US PI Intended for US HCPs

Developed and funded by Alnylam PHARMACEUTICALS

Clinical Trial Data | Lumasiran: A Treatment Option for Primary Hyperoxaluria Type 1 (PH1) Across a Range of Ages and Kidney Function, Including Hemodialysis[1-12]

Lumasiran is indicated to reduce UOx and POx levels in pediatric and adult patients with PH1; dosing is weight based with three monthly loading doses followed by quarterly maintenance dosing in patients > 10 kg or monthly maintenance dosing in patients ≤ 10 kg[13]

References and Abbreviations

PH Pathophysiology and Lumasiran Mechanism of Action

Phase 1/2 Study

Phase 1/2, randomized, single-blind, placebo-controlled study with single and multiple ascending doses of lumasiran[2–4]

Part A
- Healthy participants (N = 32)
- 18-64 years old
- BMI 18-30 kg/m^2

Part B
- Patients with PH1 (N = 20)
- 6-64 years old
- eGFR > 45 mL/min/1.73 m^2

Study design *BL characteristics*

Primary endpoint[2]

Incidence of AEs

Safety data *Efficacy data*

Phase 2, multicenter, 54-month OLE study[4]

Patients who had completed Part B of the Phase 1/2 study (N = 20)

Study design *BL characteristics*

Long-term data[4]

Long-term efficacy and safety assessed through Month 54

Efficacy data *Safety data*

ILLUMINATE-A Phase 3 Study

Double-blind, placebo-controlled study: 6-month primary treatment period with 54-month OLE[5–7]

- Patients with PH1 (N = 39)
- ≥ 6 years old
- eGFR ≥ 30 mL/min/1.73 m^2[2,5-7]

Study design *BL characteristics*

Primary endpoint[5]

Percent change in 24H UOx excretion from BL through Month 6

Long-term data[7]

Long-term efficacy and safety assessed through Month 60

Efficacy data *Safety data*

60M: Complete[14]

ILLUMINATE-B Phase 3 Study

Single-arm, open-label study: 6-Month primary treatment period with 54-month OLE[8,9]

- Patients with PH1 (N = 18)
- < 6 years old
- eGFR > 45 mL/min/1.73 m^2[2,8,9,*]

*or normal SCr if < 12 months old[8,9]

Study design *BL characteristics*

Primary endpoint[8]

Percent change in spot UOx:Cr from BL through Month 6

Long-term data[9]

Long-term efficacy and safety assessed through Month 60

Efficacy data *Safety data*

60M: Complete[15]

ILLUMINATE-C Phase 3 Study

Single-arm, open-label study 6-Month primary treatment period with 54-month OLE[10,11]

- Patients with PH1 (N = 21)
- All ages
- eGFR ≤ 45 mL/min/1.73 m^2[2,10,11,*]

*or increased SCr if aged < 12 months old[10,11]

Study design *BL characteristics*

Primary endpoints[10]

Percent change in POx (cohort A) and predialysis POx (cohort B) relative to BL through Month 6

Long-term data[11]

Long-term efficacy and safety assessed through Month 24

Efficacy data *Safety data*

60M: Ongoing (complete through Month 24)[11,16]

This resource is intended to support scientific exchange.
The information provided is not intended to serve as recommendations for clinical practice.

MED-US-GO1-2400027 I Prepared: March 2026

References

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2. Frishberg Y, Deschênes G, Groothoff JW, et al. Phase 1/2 study of lumasiran for treatment of primary hyperoxaluria type 1: a placebo-controlled randomized clinical trial. *Clin J Am Soc Nephrol.* 2021;16(7):1025-1036. doi:10.2215/CJN.14730920
3. Frishberg Y, Deschênes G, Groothoff JW, et al. Phase 1/2 study of lumasiran for treatment of primary hyperoxaluria type 1: a placebo-controlled randomized clinical trial. *Clin J Am Soc Nephrol.* 2021;16(7):1025-1036. doi:10.2215/CJN.14730920 (Supplementary appendix)
4. Frishberg Y, Groothoff JW, Hulton SA, et al. Long-term treatment with lumasiran: final results from the phase 2 open-label extension study. Poster presented at: 61st ERA Congress, May 23-26, 2024; Stockholm, Sweden
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9. Frishberg Y, Hayes W, Ben-Shalom E, et al. Long-term efficacy and safety in the phase 3 ILLUMINATE-B trial of lumasiran for primary hyperoxaluria type 1 in infants and young children. Poster presented at: NKF Congress; April 10-13, 2025; Boston, MA
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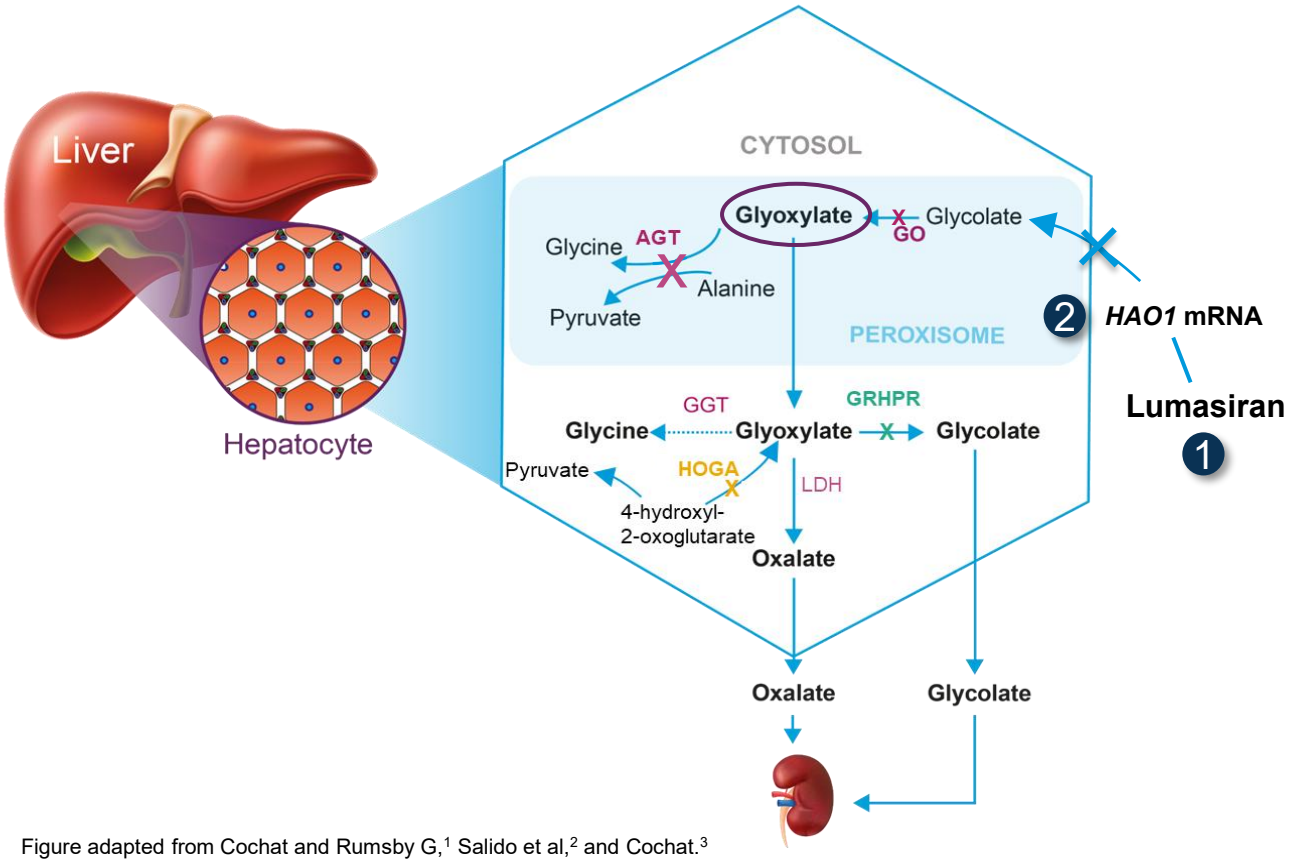
Abbreviations

AE, adverse event; BL, baseline; BMI, body mass index; eGFR, estimated glomerular filtration rate; HCP, healthcare professional; M, months; OLE, open-label extension; PH, primary hyperoxaluria; PH1, PH type 1; PI, Prescribing Information; POx, plasma oxalate; SCr, serum creatinine; UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio.

Primary Hyperoxaluria Subtypes

Different PH Subtypes Result From Different Pathologic Mutations[1,*]



Mutations in genes coding for key enzymes in the **glyoxylate** detoxification pathway result in overproduction of oxalate, causing PH[1]

- ***AGXT:*** PH1 is caused by a deficiency of liver-specific peroxisomal AGT
- ***GRHPR:*** PH2 is caused by a lack of GRHPR
- ***HOGA1:*** PH3 results from defects in mitochondrial HOGA

Figure adapted from Cochat and Rumsby G,[1] Salido et al,[2] and Cochat.[3]

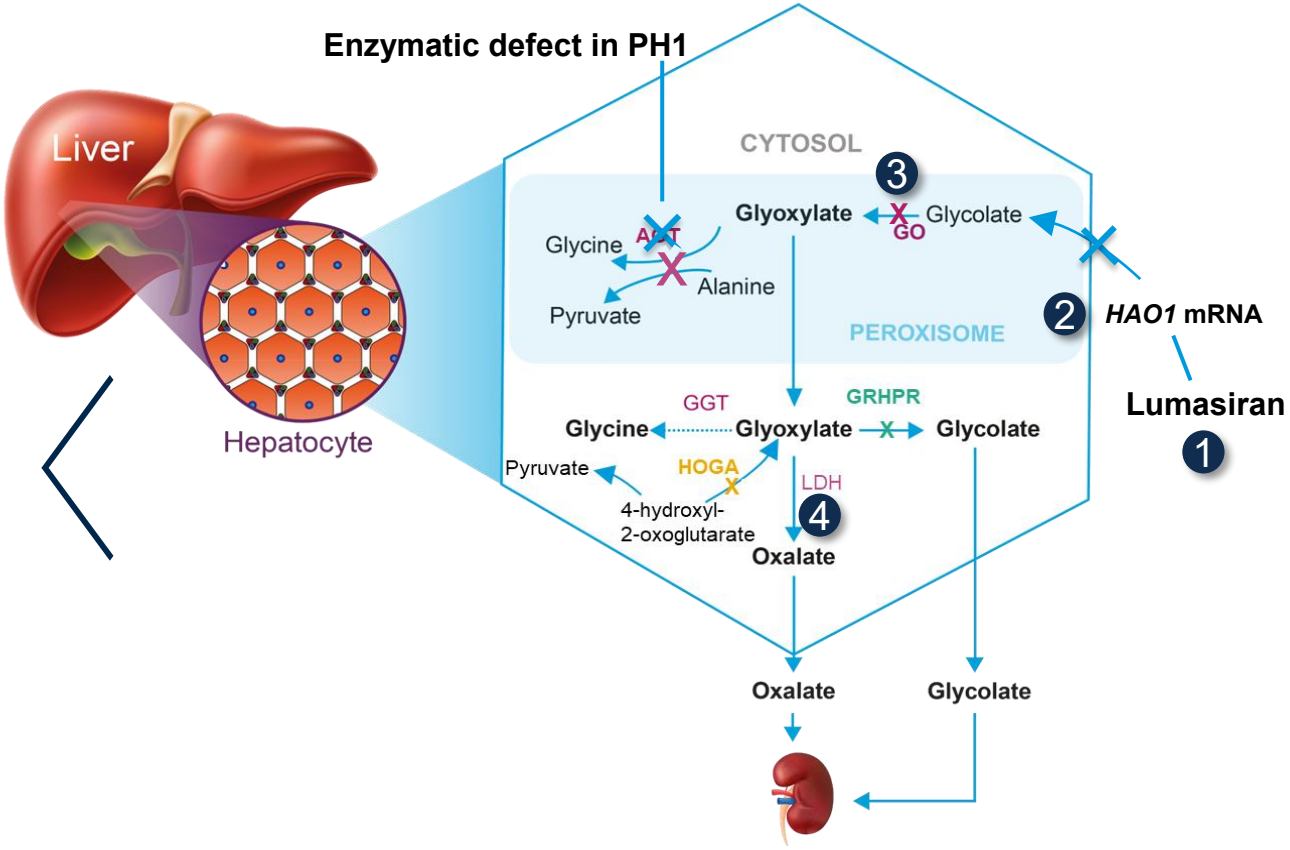
*The prevalence of diagnosed PH1 in North America and Europe is estimated to be 1-3 patients per million people.[1,4]

AGT, alanine-glyoxylate aminotransferase [enzyme]; *AGXT*, alanine-glyoxylate aminotransferase [gene]; GGT, glutamate:glyoxylate aminotransferase; GO, glycolate oxidase; GRHPR, glyoxylate reductase/hydroxypyruvate reductase [enzyme]; *GRHPR*, glyoxylate reductase/hydroxypyruvate reductase [gene]; *HAO1*, hydroxyacid oxidase [gene]; HOGA, 4-hydroxy-2-oxoglutarate aldolase [enzyme]; *HOGA1*, 4-hydroxy-2-oxoglutarate aldolase [gene]; LDH, lactate dehydrogenase; mRNA, messenger RNA; PH, primary hyperoxaluria; PH1, PH type 1; PH2, PH type 2; PH3, PH type 3.

1. Cochat P, Rumsby G. Primary hyperoxaluria. *N Engl J Med.* 2013;369(7):649-658. doi:10.1056/NEJMra1301564; 2. Salido E, Pey AL, Rodriguez R, Lorenzo V. Primary hyperoxalurias: disorders of glyoxylate detoxification. *Biochim Biophys Acta.* 2012;1822(9):1453-1464. doi:10.1016/j.bbadis.2012.03.004; 3. Cochat P. Primary hyperoxaluria type 1. *Kidney Int.* 1999;55(6):2533-2547. doi:10.1046/j.1523-1755.1999.00477.x; 4. Wang X, Danese D, Brown T, et al. Primary hyperoxaluria type 1 disease manifestations and healthcare utilization: a multi-country, online, chart review study. *Front Med (Lausanne).* 2021;8:703305. doi: 10.3389/fmed.2021.703305

Lumasiran Mechanism of Action

Lumasiran Is a Subcutaneously Administered, Liver-Directed RNAi Therapeutic That Decreases Hepatic Oxalate Production by Inhibiting the Production of GO[1]



1. Lumasiran is a double-stranded RNAi therapeutic[1,2]
2. Lumasiran reduces GO levels in the liver by targeting *HAO1* mRNA[1,2]
   GO is an enzyme upstream of AGT[1,2]
3. Decreased hepatic **GO levels** lead to **reduced levels of glyoxylate**, a substrate required for oxalate production[1,2]
4. The **reduction in glyoxylate levels** leads to **decreased oxalate production**[1,2]

Figure adapted from Salido et al,[3] Cochat,[4] and Cochat and Rumsby.[5]
AGT, alanine-glyoxylate aminotransferase [enzyme]; GGT, glutamate:glyoxylate aminotransferase; GO, glycolate oxidase; *HAO1*, Hydroxyacid oxidase [gene]; HOGA, 4-hydroxy-2-oxoglutarate aldolase [enzyme]; LDH, lactate dehydrogenase; mRNA, messenger RNA; PH1, primary hyperoxaluria type 1; RNAi, ribonucleic acid interference.

