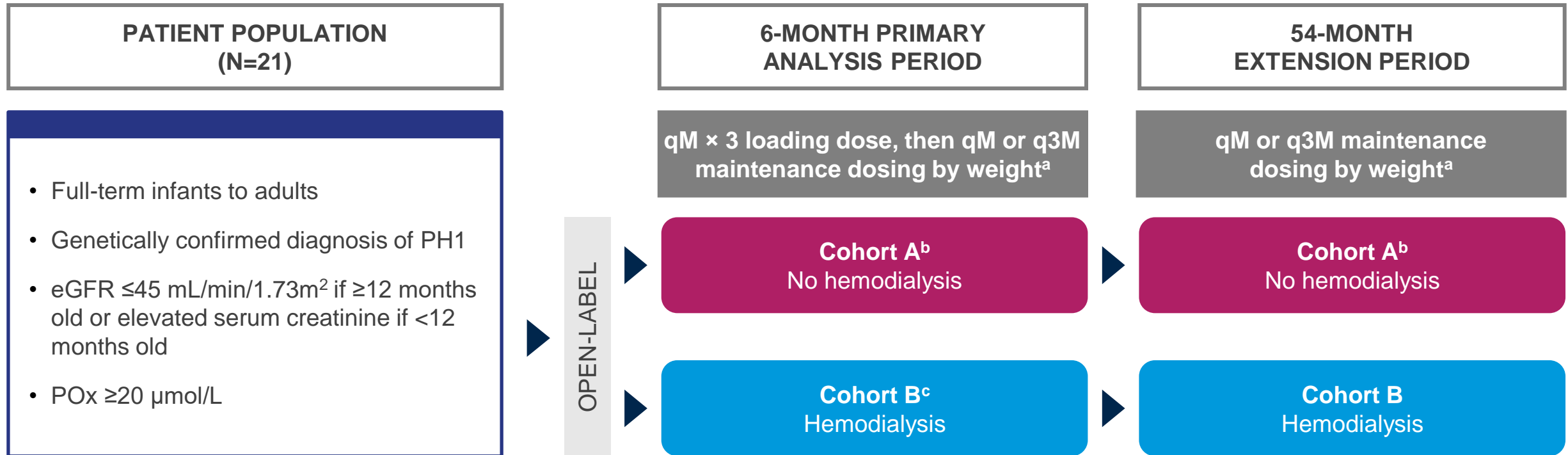


Here, we present additional results from the 6-month primary analysis period of ILLUMINATE-C

AE, adverse event; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

1. Garrelfs SF, et al. *N Engl J Med.* 2021;384:1216-26. 2. Sas DJ, et al. *Genet Med.* 2022;24:654-62. 3. Milliner DS, et al. *Clin J Am Soc Nephrol.* 2020;15:1056-65.

ILLUMINATE-C Study Design



EudraCT: 2019-001346-17; ClinicalTrials.gov: NCT04152200.

^aPatients < 10 kg received loading doses of 6.0 mg/kg qM for 3 months and then maintenance doses of 3.0 mg/kg qM; patients ≥ 10 to < 20 kg received loading doses of 6.0 mg/kg qM for 3 months and then maintenance doses of 6.0 mg/kg q3M; patients ≥ 20 kg received loading doses of 3.0 mg/kg qM for 3 months and then maintenance doses of 3.0 mg/kg q3M. Maintenance dose was started 1 month after the last loading dose. ^bCohort A patients who experience progression of kidney impairment over time and begin to require dialysis therapy will cross over to Cohort B. No patients crossed over in the primary analysis period.

^cNo changes to dialysis regimen (except when medically necessary) or kidney transplantation were permitted during the primary analysis period. q3M, once every 3 months; qM, once monthly; qM \times 3, once monthly for 3 consecutive months.