1. Liebow A, Li X, Racie T, et al. An investigational RNAi therapeutic targeting glycolate oxidase reduces oxalate production in models of primary hyperoxaluria. *J Am Soc Nephrol.* 2017;28(2):494-503. doi:10.1681/ASN.2016030338; 2.OXLUMO. Prescribing information. Alnylam Pharmaceuticals; 2025. Accessed August 1, 2025. https://www.alnylam.com/sites/default/files/pdfs/OXLUMO-Prescribing-Information.pdf;
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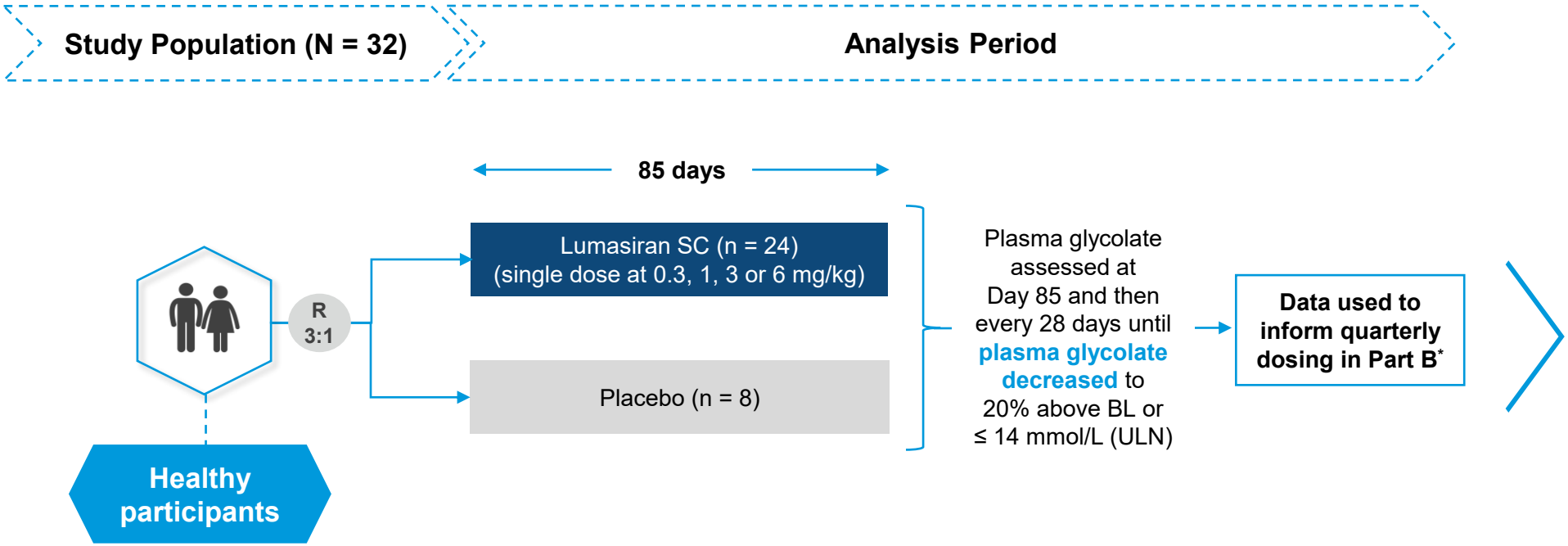
Phase 1/2 Study: Study Design

First-in-Human Randomized Controlled Study to Evaluate the Safety, Pharmacokinetic, and Pharmacodynamic Profiles of Lumasiran

Part A



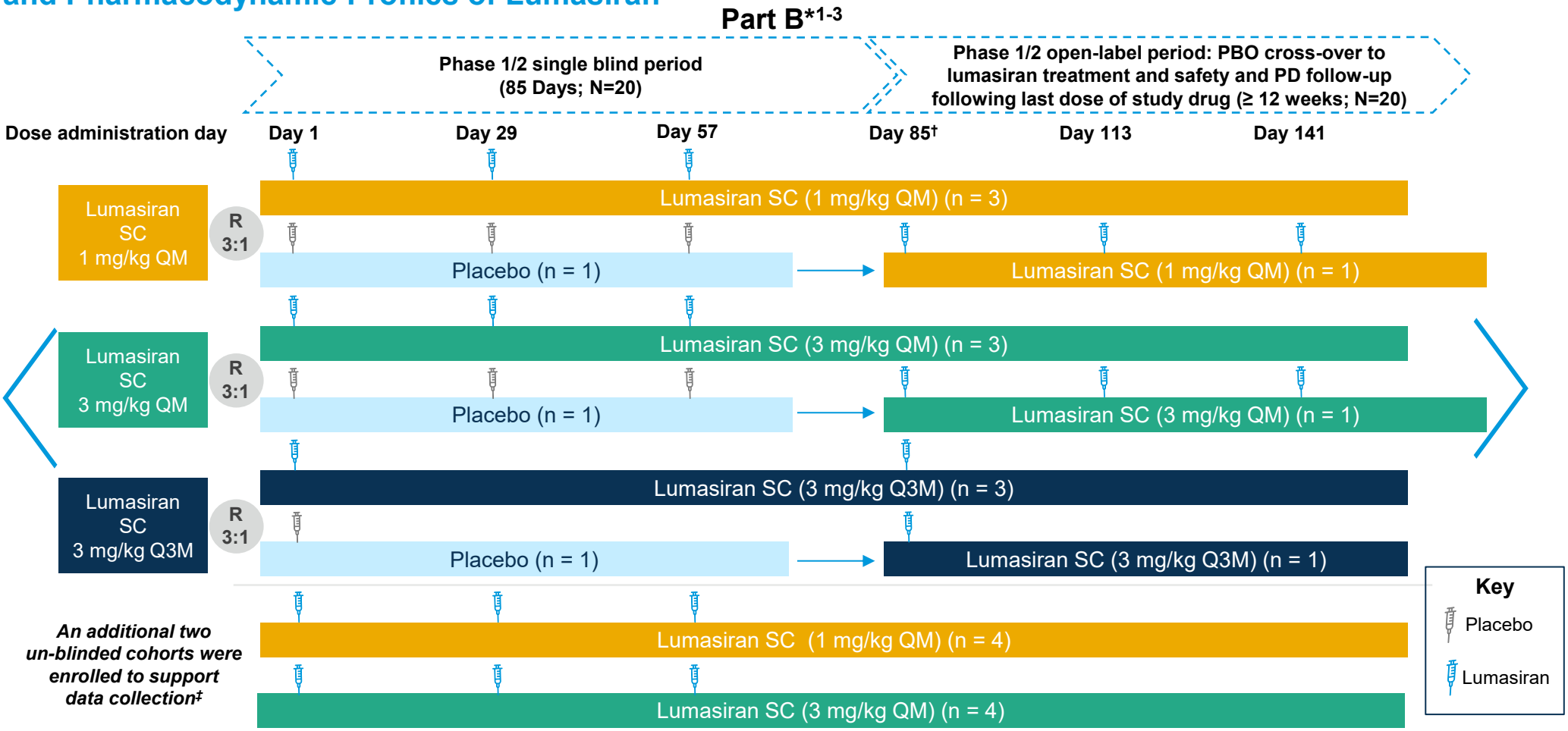
*The lowest dose to have a pharmacologic effect in Part A, in the opinion of the safety review committee, was selected as the starting dose in Part B

BL, baseline; R, randomized; SC, subcutaneous; ULN, upper limit of normal.

Frishberg Y, Deschênes G, Groothoff JW, et al. Phase 1/2 study of lumasiran for treatment of primary hyperoxaluria type 1: a placebo-controlled randomized clinical trial. *Clin J Am Soc Nephrol.* 2021;16(7):1025-1036. doi:10.2215/CJN.14730920.

Phase 1/2 Study: Study Design

First-in-Human Randomized Controlled Study to Evaluate the Safety, Pharmacokinetic, and Pharmacodynamic Profiles of Lumasiran[1]



*The lowest dose to have a pharmacologic effect in Part A, in the opinion of the safety review committee, was selected as the starting dose in Part B[1]; †On day 85 patients initially receiving placebo crossed over to receive lumasiran at the same dose administered to the cohort into which they were initially randomized[1]; ‡These patients were not randomized or blinded, as each patient received open-label lumasiran starting on Day 1[1].
PBO, placebo; PD, post-dose; Q3M, once every 3 months; QM, once monthly; R, randomized; SC, subcutaneous. 1. Frishberg Y, Deschênes G, Groothoff JW, et al. Phase 1/2 study of lumasiran for treatment of primary hyperoxaluria type 1: a placebo-controlled randomized clinical trial. *Clin J Am Soc Nephrol.* 2021;16(7):1025-1036. doi:10.2215/CJN.14730920; 2. Frishberg Y, Deschênes G, Groothoff JW, et al. Phase 1/2 study of lumasiran for treatment of primary hyperoxaluria type 1: a placebo-controlled randomized clinical trial. *Clin J Am Soc Nephrol.* 2021;16(7):1025-1036. doi:10.2215/CJN.14730920 (supplementary appendix); 3. ClinicalTrials.gov identifier: NCT02706886. Updated January 30, 2020. Accessed August 1, 2025. https://clinicaltrials.gov/study/NCT02706886.

Click to view the Frishberg *Clin J Am Soc Nephrol* 2021 study publication for the full inclusion and exclusion criteria

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Phase 1/2 Study: Study Design

Healthy Participants or Patients With PH1 Were Enrolled in Part A or B, Respectively, of the Phase 1/2 Study[1,*]

Part A: Healthy Participants[1,2]

- Aged 18-64 years
- BMI 18-30 kg/m^2 at screening and Day −1

Part B: Patients With PH1[1]

- Aged 6-64 years
- PH1 diagnosis confirmed by genetic analysis or reduced AGT activity†
- 24-hour UOx > 0.7 mmol/24 h/1.73 m^2
- eGFR > 45 mL/min/1.73 m^2

*Age-, weight-, kidney-, and PH1-related inclusion criteria are presented here. Please see the study protocol for a full list of inclusion and exclusion criteria.[1] †Diagnosis based on a documented genetic analysis, biochemical criteria, and the presence of *AGXT* gene variants or reduced hepatic AGT enzyme activity that was considered evidence of the disease state (medical history).[3]

AGT, alanine-glyoxylate aminotransferase [enzyme]; *AGXT*, alanine-glyoxylate aminotransferase [gene]; BL, baseline; BMI, body mass index; eGFR, estimated glomerular filtration rate; PH1, primary hyperoxaluria type 1; UOx, urinary oxalate.

1. Frishberg Y, Deschênes G, Groothoff JW, et al. Phase 1/2 study of lumasiran for treatment of primary hyperoxaluria type 1: a placebo-controlled randomized clinical trial. *Clin J Am Soc Nephrol.* 2021;16(7):1025-1036. doi:10.2215/CJN.14730920; 2. Frishberg Y, Deschênes G, Groothoff JW, et al. Phase 1/2 study of lumasiran for treatment of primary hyperoxaluria type 1: a placebo-controlled randomized clinical trial. *Clin J Am Soc Nephrol.* 2021;16(7):1025-1036. doi:10.2215/CJN.14730920 (Supplementary appendix); 3. Frishberg Y, Groothoff JW, Hulton SA, et al. Long-term treatment with lumasiran: final results from the phase 2 open-label extension study. Poster presented at: 61st ERA Congress, May 23-26, 2024; Stockholm, Sweden.

Click to view the Frishberg *Clin J Am Soc Nephrol* 2021 study publication for the full list of endpoints

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Phase 1/2 Study: Endpoints

Primary Endpoint Assessed Safety Outcomes and Secondary Endpoints assessed UOx and PK parameters (Part B)

Primary

- Incidence of AEs (**Parts A and B**)

Secondary

- Plasma PK profile and ADA levels
- 24-hour UOx excretion and UOx:Cr clearance from BL (**Part B**)

This is not inclusive of all available endpoints or data, please refer to the Frishberg *Clin J Am Soc Nephrol* 2021 publication linked above.
ADA, antidrug antibody; AE, adverse event; BL, baseline; PK, pharmacokinetics; UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio.
Frishberg Y, Deschênes G, Groothoff JW, et al. Phase 1/2 study of lumasiran for treatment of primary hyperoxaluria type 1*:* a placebo-controlled randomized clinical trial. *Clin J Am Soc Nephrol.* 2021;16(7):1025-1036. doi:10.2215/CJN.14730920

Click to view the Frishberg *Clin J Am Soc Nephrol* 2021 study publication for BL characteristics

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Phase 1/2 Study: BL Characteristics

BL Characteristics Were Generally Balanced Between Participants in Parts A and B

BL Characteristics for Part A and B of the Phase 1/2 Study

Baseline Characteristic	Part A: Healthy Participants		Part B: Patients With PH1		
	Lumasiran (n = 24)	Placebo (n = 8)	Lumasiran (n = 17)	Placebo (n = 3)	Overall* (N = 20)
Age, years, mean (SD)	29 (6)	30 (6)	14 (8)	21 (19)	15 (10)
Female, n (%)	11 (46)	5 (63)	12 (71)	1 (33)	13 (65)
Race, n (%)					
White	18 (75)	7 (88)	13 (77)	2 (67)	15 (75)
Black	2 (8)	0 (0)	0 (0)	0 (0)	0 (0)
Asian	1 (4)	1 (13)	3 (18)	1 (33)	4 (20)
Other	3 (13)	0 (0)	1 (6)	0 (0)	1 (5)
Body weight, kg, mean (SD)	72 (12)	67 (14)	47 (25)	64 (43)	50 (27)
Height, cm, mean (SD)	172 (9)	173 (8)	146 (20)	158 (30)	148 (21)
BMI, kg/m^2, mean (SD)	24.3 (2.4)	22.3 (3.0)	20.7 (5.3)	23.0 (8.2)	21.0 (5.6)