Baseline and Clinical Characteristics

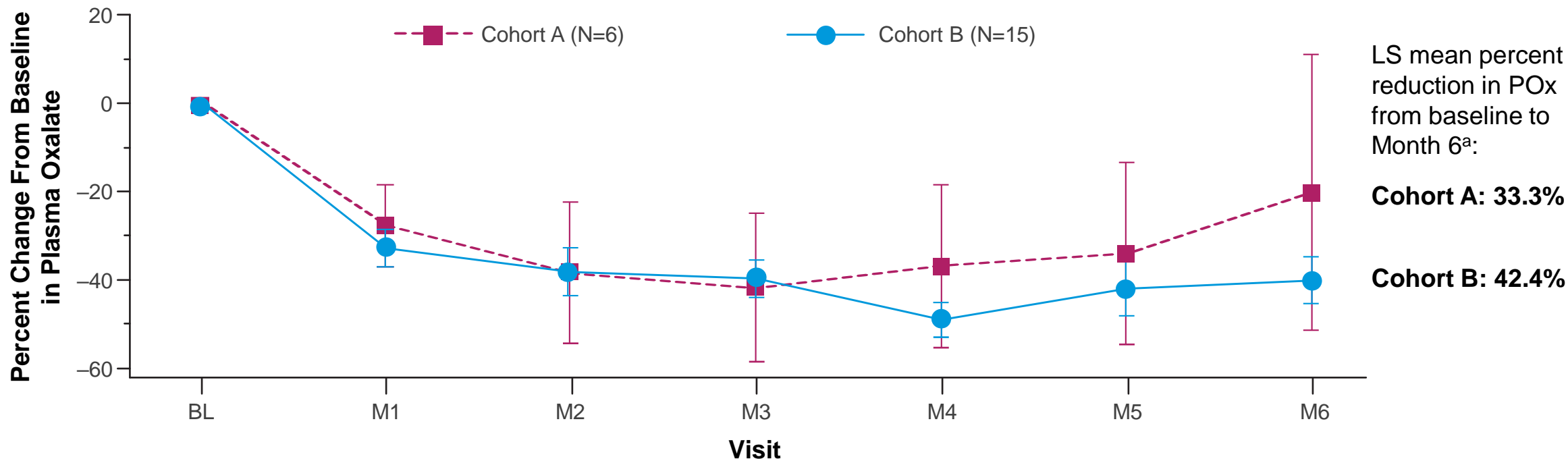
- **21 patients** across 13 sites in 10 countries were enrolled in the study; all completed the 6-month primary analysis period

Baseline/Clinical Characteristic	Cohort A (N=6)	Cohort B (N=15)	All Treated (N=21)
Age at consent, median (range), years	9 (0–40)	6 (1–59)	8 (0–59)
Female, n (%)	3 (50)	6 (40)	9 (43)
Race, n (%)			
Asian	1 (17)	3 (20)	4 (19)
White	4 (67)	12 (80)	16 (76)
Other	1 (17)	0	1 (5)
POx, median (range) ^a , µmol/L	57.94 (22.7–134.0)	103.65 (56.3–167.0)	100.93 (22.7–167.0)
Spot UOx:Cr ^b , median (range), mmol/mmol	N=6 0.332 (0.075–1.380)	N=2 ^c 0.535 (0.451–0.618)	N=8 0.391 (0.075–1.380)
24-hour UOx excretion corrected for BSA ^d , median (range), mmol/24h/1.73m ²	N=5 2.011 (0.56–2.47)	N=1 ^c 1.277 (1.28–1.28)	N=6 1.644 (0.56–2.47)
eGFR ^e , median (range), mL/min/1.73m ²	N=5 ^e 16.541 (8.61–34.09)	Not applicable	Not applicable
Number of dialysis therapy sessions per week, median (range)	Not applicable	6 (3–7)	Not applicable

^aULN=12.11 µmol/L for POx, as determined based on data from 75 healthy adults. ^b1 mmol/mmol=0.796 mg/mg. ^cUrinary measures of oxalate were collected in Cohort B for patients who were not anuric and able to supply an acceptable urine sample. ^dULN=0.514 mmol/24h/1.73m² for 24-hour UOx corrected for BSA. ^eeGFR was calculated only in patients age ≥12 months. eGFR (mL/min/1.73m²) was calculated from serum creatinine based on the Modification of Diet in Renal Disease formula for patients age ≥18 years and the Schwartz Bedside Formula for patients age 1 to <18 years. BSA, body surface area; UOx:Cr, urinary oxalate:creatinine ratio; ULN, upper limit of normal.