*Patients initially randomized to receive placebo were re-baselined and their first day of lumasiran administration was set to Day 1.
BL, baseline; BMI, body mass index; PH1, primary hyperoxaluria type 1; SD, standard deviation.
Frishberg Y, Deschênes G, Groothoff JW, et al. Phase 1/2 study of lumasiran for treatment of primary hyperoxaluria type 1: a placebo-controlled randomized clinical trial. *Clin J Am Soc Nephrol.* 2021;16(7):1025-1036. doi:10.2215/CJN.14730920

Click to view the Frishberg *Clin J Am Soc Nephrol* 2021 study publication for BL characteristics

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Phase 1/2 Study: BL Characteristics

Part B enrolled 20 Patients with PH1

BL Clinical Characteristics for Patients with PH1 (Part B*) of the Phase 1/2 Study

BL Characteristic	Part B: Patients With PH1		
	Lumasiran (n = 17)	Placebo (n = 3)	Overall† (N = 20)
Age at diagnosis, years, mean (SD)	4 (3)	9 (3)	4 (4)
Genotype, n (%) PR/any genotype Missense/Missense or Missense/Nonsense Nonsense/Nonsense	 1 (6) 9 (53) 7 (41)	 1 (33) 1 (33) 1 (33)	 2 (10) 10 (50) 8 (40)
Pyridoxine use, n (%)	10 (59)	3 (100)	13 (65)
24-hour UOx excretion, mmol/24 h/1.73 m^2, mean (SD)‡	1.66 (0.64)	1.96 (0.32)	1.71 (0.60)
24-hour UOx:Cr, mg/mg, mean (SD)§	0.17 (0.08)	0.18 (0.04)	0.17 (0.07)
eGFR, mL/min/1.73 m^2, mean (SD)¶	82 (21); n = 11	61 (12); n = 2	78 (21); n = 14
Plasma oxalate, µmol/L, mean (SD)**	7.9 (4.1)	15.6 (6.9)	8.8 (4.8)

*Part A not shown as these were healthy participants; †Patients initially randomized to receive placebo were re-baselined, and their first day of lumasiran administration set to Day 1; ‡ULN: 0.46 mmol/24 h/1.73 m^2; 1 mmol/24 h/1.73 m^2 = 88 mg/24 h/1.73 m^2; §1 mg/mg = 1.256 mmol/mmol; ¶eGFR was calculated based on the Modification of Diet in Renal Disease formula for patients aged ≥18 years or the Bedside Schwartz formula for patients aged <18 years; **ULN: 1.6 µmol/L.

BL, baseline; eGFR, estimated glomerular filtration rate; PH1, primary hyperoxaluria type 1; PR, pyridoxine-responsive; SD, standard deviation; ULN, upper limit of normal; UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio.

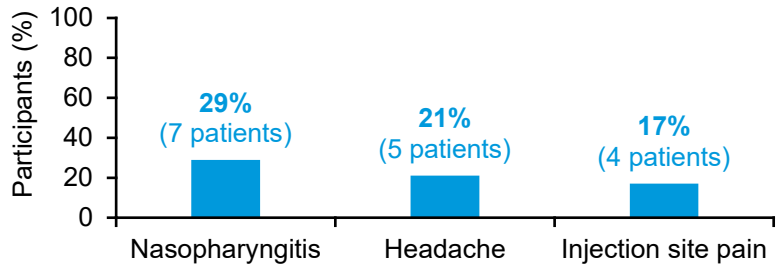
Frishberg Y, Deschênes G, Groothoff JW, et al. Phase 1/2 study of lumasiran for treatment of primary hyperoxaluria type 1*:* a placebo-controlled randomized clinical trial. *Clin J Am Soc Nephrol.* 2021;16(7):1025-1036. doi:10.2215/CJN.14730920

Phase 1/2 Study: Primary Endpoint

Incidence of AEs Through Day 85

Part A
N = 32

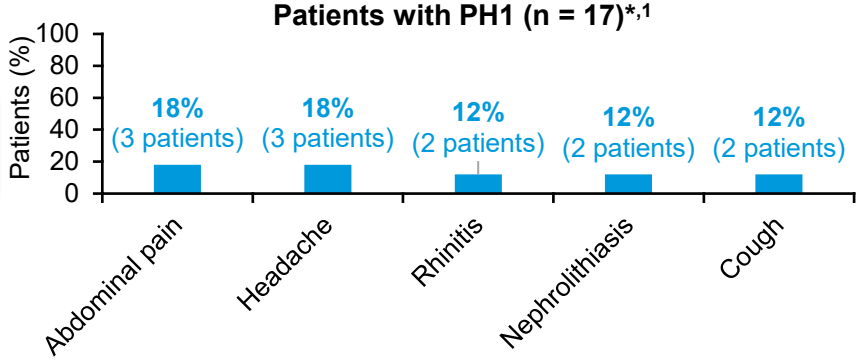
Most Common AEs in Lumasiran-Treated Healthy Participants (n = 24)*,[1,2]



- AEs were reported in **83% (n = 20) of participants** who received lumasiran and **63% (n = 5) of participants** who received placebo (Days 1-85)[1]
- **No serious AEs** were reported[2]
- **One participant (4%)** who received lumasiran 0.3 mg/kg experienced a **severe AE** (increased serum creatine phosphokinase) that was **not considered TR**[1]
- **All reports of injection site pain** were **mild, transient**, and considered TR[1]
- The **majority of AEs were mild to moderate** in severity and considered unrelated to lumasiran[1]

Part B
N = 20

Most Common AEs in Lumasiran-Treated Patients with PH1 (n = 17)*,[1]



- AEs were reported in **59% (n = 10) of patients** who received lumasiran and **67% (n = 2) of patients** who received placebo (Days 1-85)[1]
- **No severe AEs** were reported in patients receiving lumasiran[1]
- **Serious AEs** were reported in one patient (33%) who received placebo and two patients (12%) who received lumasiran; **none were considered TR**[1]
- **Two patients (12%) reported mild to moderate, transient ISRs†** considered TR[1]
- The **majority of AEs were mild to moderate** in severity and considered unrelated to lumasiran[1]

*Experienced by > 10% of participants/patients.[1] †Includes all AEs mapping to the *Medical Dictionary for Regulatory Activities* high-level term ISRs.[1]
AE, adverse event; BL, baseline; ISR, injection site reaction; PH1, primary hyperoxaluria type 1; TR, treatment related.

1. Frishberg Y, Deschênes G, Groothoff JW, et al. Phase 1/2 study of lumasiran for treatment of primary hyperoxaluria type 1*:* a placebo-controlled randomized clinical trial. *Clin J Am Soc Nephrol.* 2021;16(7):1025-1036. doi:10.2215/CJN.14730920; 2. Frishberg Y, Deschênes G, Groothoff JW, et al. Phase 1/2 study of lumasiran for treatment of primary hyperoxaluria type 1*:* a placebo-controlled randomized clinical trial. *Clin J Am Soc Nephrol.* 2021;16(7):1025-1036. doi:10.2215/CJN.14730920 (supplementary appendix).

Click to view the Frishberg *Clin J Am Soc Nephrol* 2021 study publication for all endpoint results

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Phase 1/2 Study: Primary Endpoint

No Treatment-Related Severe AEs or Treatment Discontinuations Were Reported Through Day 85 by Patients With PH1 in Part B

Safety Overview During the Placebo Comparison Period (Days 1-85) – Part B

AE, n (%)	Placebo (n = 3)	Lumasiran			
		1 mg/kg QM (n = 7)	3 mg/kg QM (n = 7)	3 mg/kg Q3M (n = 3)	All Lumasiran (n = 17)
Any AE	2 (67)	5 (71)	4 (57)	1 (33)	10 (59)
Serious AE*	1 (33)	0	2 (29)	0	2 (12)
Severe AE†	1 (33)	0	0	0	0
AE leading to treatment discontinuation	0	0	0	0	0
Death	0	0	0	0	0
ISRs‡	0	1 (14)	1 (14)	0	2 (12)

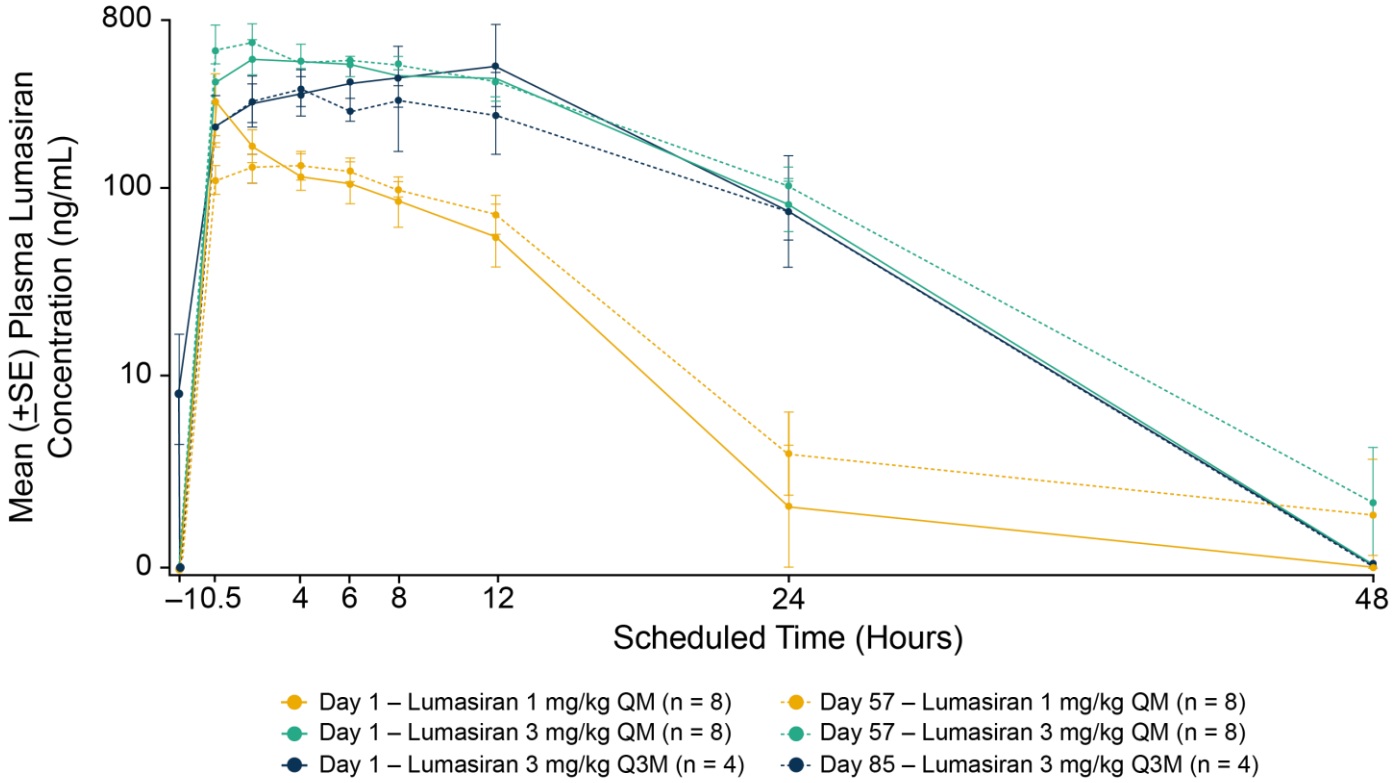
*Patient who received placebo: nephrolithiasis and acute pyelonephritis. Patients who received lumasiran: vomiting and nephrolithiasis; †Acute pyelonephritis;
‡Includes all AEs included in the *Medical Dictionary for Regulatory Activities* high-level term ISRs.
AE, adverse event; BL, baseline; ISR, injection site reaction; PH1, primary hyperoxaluria type 1; Q3M, once every 3 months; QM, once monthly.
Frishberg Y, Deschênes G, Groothoff JW, et al. Phase 1/2 study of lumasiran for treatment of primary hyperoxaluria type 1*:* a placebo-controlled randomized clinical trial. *Clin J Am Soc Nephrol.* 2021;16(7):1025-1036. doi:10.2215/CJN.14730920

Phase 1/2 Study: Secondary Endpoint

PK Responses in Healthy Participants Informed Lumasiran Dose Selection in Patients With PH1[1]

Part A: *Identified the lowest dose producing an appreciable pharmacologic effect* in healthy participants as 1 mg/kg, informing Part B starting dose[1,†] (data not presented)*
Part B: Lumasiran response in patients with PH1 (data presented throughout this section)

Part B: Plasma PK Profile for Lumasiran After a Single or Multiple SC Doses in Patients with PH1[2]



Part A & B

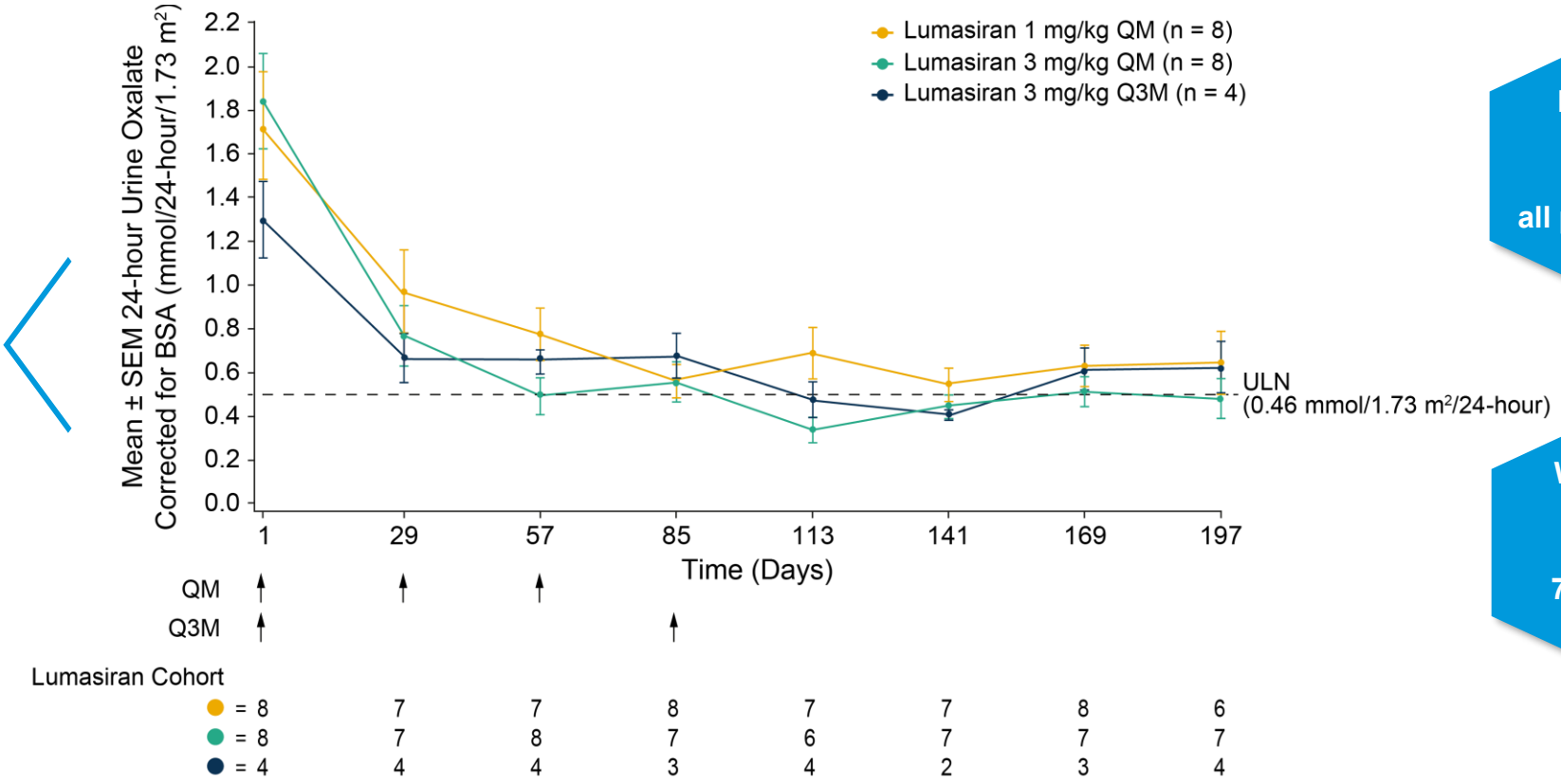
- Lumasiran is **rapidly** absorbed and eliminated from the plasma[1]
- Kidney excretion is a **minor elimination** pathway for lumasiran[1]

*Based on the opinion of the safety review committee;[1]†PK response to lumasiran among heathy participants from Part A are not shown in the graph.[1]
BL, baseline; PH1, primary hyperoxaluria type 1; PK, pharmacokinetics; Q3M, once quarterly; QM, once monthly; SC, subcutaneous; SE, standard error.
1. Frishberg Y, Deschênes G, Groothoff JW, et al. Phase 1/2 study of lumasiran for treatment of primary hyperoxaluria type 1*:* a placebo-controlled randomized clinical trial. *Clin J Am Soc Nephrol.* 2021;16(7):1025-1036. doi:10.2215/CJN.14730920; 2. Frishberg Y, Deschênes G, Groothoff JW, et al. Phase 1/2 study of lumasiran for treatment of primary hyperoxaluria type 1*:* a placebo-controlled randomized clinical trial. *Clin J Am Soc Nephrol.* 2021;16(7):1025-1036. doi:10.2215/CJN.14730920 (supplementary appendix).

Phase 1/2 Study: Secondary Endpoint

Patients With PH1 Achieved Either Normal or Near-Normal Levels of Urinary Oxalate Excretion Following Lumasiran Treatment

24-Hour UOx with Lumasiran QM (1.0 or 3.0 mg/kg) or Q3M (3.0 mg/kg) Dosing Through Day 197



Near-normal* 24-hour UOx excretion in **all patients** (N = 20)

Within-normal† 24-hour UOx excretion in **75% of patients** (n = 15)

*Near-normal UOx defined as ≤ 1.5 × ULN (≤ 0.69 mmol/24h/1.73 m²); †Normal UOx defined as ≤ 0.46 mmol/24h/1.73m².
BL, baseline; BSA, body surface area; PH1, primary hyperoxaluria type 1; Q3M, once every 3 months; QM, once monthly; SEM, standard error of the mean; ULN, upper limit of normal; UOx, urinary oxalate.

Frishberg Y, Deschênes G, Groothoff JW, et al. Phase 1/2 study of lumasiran for treatment of primary hyperoxaluria type 1*:* a placebo-controlled randomized clinical trial. *Clin J Am Soc Nephrol.* 2021;16(7):1025-1036. doi:10.2215/CJN.14730920

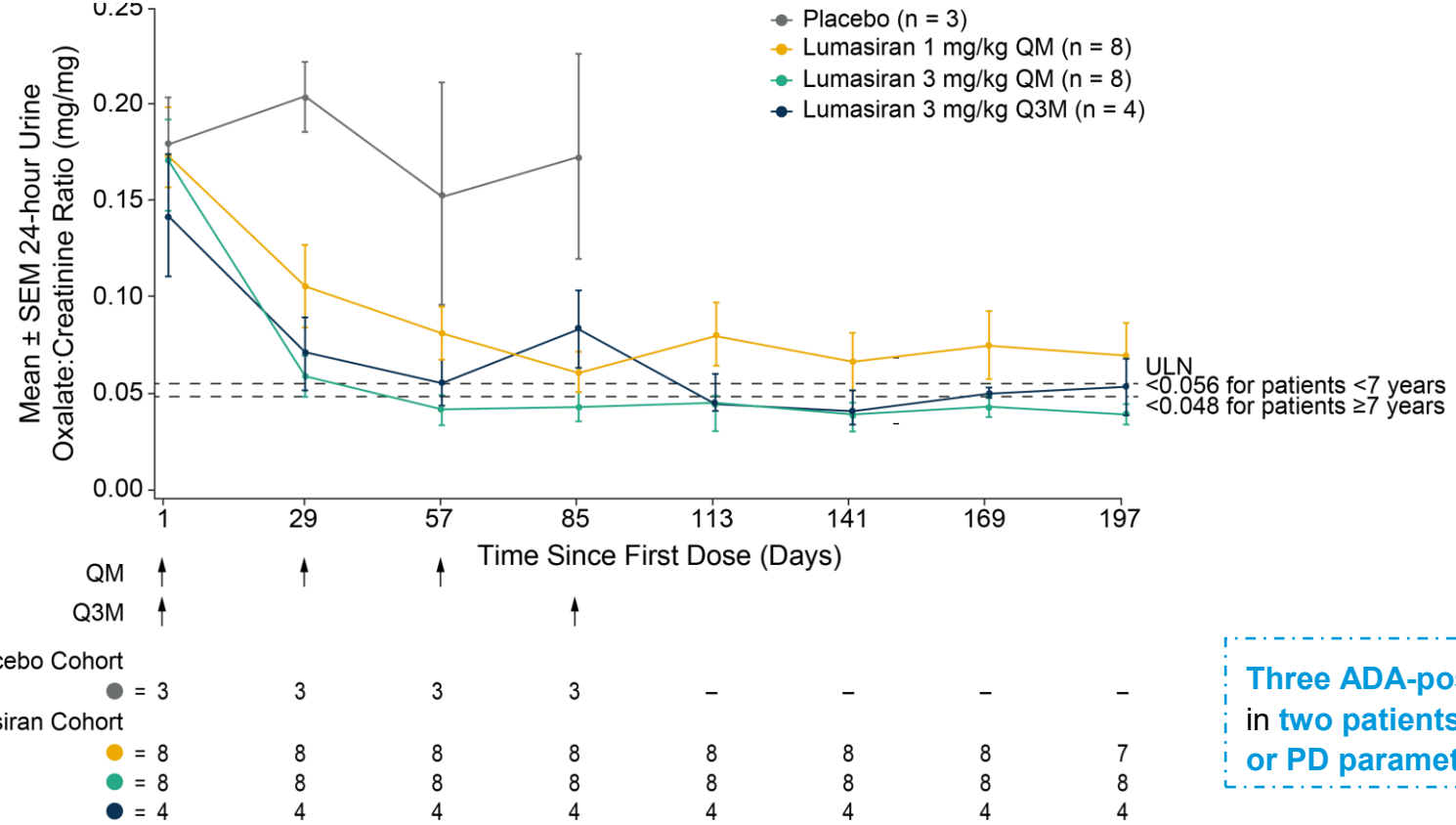
Click to view the Frishberg *Clin J Am Soc Nephrol* 2021 study publication for all endpoint results

US PI

Phase 1/2 Study: Secondary Endpoint

Following Lumasiran Treatment, Reductions in UOx:Cr Were Observed Among Patients With Available Data

24-Hour UOx:Cr with Lumasiran QM (1.0 or 3.0 mg/kg) or Q3M (3.0 mg/kg) Dosing Through Day 197*



Trends in 24-hour UOx:Cr **corresponded to reductions** in 24-hour UOx levels

Three ADA-positive results were reported in **two patients**, but this **did not affect PK or PD parameters**

*Patients initially randomized to placebo received their first dose of lumasiran on Day 85. For the purpose of this analysis, they are also included in the lumasiran dosing cohort in which they were randomized, with Day 1 relative to first dose of lumasiran; the patient randomized to placebo in the Q3M-dosing cohort received a single dose of lumasiran, designated as Day 1.

ADA, antidrug antibody; BL, baseline; PD, pharmacodynamics; PK, pharmacokinetics; POx, plasma oxalate; Q3M, once every 3 months; QM, once monthly; SEM, standard error of the mean; ULN, upper limit of normal; UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio.

Frishberg Y, Deschênes G, Groothoff JW, et al. Phase 1/2 study of lumasiran for treatment of primary hyperoxaluria type 1*:* a placebo-controlled randomized clinical trial. *Clin J Am Soc Nephrol.* 2021;16(7):1025-1036. doi:10.2215/CJN.14730920

Phase 2 OLE Study: Study Design

Patients With PH1 Who Completed the Phase 1/2 Study Were Enrolled in the 54-Month Phase 2 OLE Study[1]

Patient Population (N = 20)*,[1]

54-Month Phase 2 OLE Study[1,2]

Patients

Initial dosing was based on patient's dose/regimen in Part B of the Phase 1/2 parent study

- Lumasiran SC (1 mg/kg QM) (n = 8)[2]
- Lumasiran SC (3 mg/kg QM) (n = 8)[2]
- Lumasiran SC (3 mg/kg Q3M) (n = 4)[2]

Dose adjustments permitted (up to 3 mg/kg QM)

All patients transitioned to the maintenance dose (3 mg/kg Q3M) by Month 21

Selected eligibility criteria[1,2]

- Aged 6-64 years
- Confirmed PH1 diagnosis†
- eGFR > 45 mL/min/1.73 m^2
- 24-hour UOx excretion > 0.7 mmol/24 h/1.73 m^2
- Stable pyridoxine regimen

*Enrollment within 12 months of completing Part B of the Phase 1/2 parent study;[1] †Diagnosis based on a documented genetic analysis, biochemical criteria, and the presence of *AGXT* gene variants or reduced hepatic AGT enzyme activity that was considered evidence of the disease state (medical history).[1]

AGT, alanine-glyoxylate aminotransferase [enzyme]; *AGXT*, alanine-glyoxylate aminotransferase [gene]; BL, baseline; eGFR, estimated glomerular filtration rate; OLE, open-label extension; PH1, primary hyperoxaluria type 1; Q3M, once every 3 months; QM, once monthly; SC, subcutaneous; UOx, urinary oxalate.

1. Frishberg Y, Groothoff JW, Hulton SA, et al. Long-term treatment with lumasiran: final results from the phase 2 open-label extension study. Poster presented at: 61st ERA Congress, May 23-26, 2024; Stockholm, Sweden; 2. Frishberg Y, Deschênes G, Groothoff JW, et al. Phase 1/2 study of lumasiran for treatment of primary hyperoxaluria type 1: a placebo-controlled randomized clinical trial. *Clin J Am Soc Nephrol.* 2021;16(7):1025-1036. doi:10.2215/CJN.14730920

Phase 2 OLE Study: Endpoints

Primary Endpoint Assessed Incidence of AEs Up To Month 54 while Secondary and Exploratory Endpoints Assessed Efficacy Up To Month 54

Primary

- Incidence of AEs, including kidney stone-related AEs, over the 54-month extension period

Secondary

- Change in 24-hour UOx corrected for BSA, and eGFR over the 54-month extension period

Exploratory

- Change in POx and plasma glycolate levels over the 54-month extension period
- Incidence of ADAs over the 54-month extension period

This is not inclusive of all available endpoints or data, please refer to the Frishberg ERA Congress 2024 poster linked above.
ADA, antidrug antibody; AE, adverse event; BSA, body surface area; eGFR, estimated glomerular filtration rate; OLE, open-label extension; POx, plasma oxalate; UOx, urinary oxalate.
Frishberg Y, Groothoff JW, Hulton SA, et al. Long-term treatment with lumasiran: final results from the phase 2 open-label extension study. Poster presented at: 61st ERA Congress, May 23-26, 2024; Stockholm, Sweden.

Phase 2 OLE Study: BL Characteristics

Patients With PH1 Who Were Evaluated in the Phase 2 OLE Study Had a Median Age of 11.5 Years, and Were Predominantly Female and Taking Pyridoxine[1]

BL Characteristics* of Patients in the Phase 2 OLE Study[1]

Characteristic	All Treated (N = 20)
Median age at screening, median (range), years	11.5 (6-43)
Female, n (%)	13 (65)
White, n (%)	15 (75)
Pyridoxine (B6) use, n (%)	13 (65)
Genotype,† n (%) PR/any genotype Missense/Missense or Missense/Nonsense Nonsense/Nonsense	 2 (10) 10 (50) 8 (40)
Median 24-Hour UOx corrected for BSA,‡ (range), mmol/24 h/1.73m^2	n = 19 2.20 (0.94-5.18)
Median 24-Hour UOx:Cr, (range), mmol/mmol	0.256 (0.113-0.561)
Median POx, (range),§ µmol/L	n = 19 14.1 (6.3-28.7)
Median plasma glycolate, (range), µmol/L	n = 17 146.0 (49-325)
Median eGFR,¶ (range), mL/min/1.73m^2	72.2 (42.5-130.7)

*BL data were derived from the Phase 1/2 parent study [1]; †PR was defined as NM_000030.3(AGXT):c.508G>A (p.Gly170Arg) or NM_000030.3(AGXT):c.454T>A (p.Phe152Ile). Missense and Nonsense were defined based on Mandrile et al[1,2]; ‡ULN: 0.514 mmol/24h/1.73m^2 for 24-hour UOx corrected for BSA; §ULN: 12.11 µmol/L for POx, as determined based on data from 75 healthy adult participants[1]; ¶eGFR was calculated based on the Modification of Diet in Renal Disease formula (for patients aged ≥18 years at enrollment) or the Bedside Schwartz formula (for patients aged <18 years at enrollment).[1]

BL, baseline; BSA, body surface area; eGFR, estimated glomerular filtration rate; OLE, open-label extension; PH1, primary hyperoxaluria type 1; POx, plasma oxalate; PR, pyridoxine responsive; ULN, upper limit of normal; UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio.