Efficacy: Primary Endpoint

Primary Endpoint: Mean (SEM) Percent Change From Baseline in POx



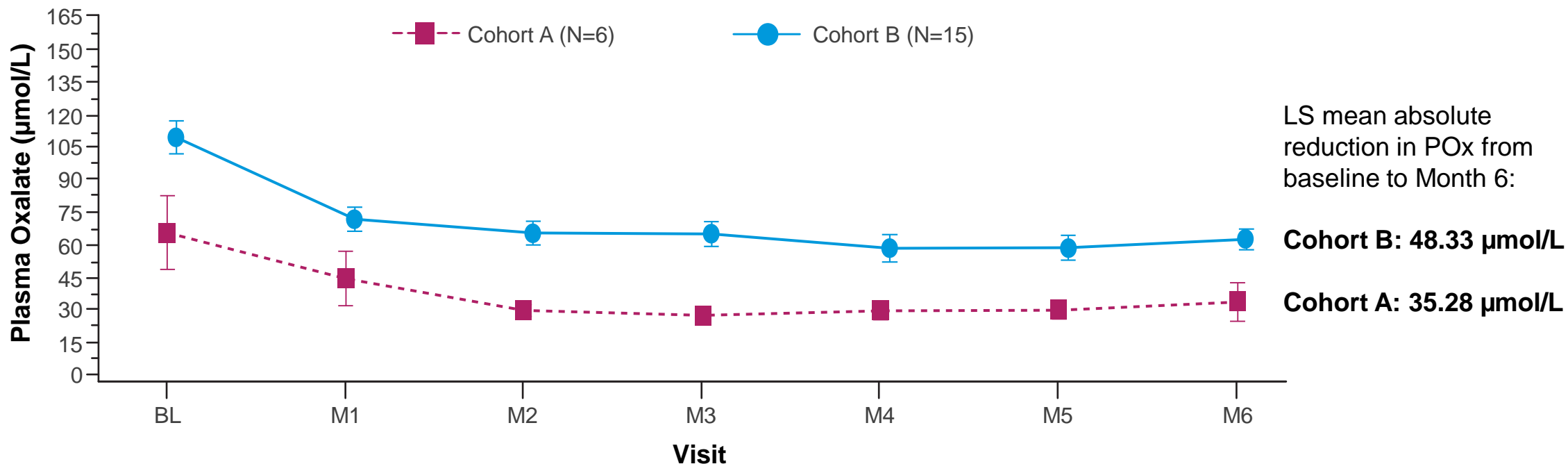
No. of Patients:

■ N=	6	6	6	6	6	6	6
● N=	15	15	15	15	13	14	15

^aThe primary analysis of percent change from baseline in POx (Cohort A) and predialysis POx (Cohort B) was based on the MMRM model with the estimate calculated as the LS mean of the primary outcome variable averaged across Months 3 to 6. Baseline value was the mean of the last 4 POx level values collected prior to the first dose of lumasiran (predialysis in Cohort B).
BL, baseline; M, month; MMRM, mixed model for repeated measures; SEM, standard error of the mean.

Efficacy: Secondary Endpoint

Secondary Endpoint: Mean (SEM) Actual POx Values



No. of Patients:

■ N=	6	6	6	6	6	6	6
● N=	15	15	15	15	13	14	15

Baseline value was the mean of the last 4 POx level values collected prior to the first dose of lumasiran (predialysis in Cohort B). ULN=12.11 µmol/L for POx, as determined based on data from 75 healthy adults.

Additional Outcomes During the 6-Month Primary Analysis Period

- Cardiac measures of systemic oxalosis, as assessed by echocardiography
- Medullary nephrocalcinosis by kidney ultrasound
- Kidney stone event rates
- Burdensome symptoms of PH1

LVEF and GLS With Lumasiran Treatment

- Left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) were chosen as cardiac measures of systemic oxalosis^a
- Abnormalities and improvements were predefined

Abnormal LVEF (LVEF <55%)

- Among patients with abnormal LVEF at baseline, at Month 6, $\geq 5\%$ improvement was seen in:
 - Cohort A: 1/1 patient
 - Cohort B: 2/4 patients

Abnormal GLS ($|\text{GLS}| < 15\%$)

- Measure of LV contractility more sensitive than LVEF for predicting outcomes in advanced kidney disease¹
- Among patients with abnormal GLS at baseline, $\geq 2\%$ increase from baseline in $|\text{GLS}|$ was seen at Month 6 in:
 - Cohort A: 1/1 patient
 - Cohort B: 3/3 patients