1. Frishberg Y, Groothoff JW, Hulton SA, et al. Long-term treatment with lumasiran: final results from the phase 2 open-label extension study. Poster presented at: 61st ERA Congress, May 23-26, 2024; Stockholm, Sweden; 2. Mandrile G, van Woerden CS, Berchialla P, et al. *Kidney Int.* 2014;86(6):1197-1204. doi:10.1038/ki.2014.222

Phase 2 OLE Study: Primary Endpoint

Safety Profile in Patients With PH1 Through 54 Months of Lumasiran Treatment[1,2]

ISRs[1]
(all mild in severity) were the most common treatment-related AE
- 13 events reported in 8 out of 20 (40%) patients
- No ISRs were reported after Month 18

Rates of kidney stone-related AEs were low (0.17/PY)[1,*]

A serious AE of eGFR decrease was reported in one patient[1,†]
- Deemed unrelated to the study drug
- Patient continued with the study

0%

No AEs leading to[1]
- Discontinuation/withdrawal
- Death

Safety Summary Table

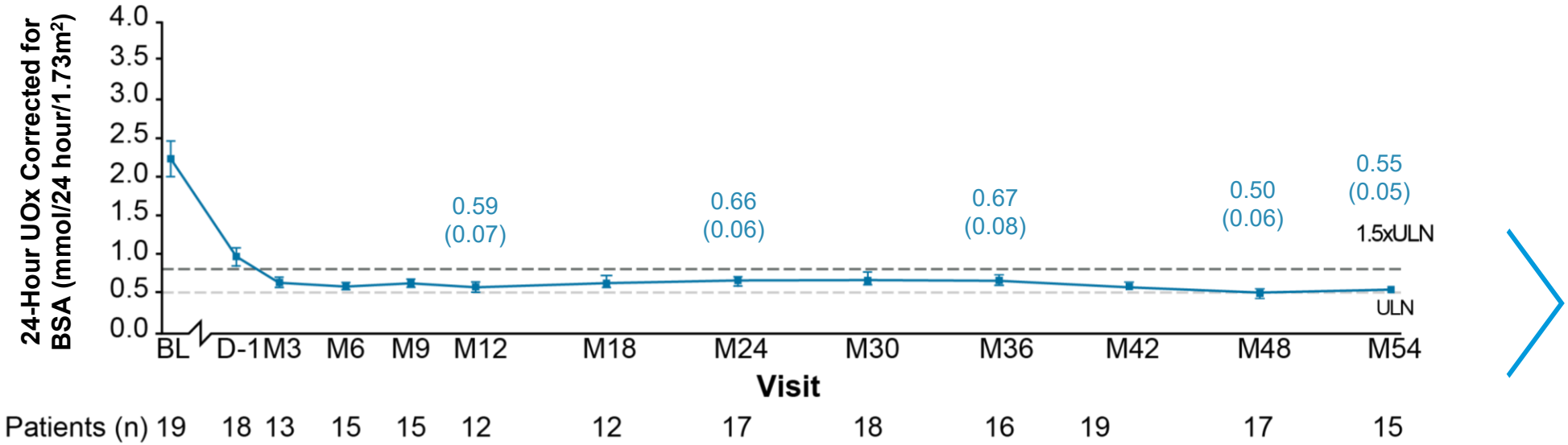
*Kidney stone-related AEs were identified by independent review of AE data by three Alnylam physicians, who met to obtain consensus for any discrepancies[1];
†This patient had one of the lowest eGFRs in the cohort (51.7 mL/min/1.73m^2) and a kidney stone at BL; serious AEs were therefore thought to be due to urinary tract obstruction from ureterolithiasis.[1]
AE, adverse event; BL, baseline; eGFR, estimated glomerular filtration rate; ISR, injection site reaction; PH1, primary hyperoxaluria type 1; PY, patient-years.

1. Frishberg Y, Groothoff JW, Hulton SA, et al. Long-term treatment with lumasiran: final results from the phase 2 open-label extension study. Poster presented at: 61st ERA Congress, May 23-26, 2024; Stockholm, Sweden; 2. Frishberg Y, Deschênes G, Groothoff JW, et al. Phase 1/2 study of lumasiran for treatment of primary hyperoxaluria type 1: a placebo-controlled randomized clinical trial. *Clin J Am Soc Nephrol.* 2021;16(7):1025-1036. doi:10.2215/CJN.14730920.

Phase 2 OLE Study: Secondary Endpoint

Sustained Reductions Observed in Mean 24-Hour UOx Levels in Patients with PH1 Through 54 Months of Lumasiran Treatment

Mean (SEM) 24-Hour UOx Levels With Lumasiran Relative to the Phase 1/2 Parent-Study–Derived BL



UOx

At Month 54, the **mean percent change** in 24-hour UOx from BL was **−68%** and the **mean absolute change** in 24-hour UOx from BL was **−1.5 mmol/24h/1.73m²**

Normalization of UOx

Dotted horizontal lines represent the ULN of 0.51 mmol/24h/1.73m² (1 mmol/24 h/1.73m² = 90 mg/1.73m²) and 1.5 × ULN (0.77 mmol/24 h/1.73m²) for 24-hour UOx. Day −1 is the median of all measurements within 30 days of the first dose of lumasiran in the Phase 2 OLE study. Actual mean (SEM) UOx at M12, M24, M36, M48, and M54 is shown in the graph.

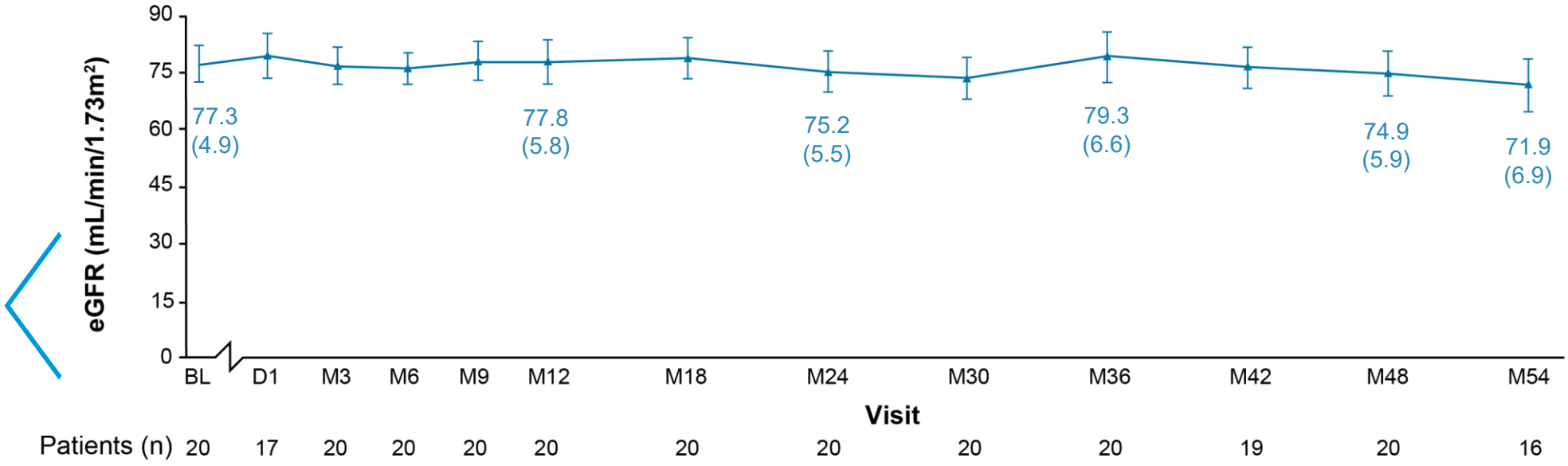
BL, baseline; BSA, body surface area; D, Day; M, Month; OLE, open-label extension; PH1, primary hyperoxaluria type 1; SEM, standard error of the mean; ULN, upper limit of normal; UOx, urinary oxalate.

Frishberg Y, Groothoff JW, Hulton SA, et al. Long-term treatment with lumasiran: final results from the phase 2 open-label extension study. Poster presented at: 61st ERA Congress, May 23-26, 2024; Stockholm, Sweden.

Phase 2 OLE Study: Secondary Endpoint

eGFR Stability Was Observed Through Month 54 of Lumasiran Treatment

Mean (SEM) eGFR Over Time With Lumasiran Treatment*



eGFR

Over 48 months of follow-up, the annualized mean (SEM) **rate of eGFR change was −0.6 (0.7) mL/min/1.73m²** for all 20 patients

POx, plasma glycolate, and ADAs

*eGFR was calculated based on the Modification of Diet in Renal Disease formula (for patients aged ≥ 18 years at enrollment) and the Bedside Schwartz Formula (for patients aged < 18 years at enrollment). Baseline is the derived baseline value from the Phase 1/2 parent study. Actual mean (SEM) eGFR values at baseline, M12, M24, M36, M48, and M54 are shown in graph.

ADA, antidrug antibody; BL, baseline; D, Day; eGFR, estimated glomerular filtration rate; M, Month; OLE, open-label extension; PH1, primary hyperoxaluria type 1; POx, plasma oxalate; SEM, standard error of the mean.

Frishberg Y, Groothoff JW, Hulton SA, et al. Long-term treatment with lumasiran: final results from the phase 2 open-label extension study. Poster presented at: 61st ERA Congress, May 23-26, 2024; Stockholm, Sweden.

ILLUMINATE-A: Study Design

ILLUMINATE-A was a Multinational, Double-Blind, Placebo-Controlled, Phase 3 Trial of the Efficacy and Safety of Lumasiran in Patients with PH1 Aged ≥ 6 Years[1,2]

Patient Population (N = 39)

6-Month Double-Blind Primary Analysis Period

54-Month OLE Period

Patients

Lumasiran SC (n = 26)[1]
QM × 3 starting dose, then Q3M 3.0 mg/kg*

Placebo SC (n = 13)[1]
QM × 3 starting dose, then Q3M

Lumasiran SC[1]
Q3M 3.0 mg/kg†

Selected eligibility criteria[1]

- Aged ≥ 6 years old
- 24-hour UOx excretion ≥ 0.7 mmol/24 h/1.73m^2
- eGFR ≥ 30 mL/min/1.73 m^2

- Treatment arms were stratified at randomization based on mean 24-hour UOx from the first two valid samples collected during screening (≤ 1.70 mmol/24 h/1.73 m^2 vs > 1.70 mmol/24 h/1.73 m^2)[1]
- Oxalate was measured using a validated liquid chromatography-tandem mass spectrometry assay[1]

*Maintenance dose of 3.0 mg/kg (Q3M) started 1 month after the last starting dose[2]; †Patients who were randomized to receive placebo received starting doses of lumasiran 3.0 mg/kg at Months 6, 7, and 8[2]; patients who were randomized to receive lumasiran received a maintenance dose of lumasiran 3.0 mg/kg at Month 6 and placebo at Months 7 and 8.[2]

BL, baseline; eGFR, estimated glomerular filtration rate; OLE, open-label extension; PH1, primary hyperoxaluria type 1; Q3M, once every 3 months; QM, once every month; SC, subcutaneous; UOx, urinary oxalate.

1. Garrelfs SF, Frishberg Y, Hulton SA, et al. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. *N Engl J Med.* 2021;384(13):1216-1226. doi:10.1056/NEJMoa2021712;
2. Garrelfs SF, Frishberg Y, Hulton S, et al. ILLUMINATE-A, a phase 3 study of lumasiran, an investigational RNAi therapeutic, in children and adults with primary hyperoxaluria type 1. Presented at: ERA-EDTA Congress; June 6-9, 2020; Virtual.

Click to view the Garrelfs *NEJM* 2021 study publication for inclusion and exclusion criteria

US PI

ILLUMINATE-A: Study Design

Patients With PH1 and Additional Key Eligibility Criteria Were Included in ILLUMINATE-A[1,2]

Inclusion Criteria[1]

- Aged ≥ 6 years old
- Diagnosis of PH1 confirmed by genetic analysis (*AGXT*)
- 24-hour UOx ≥ 0.7 mmol/24 hours/1.73m^2
- eGFR ≥ 30 mL/min/1.73 m^2
- For patients receiving SoC, treatment had to be stable*

Exclusion Criteria[2]

- Clinical evidence of extrarenal systemic oxalosis
- History of renal/liver transplant
- ALT or AST > 2 × ULN or total bilirubin > 1.5 × ULN

*For patients taking pyridoxine, they were required to be on a stable regimen for at least 90 days before randomization. All patients were to remain on their standard of care regimen including hyperhydration, crystallization therapy, pyridoxine, or a combination of these treatments at the time of enrollment through Month 12.[1]

AGXT, alanine-glyoxylate aminotransferase [gene]; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; eGFR, estimated glomerular filtration rate; PH1, primary hyperoxaluria type 1; SoC, standard of care; ULN, upper limit of normal; UOx, urinary oxalate.

1. Garrelfs SF, Frishberg Y, Hulton SA, et al. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. *N Engl J Med*. 2021;384(13):1216-1226. doi:10.1056/NEJMoa2021712;
2. ClinicalTrials.gov identifier: NCT03681184. Study protocol. Accessed August 1, 2025. https://clinicaltrials.gov/study/NCT03681184.

ILLUMINATE-A: Endpoints

Primary Endpoint Assessed Percentage Change in 24-hour UOx Up To Month 6 While Secondary and Exploratory Endpoints Further Assessed Efficacy Through the Extension Period

Primary[1-3]

- Percentage change in 24-hour UOx from BL to Month 6 corrected for BSA (mean change from BL across Month 3 through Month 6)

Secondary[1,2]

- Absolute change in 24-hour UOx and percentage change in 24-hour UOx:Cr from BL to Month 6 and Month 60
- Percent change in 24-hour UOx from BL through the extension period
- Percentage and absolute change in POx levels from BL to Month 6
- Percentage of patients with 24-hour UOx < 1.5 × ULN and no higher than ULN at Month 6
- Change in eGFR from BL to Month 6 and Month 60

Exploratory[2]

- *Post hoc* analysis assessed during extension period:
  - Change in POx, plasma glycolate, kidney stone event rate and nephrocalcinosis

This is not inclusive of all available endpoints or data, please refer to the study protocol linked above.

ADA, antidrug antibody; BL, baseline; BSA, body surface area; eGFR, estimated glomerular filtration rate; POx, plasma oxalate; ULN, upper limit of normal, UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio.

1. ClinicalTrials.gov identifier: NCT03681184. Study protocol. Accessed August 1, 2025. https://clinicaltrials.gov/study/NCT03681184; 2. Saland JM, Lieske JC, Willey R, et al. Long-term efficacy and safety of lumasiran in patients with primary hyperoxaluria type 1: final analysis of the ILLUMINATE-A trial. Poster presented at: ASN Kidney Week; October 24-27, 2024; San Diego, CA; 3. Garrelfs SF, Frishberg Y, Hulton SA, et al. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. *N Engl J Med.* 2021;384(13):1216-1226. doi:10.1056/NEJMoa2021712.