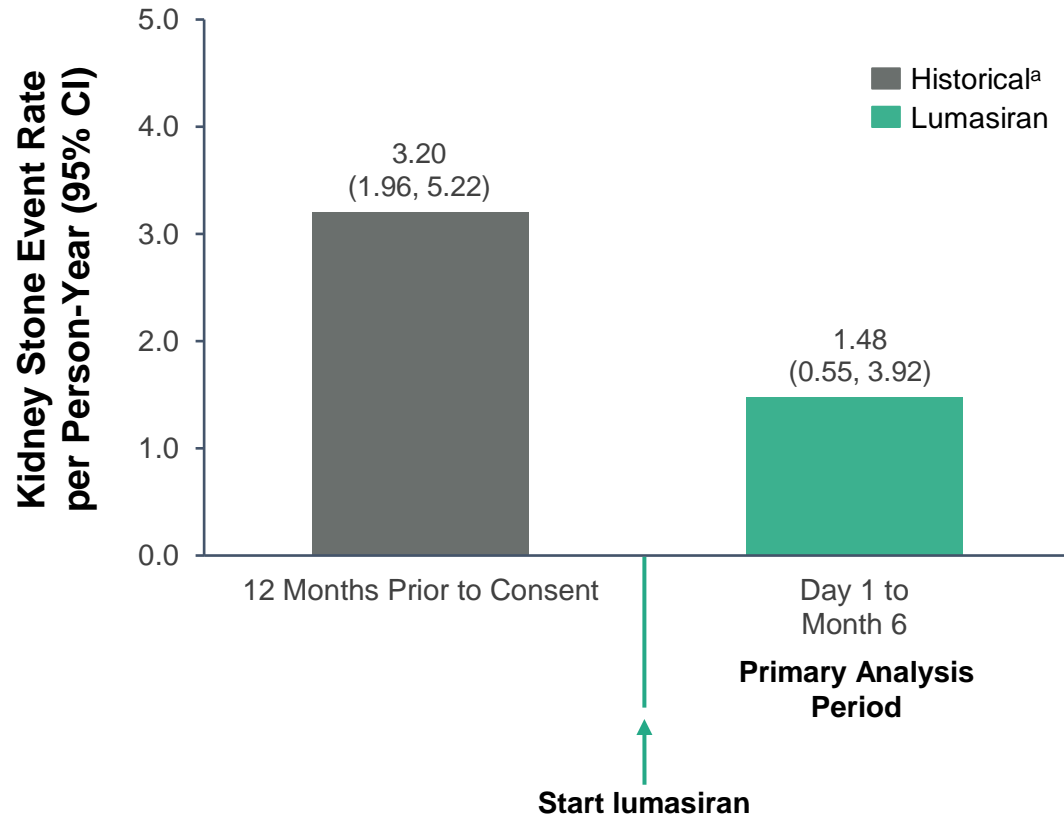
^aDiastolic E/e' was also a cardiac measure of systemic oxalosis; no abnormalities were observed for diastolic E/e' at baseline.

E/e', ratio of peak early mitral inflow velocity to early diastolic mitral annular velocity; GLS, global longitudinal strain; LV, left ventricular; LVEF, left ventricular ejection fraction.

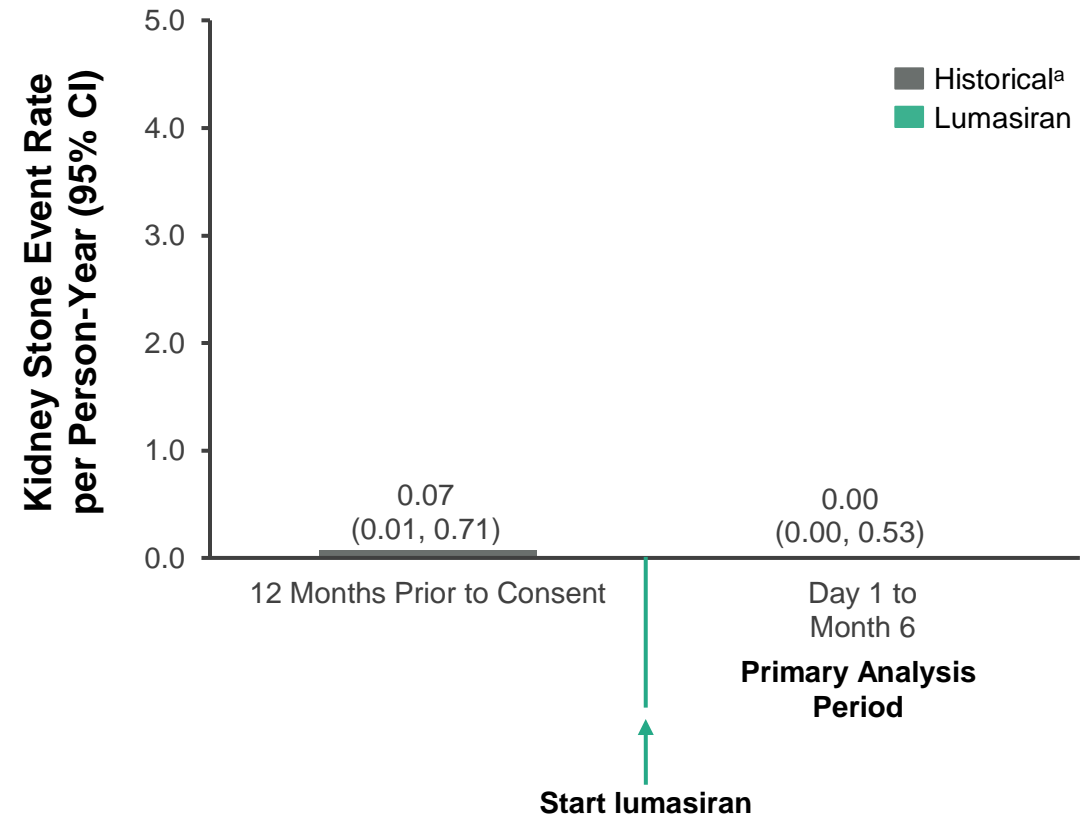
1. Krishnasamy R, et al. *PLoS One*. 2015;10:e0127044.

Kidney Stone Event Rates

Cohort A (N=6)



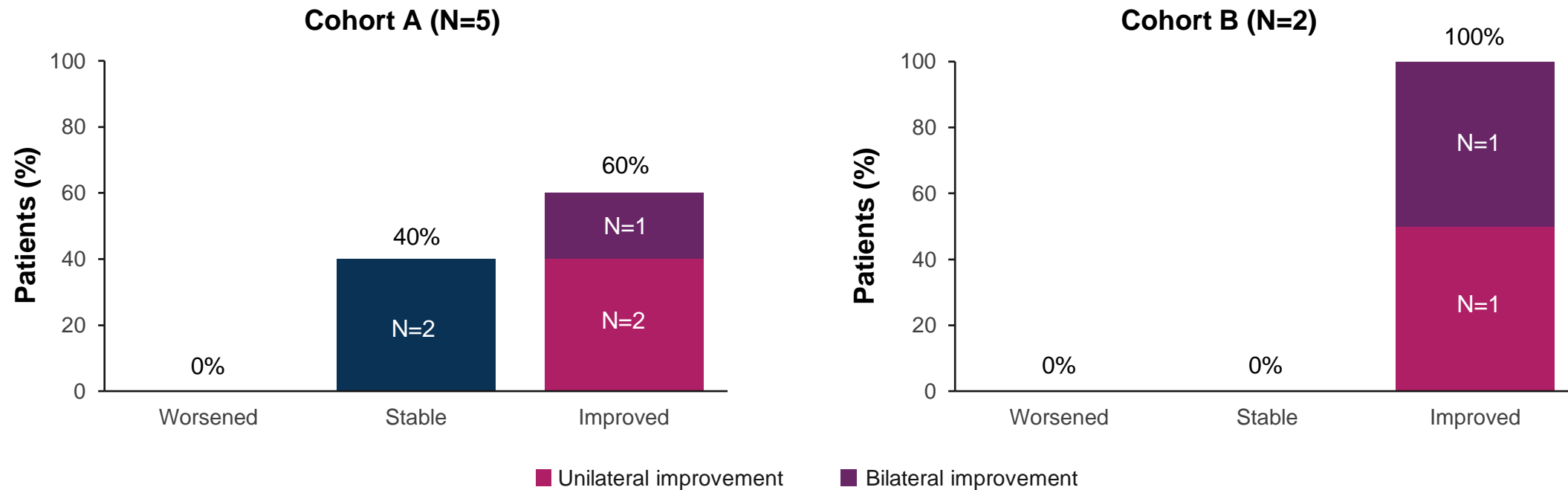
Cohort B (N=15)



^aHistorical group: patient-reported history of kidney stone events; annualized rate was not calculated for patients <6 months old.
CI, confidence interval.