ILLUMINATE-A: BL Characteristics

Baseline Characteristics Were Generally Well Balanced Between Groups

BL Characteristics for the 6-Month Double-Blind Treatment Period

BL Characteristics	Placebo (n = 13)	Lumasiran (n = 26)	Overall (N = 39)
Median age (range), years	11.0 (6-60)	16.5 (6-47)	14.0 (6-60)
Age category, n (%)			
6-< 18 years	8 (62)	14 (54)	22 (56)
18-65 years	5 (38)	12 (46)	17 (44)
Female sex, n (%)	5 (38)	8 (31)	13 (33)
Race,* n (%)			
White	9 (69)	21 (81)	30 (77)
Asian	3 (23)	3 (12)	6 (15)
Other	1 (8)	2 (8)	3 (8)
Region, n (%)			
Europe	8 (62)	10 (38)	18 (46)
North America	2 (15)	11 (42)	13 (33)
Middle East	3 (23)	5 (19)	8 (21)

*Race was reported by the patient or the patient's parent or guardian. "Other" included one patient in the placebo group who reported more than one race and two patients in the lumasiran group who reported "other".
BL, baseline.

Garrelfs SF, Frishberg Y, Hulton SA, et al. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. *N Engl J Med.* 2021;384(13):1216-1226. doi:10.1056/NEJMoa2021712

ILLUMINATE-A: BL Characteristics

Baseline Characteristics Were Generally Well Balanced Between Groups

BL Characteristics for the 6-Month Double-Blind Treatment Period

BL Characteristics	Placebo (n = 13)	Lumasiran (n = 26)	Overall (N = 39)
Pyridoxine (vitamin B6) use, n (%)	9 (69)	13 (50)	22 (56)
24-hour UOx excretion corrected for BSA, mean ± SD, mmol/24 hour/1.73 m^2*	1.79 ± 0.68	1.84 ± 0.60	1.82 ± 0.62
POx, mean ± SD, µmol/L†	15.5 ± 7.3	14.8 ± 7.6	15.0 ± 7.4
eGFR, mean ± SD, mL/min/1.73 m^2‡	78.9 ± 26.8	83.0 ± 25.5	81.6 ± 25.7
eGFR category, n (%)			
≥ 90 mL/min/1.73 m^2	4 (31)	9 (35)	13 (33)
60-< 90 mL/min/1.73 m^2	6 (46)	13 (50)	19 (49)
30-< 60 mL/min/1.73 m^2	3 (23)	4(15)	7 (18)

Overall, 38 of 39 patients completed the 6-month primary analysis period of ILLUMINATE-A

All eligible patients then entered the 54-month OLE	**13**	**25**	**38**

*The BL value is the median of the values from all valid 24-hour urine samples obtained before the first dose of lumasiran or placebo. The ULN for 24-hour UOx is 0.514 mmol/24 h/1.73 m^2 of BSA. To convert values to mg/24 hours/1.73 m^2, multiply by 90; †The ULN is 12.11 µmol/L. The POx analysis set included 23 patients in the lumasiran group and 10 patients in the placebo group; ‡The eGFR was calculated with the Modification of Diet in Renal Disease formula for patients aged ≥ 18 years and with the Schwartz Bedside Formula for patients aged 6 to < 18 years.

BL, baseline; BSA, body surface area; eGFR, estimated glomerular filtration rate; OLE, open-label extension; POx, plasma oxalate; SD, standard deviation; ULN, upper limit of normal; UOx, urinary oxalate.

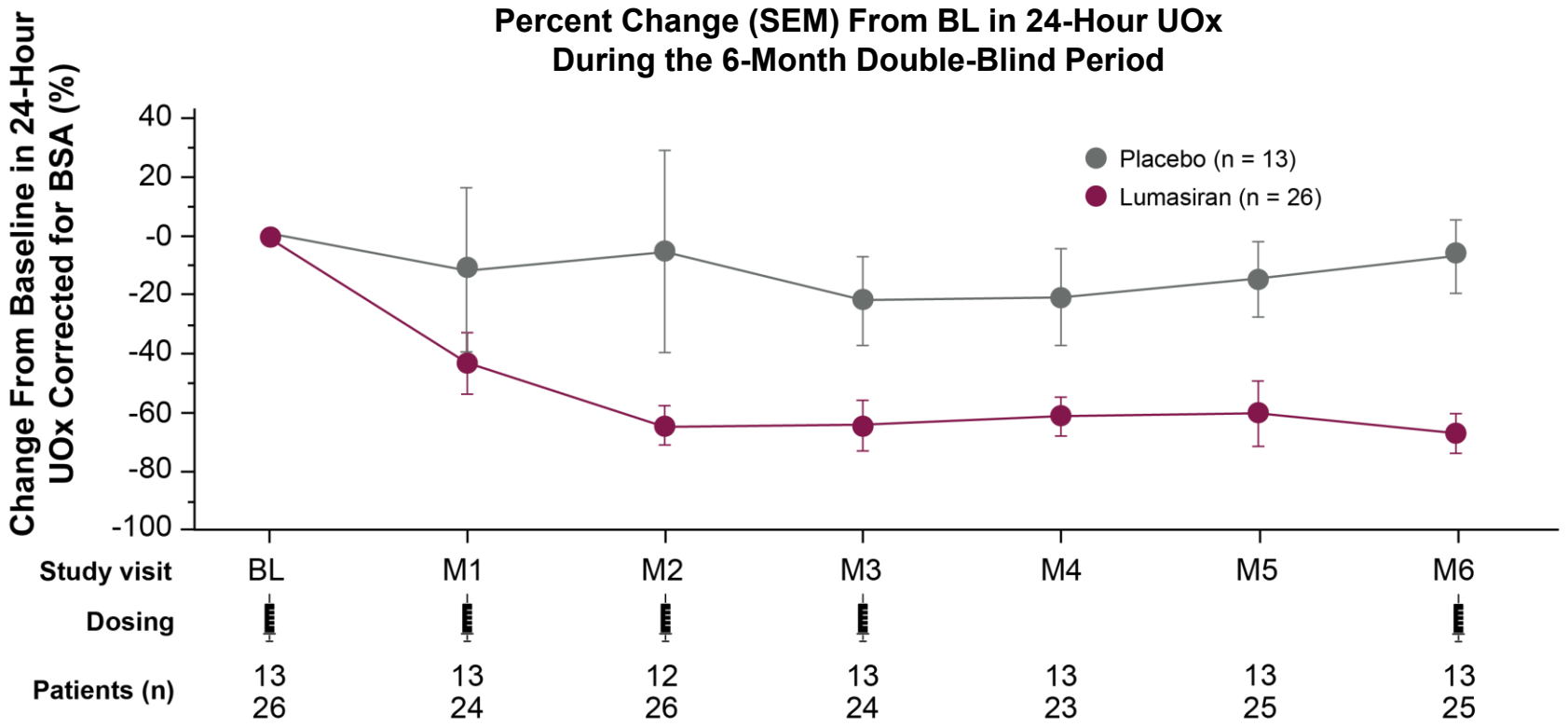
Garrelfs SF, Frishberg Y, Hulton SA, et al. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. *N Engl J Med.* 2021;384(13):1216-1226. doi:10.1056/NEJMoa2021712

Click to view the Garrelfs *NEJM* 2021 study publication for all endpoint results

US PI

ILLUMINATE-A: Primary Endpoint

Lumasiran Treatment Led to a Statistically Significant Reduction in 24-Hour UOx Compared With Placebo From Baseline to Month 6



Month 6

There was a statistically significant reduction in **24-hour UOx with lumasiran** (**−65.4%**) versus placebo (**−11.8%**) at Month 6. LS mean difference of **−53.5%** (95% CI, –62.3 to –44.8; $p < 0.001$).

BL, baseline; BSA, body surface area; CI, confidence interval; LS, least squares; M, Month; SEM, standard error of the mean; UOx, urinary oxalate.

Garrelfs SF, Frishberg Y, Hulton SA, et al. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. *N Engl J Med.* 2021;384(13):1216-1226. doi:10.1056/NEJMoa2021712

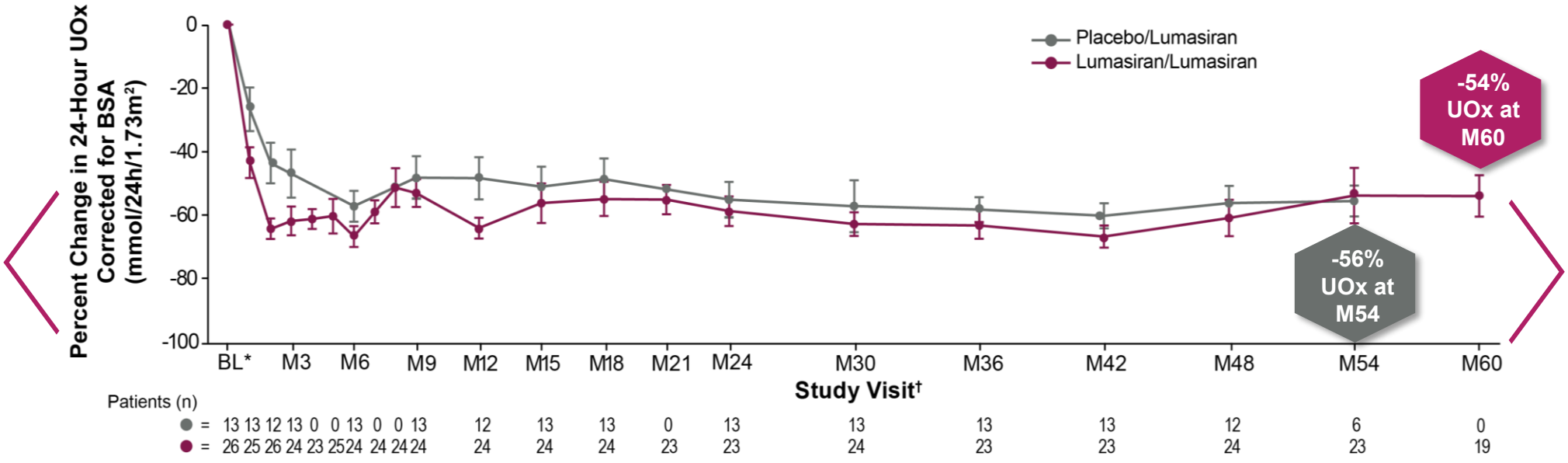
Click to view the Saland ASN 2024 poster for all endpoint results

US PI

ILLUMINATE-A: Secondary Endpoint

Sustained Reductions in 24-hr UOx Levels Were Observed Over 54 to 60 Months of Lumasiran Treatment

Mean (SEM) Percent Change in 24-Hour UOx Levels Over Time During Lumasiran Treatment



*For the lumasiran/lumasiran group, BL is the median of all valid 24-hour urine assessments collected prior to the first dose date/time of lumasiran without any non-protocol-related sample issues. For the placebo/lumasiran group, BL is the median of all valid 24-hour urine assessments at Month 6 without any non-protocol-related sample issues (or, if the patient did not have 2 valid 24-hour urine pharmacodynamic assessments at Month 6, then the BL was calculated using the latest 3 valid 24-hour urine pharmacodynamic collections prior to the first dose date/time of lumasiran);

†Visit is relative to the first dose of lumasiran.

BL, baseline; BSA, body surface area; M, Month; SEM, standard error of the mean; UOx, urinary oxalate.

Saland JM, Lieske JC, Willey R, et al. Long-term efficacy and safety of lumasiran in patients with primary hyperoxaluria type 1: final analysis of the ILLUMINATE-A trial. Poster presented at: ASN Kidney Week; October 24-27, 2024; San Diego, CA.

ILLUMINATE-A: Secondary Endpoints

Lumasiran Treatment Was Associated With Statistically Significant Improvements in Additional Measures of UOx and POx Tested Hierarchically at Month 6 Compared With Placebo[1]

Endpoint	Placebo (n = 13)	Lumasiran (n = 26)	Difference, Lumasiran – Placebo	P-value
Absolute change in 24-hour UOx excretion from BL to Month 6, (95% CI), mmol/24 hours/1.73 m^2,*,†	−0.27 (–0.44, –0.10)	–1.24 (–1.37, –1.12)	**–0.98 (–1.18, –0.77)**	**< 0.001**
Percentage change in 24-hour UOx:Cr from BL to Month 6 (95% CI)†	–10.8 (–21.6, 0.0)	–62.5 (–70.7, –54.4)	**–51.8 (–64.3, –39.3)**	**< 0.001**
Percentage change in POx from BL to Month 6 (95% CI)†,‡	-0.3 (–9.1, 8.5)	–39.8 (–45.8, –33.8)	**–39.5 (–50.1, –28.9)**	**< 0.001**
Percentage of patients with 24-hour UOx level at or below 1.5 × ULN at Month 6 (95% CI)*,§	0 (0, 25)	84 (64, 95)	**84 (55, 94)¶**	**< 0.001****
Percentage of patients with 24-hour UOx level at or below ULN at Month 6 (95% CI)*,§	0 (0, 25)	52 (31, 72)	**52 (23, 70)¶**	**0.001****
Absolute change in POx from BL to Month 6, (95% CI), µmol/L†,‡	1.3 (–1.0, 3.5)	–7.5 (–9.0, –5.9)	**–8.7 (–11.5, –6.0)**	**< 0.001**

*Measurements of UOx excretion were corrected for BSA; †The change from BL to Month 6 was calculated as the mean change or mean percentage change across Months 3 through Months 6. The least squares mean, between-group difference in the least squares mean, 95% CI, and p-value for comparisons of lumasiran and placebo were derived with a mixed model for repeated measures, and a difference of less than 0 represents a favorable outcome for lumasiran; ‡The POx analysis set included 23 patients in the lumasiran group and 10 patients in the placebo group; §Data were available for 25 patients in the lumasiran group and 13 patients in the placebo group. The ULN range is 0.514 mmol/24 hours/1.73 m^2. The CI is a Clopper-Pearson exact CI; ¶CI calculated by the Newcombe method on the basis of the Wilson score; **p value was based on a Cochran-Mantel-Haenszel test stratified according to BL 24-hour urinary oxalate excretion corrected for BSA (≤1.70 vs >1.70 mmol/24 hours/1.73 m^2).

BL, baseline; BSA, body surface area; CI, confidence interval; Cr, creatinine; POx, plasma oxalate; ULN, upper limit of normal; UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio.

1. Garrelfs SF, Frishberg Y, Hulton SA, et al. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. *N Engl J Med.* 2021;384(13):1216-1226. doi:10.1056/NEJMoa2021712.

Click to view the Saland ASN 2024 poster for all endpoint results

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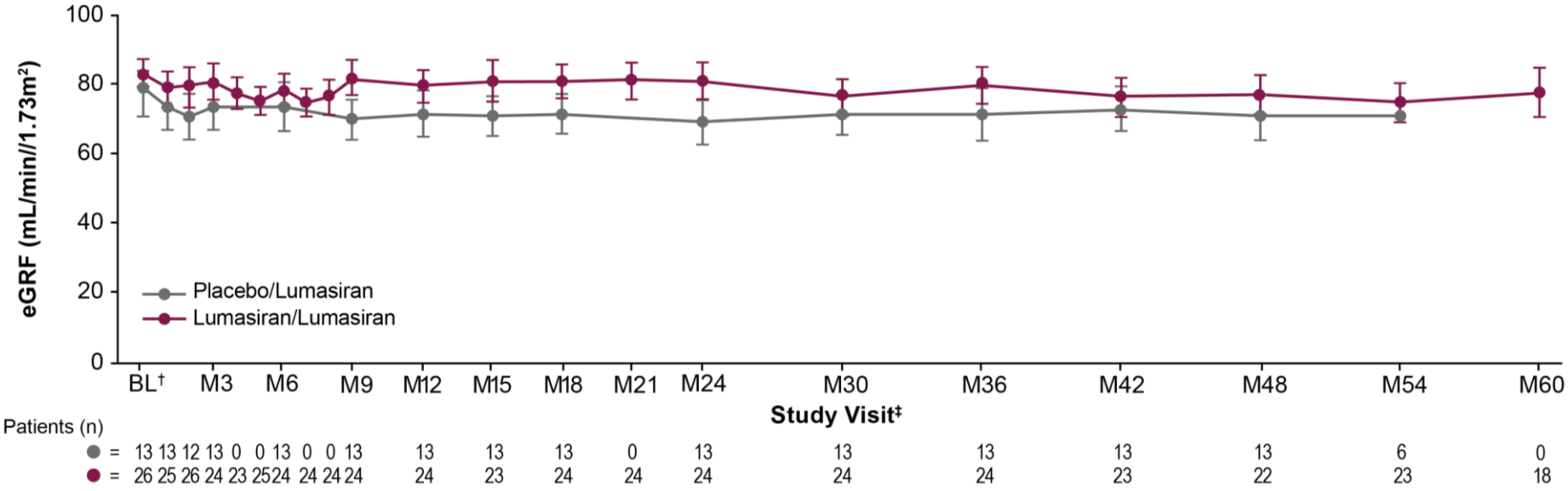
ILLUMINATE-A: Secondary Endpoint

Stabilization of eGFR from Baseline was Observed Over 54 to 60 Months of Lumasiran Treatment[1]

Mean (SEM) eGFR* Over Time During Lumasiran Treatment[1]



Mean (SEM) change from baseline[1]

Placebo/lumasiran: -12.86 (3.89) mL/min/1.73m²
Lumasiran/lumasiran: -2.89 (2.75) mL/min/1.73m²

***Post hoc* analysis[2]**

Annual rate of change in mean (SD) eGFR:
–0.6 (0.7) ml/min/1.73m² per year at Month 60

*eGFR was calculated with the Modification of Diet in Renal Disease formula for patients ≥ 18 years of age at screening and the Schwartz Bedside formula for patients aged 6 to < 18 years at screening.
†Baseline is the last assessment collected prior to the first dose date/time of lumasiran. ‡Visit is relative to the first dose of lumasiran.
BL, baseline; eGFR, estimated glomerular filtration rate; M, Month; OLE, open-label extension; SEM, standard error of the mean.

1. Saland JM, Lieske JC, Willey R, et al. Long-term efficacy and safety of lumasiran in patients with primary hyperoxaluria type 1: final analysis of the ILLUMINATE-A trial. Poster presented at: ASN Kidney Week; October 24-27, 2024; San Diego, CA; 2. Saland JM, Lieske JC, Willey R, et al. Long-term efficacy and safety of lumasiran in patients with primary hyperoxaluria type 1 in a final analysis of the ILLUMINATE-A trial. Presented at: Annual ASPN Meeting at PAS 2025; April 24-28, 2025; Honolulu, HI.

ILLUMINATE-A: Exploratory Endpoints

Post Hoc Analysis*: Change in Kidney Stone Event Rates, Plasma Glycolate and POx Through Month 60

POx[1]

Mean percentage reduction from BL in POx concentration was **37% in the lumasiran/lumasiran group through 60 months of lumasiran treatment (n = 16)** and **50% in the placebo/lumasiran group through 54 months of lumasiran treatment (n = 4)**[1]

Plasma Glycolate[1]

Plasma glycolate **increased during the first 6 months** of lumasiran treatment (mean change from BL: **154% [placebo/lumasiran]** and **119% [lumasiran/lumasiran]**) then **plateaued** and **remained stable through Month 60**[1]

Kidney Stone Event Rate†,1,2

- Pre-study entry (based on 12-month historical patient recall): **0.54/PY (placebo/lumasiran)** and **3.19/PY (lumasiran/lumasiran)**[2]
- All months: **0.54/PY (placebo/lumasiran)** and **0.47/PY (lumasiran/lumasiran)**[1]
- Final 6 months: **0.68/PY (placebo/lumasiran)** and **0.09/PY (lumasiran/lumasiran)**[1]

*These *post hoc* analyses were not powered for statistical significance of the outcomes. †Kidney stone event was defined as an event that included at least 1 of the following: a visit to a healthcare professional because of a kidney stone medication for renal colic, stone passage, or macroscopic hematuria due to a kidney stone.[2]

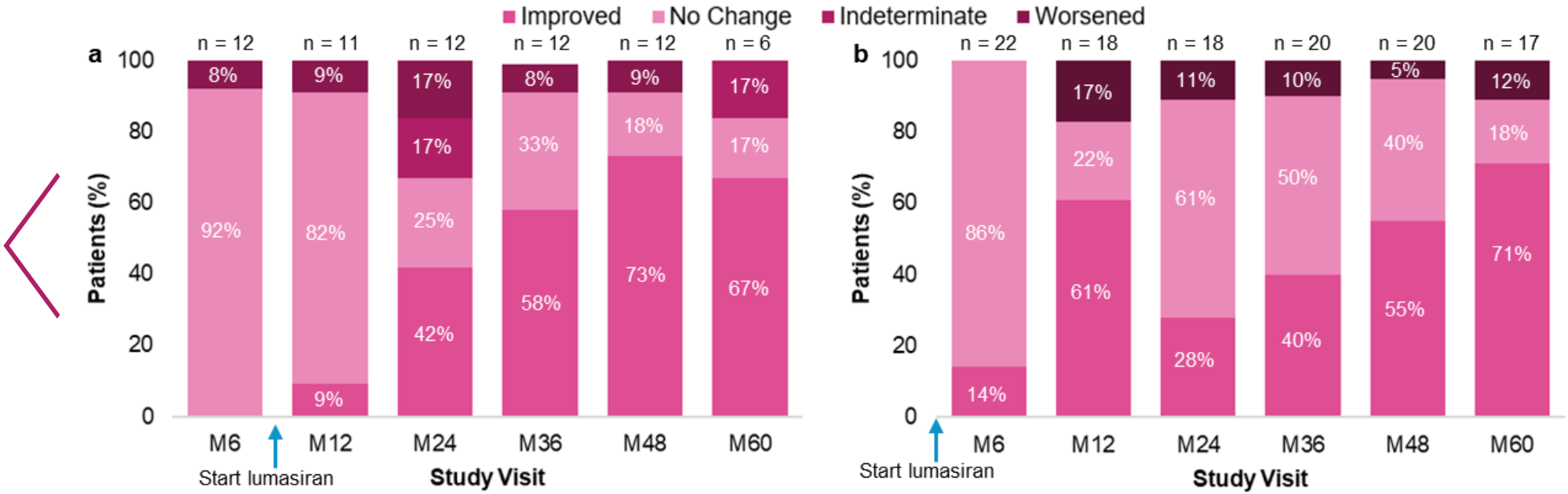
BL, baseline; PY, patient-years.

1. Saland JM, Lieske JC, Willey R, et al. Long-term efficacy and safety of lumasiran in patients with primary hyperoxaluria type 1: final analysis of the ILLUMINATE-A trial. Poster presented at: ASN Kidney Week; October 24-27, 2024; San Diego, CA; 2. Saland JM, Lieske JC, Groothoff JW, et al. Efficacy and safety of lumasiran in patients with primary hyperoxaluria type 1: results from a phase III clinical trial. *Kidney Int Rep.* 2024;9(7):2037-2046. doi:10.1016/j.ekir.2024.04.048

ILLUMINATE-A: Exploratory Endpoints

Post Hoc Analysis: Change from Baseline in Medullary Nephrocalcinosis Through Month 60

Change From Baseline in Medullary Nephrocalcinosis in the (a) Placebo/Lumasiran Group and (b) Lumasiran/Lumasiran Group[1,*,†,‡,§]



*All-lumasiran-treated set[1]; †The degree of medullary nephrocalcinosis in each kidney was graded using a validated four-point scale: stable (no change in either kidney), improving (both kidneys improving or one kidney improving and one with no change), worsening (both kidneys worsening or one kidney worsening and one with no change), and indeterminate (one kidney improving and one worsening).[1] ‡Change at each time point is with respect to BL medullary nephrocalcinosis.[1] §Medullary nephrocalcinosis was graded per kidney on a semiquantitative scale of 0-3 with the use of kidney ultrasonography, with 0 indicating the absence of nephrocalcinosis and a higher grade indicating greater severity.[2]

BL, baseline; M, Month.

1. Saland JM, Lieske JC, Willey R, et al. Long-term efficacy and safety of lumasiran in patients with primary hyperoxaluria type 1: final analysis of the ILLUMINATE-A trial. Poster presented at: ASN Kidney Week; October 24-27, 2024; San Diego, CA; 2. Garrelfs SF, Frishberg Y, Hulton SA, et al. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. N Engl J Med. 2021;384(13):1216-1226. doi:10.1056/NEJMoa2021712

ILLUMINATE-A: Safety Data

Safety Profile Through Month 60 in Children and Adults With PH1

Month 6

In the primary analysis period, **85%** of patients in the **lumasiran** group and **69%** of patients in the **placebo** group reported AEs; **all AEs were mild to moderate in severity**[1]

Final Safety Data As of Month 60 in ILLUMINATE-A[2,*]

Event, n (%)	Placebo/ Lumasiran (n = 13)	Lumasiran/ Lumasiran (n = 26)	All Lumasiran (n = 39)
Any AE	12 (92)	25 (96)	37 (95)
AE related to study drug	6 (46)	13 (50)	19 (49)
Serious AE[†]	1 (8)	5 (19)	6 (15)
Severe AE[‡]	0	4 (15)	4 (10)
AE leading to discontinuation of study treatment[§]	0	1 (4)	1 (3)
AEs occurring in ≥15% of patients (during lumasiran treatment)			
ISR[¶]	5 (38)	9 (35)	14 (36)
Abdominal pain	1 (8)	8 (31)	9 (23)
COVID-19	4 (31)	4 (15)	8 (21)
Headache	2 (15)	5 (19)	7 (18)
Nasopharyngitis	2 (15)	4 (15)	6 (15)
Death	0	0	0

*All-lumasiran-treated set[2]; [†]Abdominal pain (n = 2), dysuria (n = 1), follicular lymphoma (n = 1), postprocedural complication (n = 1), postprocedural infection (n = 1), renal impairment (n = 1), urinary tract infection (n = 1), and urosepsis (n = 1), all considered not related to lumasiran by the investigator[2]; [‡]Acute pyelonephritis (n = 1), follicular lymphoma (n = 1), postprocedural complication (n = 1), postprocedural infection (n = 1), urinary tract infection (n = 1), and urosepsis (n = 1), all considered not related to lumasiran by the investigator[2]; [§]Fatigue and disturbance in attention, considered not related to lumasiran by the investigator, which began during the double-blind period[2]; [¶]All were transient, were considered mild in severity, and resolved without sequelae.[2]

AE, adverse event; BL, baseline; ISR, injection site reaction; PH1, primary hyperoxaluria type 1.

1. Garrelfs SF, Frishberg Y, Hulton SA, et al. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. *N Engl J Med*. 2021;384(13):1216-1226. doi:10.1056/NEJMoa2021712; 2. Saland JM, Lieske JC, Willey R, et al. Long-term efficacy and safety of lumasiran in patients with primary hyperoxaluria type 1: final analysis of the ILLUMINATE-A trial. Poster presented at: ASN Kidney Week; October 24-27, 2024; San Diego, CA.

ILLUMINATE-B: Study Design

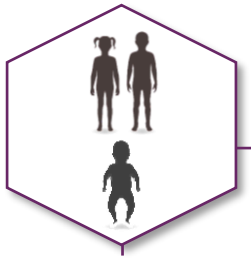
ILLUMINATE-B was a Multinational, Single-Arm, Open-Label, Phase 3 Trial, Evaluated the Efficacy and Safety of Lumasiran in Young Patients With PH1 Aged < 6 Years[1-3]

Lumasiran Was Administered According to Three Weight-Based Regimens With Dose Adjustments for Interval Weight Gain[1-4]

Patient Population (N = 18)

6-Month Primary Analysis Period

54-Month Extension Period



Patients

Open label

Lumasiran SC
QM × 3 loading dose, then QM or Q3M maintenance dosing dependent on weight*

Lumasiran SC
QM or Q3M maintenance dosing dependent on weight*,†

Selected eligibility criteria[1-3]

- Aged < 6 years
- UOx:Cr > ULN for age
- eGFR > 45 mL/min/1.73 m^2 if ≥ 12 months old; normal serum creatinine if < 12 months old

All 18 patients entered the 54-month extension period.[2]

*Dosing information: < 10kg: loading = 6.0 mg/kg QM for 3 doses, maintenance = 3.0 mg/kg QM; 10–< 20kg: loading = 6.0 mg/kg QM for 3 doses, maintenance = 6.0 mg/kg Q3M; ≥ 20kg: loading = 3.0mg/kg QM for 3 doses, maintenance = 3.0 mg/kg Q3M.[2]; †Continued weight-based dosing using weight obtained 7 days prior to dosing.[3,4]

BL, baseline; eGFR, estimated glomerular filtration rate; PH1, primary hyperoxaluria type 1; Q3M, once every 3 months; QM, once monthly; SC, subcutaneous; ULN, upper limit of normal; UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio.