Medullary Nephrocalcinosis by Ultrasonography

Change in Medullary Nephrocalcinosis Grade at Month 6 Among Patients With Medullary Nephrocalcinosis at Baseline^a



- In Cohort A, 1 patient did not have medullary nephrocalcinosis at baseline and had bilateral worsening at Month 6
- In Cohort B, 9 patients did not have medullary nephrocalcinosis at baseline; all remained stable at Month 6; 4 patients did not have adequate kidney ultrasounds

^aExcludes patients lacking medullary nephrocalcinosis at baseline.

Most Burdensome Symptoms

- The 3 most burdensome symptoms at baseline for each patient were identified by the investigator^a
- Investigators subsequently noted if each patient's most burdensome symptoms were stable/unchanged, improved, or worsened; no patient was categorized as worsened in this survey^b

Most Burdensome Symptom at Baseline	Overall (N=21)	Cohort A (N=6)		Cohort B (N=15)			
		Total N	Improved N (%)	Stable N (%)	Total N (%)	Improved N (%)	Stable N (%)
Fatigue	12	2 (33)	1 (50)	1 (50)	10 (67)	7 (70)	3 (30)
Nausea/decreased appetite	5	1 (17)	1 (100)	0	4 (27)	0	4 (100)
Bone pain	4	1 (17)	1 (100)	0	3 (20)	2 (67)	1 (33)
Decreased mobility	4	0	0	0	4 (27)	2 (50)	2 (50)
Renal stone associated pain	3	3 (50)	2 (67)	1 (33)	0	0	0
Shortness of breath	3	0	0	0	3 (20)	3 (100)	0
Daytime somnolence	1	0	0	0	1 (7)	1 (100)	0
Other symptom	3	0	0	0	3 (20)	0	3 (100)

^aInvestigators selected up to 3 symptoms from the following: renal stone associated pain, bone pain, decreased mobility, fatigue, shortness of breath, vision loss, skin ulcerations, nausea/decreased appetite, daytime somnolence, not applicable, and other.

^bAnalysis not prespecified.

Safety

- The majority of AEs were mild or moderate in severity
- There were no serious or severe AEs related to lumasiran and no deaths of patients who received lumasiran
- There were no treatment discontinuations or study withdrawals
- The most frequently reported AEs were pyrexia (29%) and injection-site reactions (24%)
- The most common AE related to lumasiran was injection-site reaction (24% [5/21] of patients)
 - All injection-site reactions were mild and transient, and the most common symptoms included erythema, discoloration, and hematoma
- There were no clinically relevant trends in laboratory measures (including hematology, blood chemistries, liver function tests), vital signs, physical examinations, or electrocardiograms related to lumasiran

Event	Number of Patients (%)		
	Cohort A (N=6)	Cohort B (N=15)	All Treated (N=21)
AEs	5 (83)	12 (80)	17 (81)
AEs occurring in ≥10% of patients in either cohort			
Pyrexia	1 (17)	5 (33)	6 (29)
Injection-site reaction	1 (17)	4 (27)	5 (24)
Device-related infection	0	2 (13)	2 (10)
Diarrhea	0	2 (13)	2 (10)
AEs leading to discontinuation of study treatment	0	0	0
AEs leading to withdrawal from the study	0	0	0
Death	0	0	0
Serious AEs	1 (17)	5 (33)	6 (29)
Severe AEs	0	3 (20)	3 (14)

Data are presented for the 6-month primary analysis period.

Conclusions

- Lumasiran treatment resulted in substantial reductions in POx in patients of all ages with PH1 and advanced kidney disease
- Additional outcomes related to PH1 generally improved or remained stable with lumasiran treatment
- The most common adverse event related to lumasiran was injection-site reaction
- These results, along with previous reports from ILLUMINATE-A and ILLUMINATE-B, provide evidence supporting the general safety and effectiveness of lumasiran in lowering the oxalate burden of patients with PH1
- Long-term data on clinical outcomes are warranted to confirm initial findings

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