1. Sas DJ, Magen D, Hayes W, et al. Phase 3 trial of lumasiran for primary hyperoxaluria type 1: a new RNAi therapeutic in infants and young children. *Genet Med.* 2022;24(3):654-662. doi:10.1016/j.gim.2021.10.024; 2. Frishberg Y, Hayes W, Shasha-Lavsky H, et al. Efficacy and safety of lumasiran for infants and young children with primary hyperoxaluria type 1: 30-month analysis of the phase 3 ILLUMINATE-B trial. *Front Pediatr.* 2024;12:1392644. doi:10.3389/fped.2024.1392644; 3. Hayes W, Sas DJ, Shasha-Lavsky H, et al. Efficacy and safety of lumasiran for infants and young children with primary hyperoxaluria type 1: 12-month analysis of the phase 3 ILLUMINATE-B trial. *Pediatr Nephrol.* 2023;38(4):1075-1086. doi:10.1007/s00467-022-05684-1; 4. McGregor TL. GO forward for PH1 patients. Presented at: 2nd OxalEurope Meeting; December 1, 2020; Amsterdam, The Netherlands and Virtual.

Click to view the Sas *Genet Med* 2022 study publication for the full inclusion and exclusion criteria

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ILLUMINATE-B: Study Design

Key Eligibility Criteria for Infants and Young Children with PH1 Enrolled in ILLUMINATE-B[1-4]

Inclusion Criteria[1-4]

- Aged < 6 years
- Diagnosis of PH1 confirmed by genetic analysis
- UOx:Cr > ULN for age
- eGFR > 45 mL/min/1.73m^2 if aged ≥ 12M or normal SCr if < 12M
- For patients receiving SoC, treatment must be stable*

Exclusion Criteria[4]

- Clinical evidence of extrarenal systemic oxalosis
- History of kidney/liver transplant

Age, kidney and PH1-related inclusion and exclusion criteria presented here.[1,2]
*Patients on therapeutic pyridoxine (vitamin B6) were required to have been on a stable regimen for ≥ 90 days before screening. All patients continued standard-of-care therapies, including hyperhydration, crystallization inhibitors, and/or pyridoxine therapy, through the 6-month primary analysis period.[2]
BL, baseline; eGFR, estimated glomerular filtration rate; M, months; PH1, primary hyperoxaluria type 1; SCr , serum creatinine; SoC, standard of care; UOx:Cr, urinary oxalate:creatinine ratio.

1. Frishberg Y, Hayes W, Shasha-Lavsky H, et al. Efficacy and safety of lumasiran for infants and young children with primary hyperoxaluria type 1: 30-month analysis of the phase 3 ILLUMINATE-B trial. *Front Pediatr.* 2024;12:1392644. doi:10.3389/fped.2024.1392644; 2. Sas DJ, Magen D, Hayes W, et al. Phase 3 trial of lumasiran for primary hyperoxaluria type 1: a new RNAi therapeutic in infants and young children. *Genet Med.* 2022;24(3):654-662. doi:10.1016/j.gim.2021.10.024; 3. Hayes W, Sas DJ, Shasha-Lavsky H, et al. Efficacy and safety of lumasiran for infants and young children with primary hyperoxaluria type 1: 12-month analysis of the phase 3 ILLUMINATE-B trial. *Pediatr Nephrol.* 2023;38(4):1075-1086. doi:10.1007/s00467-022-05684-1; 4. ClinicalTrials.gov identifier: NCT03905694. Updated February 2, 2025. Accessed August 1, 2025. https://clinicaltrials.gov/study/NCT03905694

ILLUMINATE-B: Endpoints

Primary Endpoint Assessed Percentage Change in 24-hour UOx up to Month 6 While Secondary and Exploratory Endpoints Further Assessed Efficacy Up To Month 60

Primary[1,2]

- Percentage change in UOx excretion from BL to Month 6, as measured by spot UOx:Cr (averaged across Month 3 through Month 6)

Secondary[1,2]

- Absolute and percentage change from BL in UOx excretion from BL through Month 60
- Proportion of patients with UOx excretion ≤ ULN and 1.5 x ULN for age through Month 60
- Absolute and percent change in POx levels from BL through Month 60
- Change in eGFR from BL through Month 60

Exploratory[1,2]

- *Post hoc* analysis assessed during extension period:
  - Change in nephrocalcinosis and kidney stone events

This is not inclusive of all available endpoints or data, please refer to the Sas *Genet Med* 2022 publication linked above.
ADA, antidrug antibody; BL, baseline; eGFR, estimated glomerular filtration rate; PK, pharmacokinetics; POx, plasma oxalate; ULN, upper limit of normal; UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio.

1. Sas DJ, Magen D, Hayes W, et al. Phase 3 trial of lumasiran for primary hyperoxaluria type 1: a new RNAi therapeutic in infants and young children. *Genet Med.* 2022;24(3):654-662. doi:10.1016/j.gim.2021.10.024;
2. Frishberg Y, Hayes W, Ben-Shalom E, et al. Long-term efficacy and safety in the phase 3 ILLUMINATE-B trial of lumasiran for primary hyperoxaluria type 1 in infants and young children. Poster presented at: NKF Congress; April 10-13, 2025; Boston, MA.

ILLUMINATE-B: BL Demographic and Clinical Characteristics

Patients Enrolled in ILLUMINATE-B Had a Median Age of 50.1 Months and the Majority Were Taking Pyridoxine[1-3]

BL Characteristic	All Treated (N = 18)
Age at informed consent, median (range), months	50.1 (3-72)
Age at diagnosis, median, months	16.3
Time from diagnosis to first dose date, median, months	23.5
Sex, female, n (%)	10 (56)
Genotype, n (%) PR/any genotype* Missense/Missense or Missense/Nonsense Nonsense/Nonsense	 3 (17) 10 (56) 5 (28)
Pyridoxine (vitamin B6) use, n (%)	11 (61)
Spot UOx:Cr, median (range), mmol/mmol†,‡	0.469 (0.166-1.708)
24-hour UOx corrected for BSA, mean (SEM), mmol/24 hours/1.73 m²	2.083 (0.3170)
POx, median (range), µmol/L§	11.5 (6.6-30.6)
eGFR, median (range), mL/min/1.73 m²¶	111 (65-174)
Patient-reported history of kidney stone events in the past 12 months, n (%)	3 (17)
Presence of nephrocalcinosis at BL, n (%)	14 (78)

Extension period

All 18 patients who enrolled in the study entered the 54-month extension period[1]

*PR was defined as NM_000030.3(*AGXT*):c.508G>A (p.Gly170Arg) or NM_000030.3 (*AGXT*):c.454T>A (p.Phe152Ile).[2] Missense and Nonsense were defined based on a publication by Mandrile et al[1,4]; †1 mmol/mmol = 0.796 mg/mg; ‡Age-related reference ranges in spot UOx:Cr: <1 year, 0.015-0.26 mmol/mmol; 1 to <5 years, 0.011-0.12 mmol/mmol; 5-12 years, 0.06-0.15 mmol/mmol[1]; §ULN = 12.11 µmol/L for POx, as determined based on data from 75 healthy adult participants[1]; ¶eGFR was calculated based on the Schwartz Bedside formula for patients ≥12 months, n = 16; eGFR was not calculated for two patients because their age at BL was <12 months.[2]

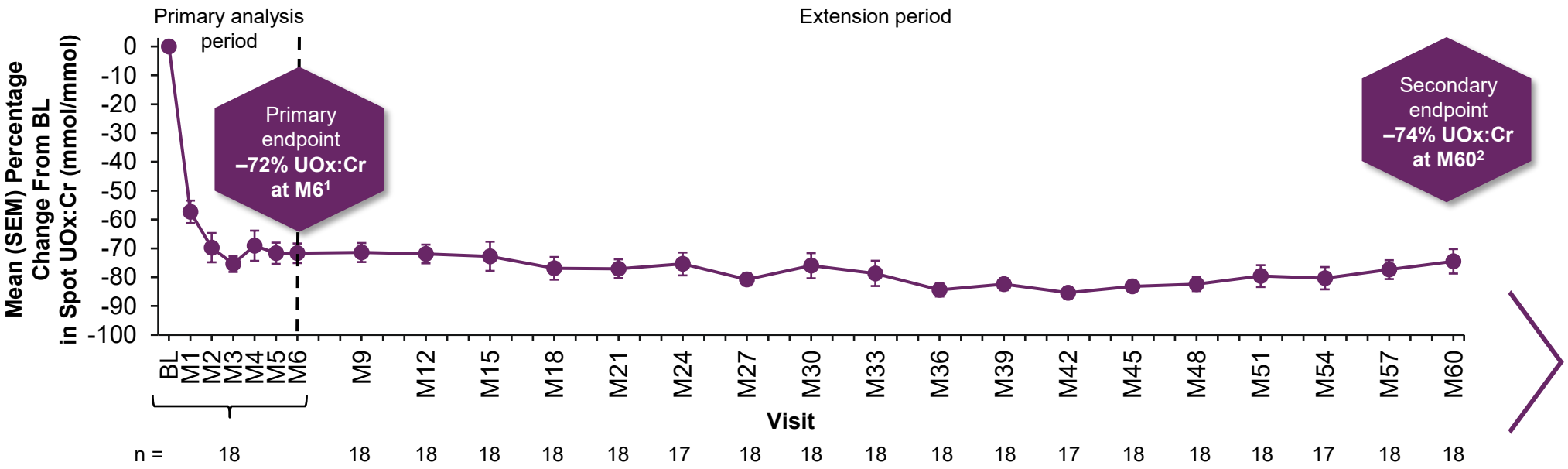
AGXT, alanine-glyoxylate aminotransferase [gene]; BL, baseline; BSA, body surface area; eGFR, estimated glomerular filtration rate; OLE, open-label extension; POx, plasma oxalate; PR, pyridoxine-responsive; SEM, standard error of the mean; ULN, upper limit of normal; UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio.

1. Frishberg Y, Hayes W, Ben-Shalom E, et al. Long-term efficacy and safety in the phase 3 ILLUMINATE-B trial of lumasiran for primary hyperoxaluria type 1 in infants and young children. Poster presented at: NKF Congress; April 10-13, 2025; Boston, MA; 2. Frishberg Y, Hayes W, Shasha-Lavsky H, et al. Efficacy and safety of lumasiran for infants and young children with primary hyperoxaluria type 1: 30-month analysis of the phase 3 ILLUMINATE-B trial. *Front Pediatr.* 2024;12:1392644. doi:10.3389/fped.2024.1392644; 3. Sas DJ, Magen D, Hayes W, et al. Phase 3 trial of lumasiran for primary hyperoxaluria type 1: a new RNAi therapeutic in infants and young children. *Genet Med.* 2022;24(3):654-662. doi:10.1016/j.gim.2021.10.024; 4. Mandrile G, van Woerden CS, Berchialla P, et al. *Kidney Int.* 2014;86(6):1197-1204. doi:10.1038/ki.2014.222

ILLUMINATE-B: Primary and Secondary Endpoints

Reductions in Spot UOx:Cr from Baseline Were Observed at Month 6 and Sustained Through Month 60[1,2]

Percentage Change From BL* in UOx:Cr Through Month 60[2]



Secondary endpoint

- **All patients** had a **spot UOx:Cr ≤ ULN** at one or more post-BL visit[1,2]
- Mean spot **UOx:Cr decreased from 0.63 mmol/mmol at BL to 0.11 mmol/mmol at Month 60**[2]
  - Age-related reference ranges in spot UOx:Cr: < 1 year, 0.015-0.26 mmol/mmol; 1 to < 5 years, 0.011-0.12 mmol/mmol; 5 to 12 years, 0.06-0.15 mmol/mmol[2]

*BL value represents the mean of all assessments collected prior to the first dose of lumasiran; 1 mmol/mmol = 0.796 mg/mg; 1 mmol/mmol = 1000 mmol/mol[2]; †End of the primary analysis period is represented by the vertical dashed line.[2]

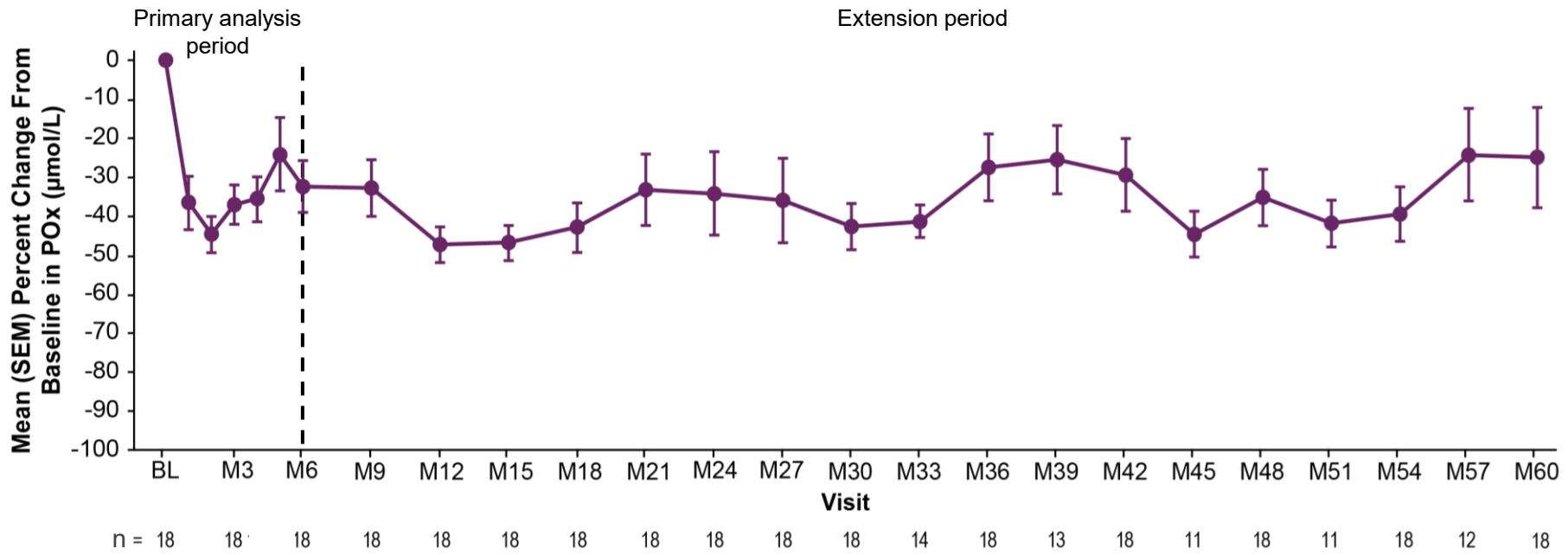
BL, baseline; M, Month; SEM, standard error of the mean; ULN, upper limit of normal; UOx:Cr, urinary oxalate:creatinine ratio.

1. Sas DJ, Magen D, Hayes W, et al. Phase 3 trial of lumasiran for primary hyperoxaluria type 1: a new RNAi therapeutic in infants and young children. *Genet Med.* 2022;24(3):654-662. doi:10.1016/j.gim.2021.10.024;
2. Frishberg Y, Hayes W, Ben-Shalom E, et al. Long-term efficacy and safety in the phase 3 ILLUMINATE-B trial of lumasiran for primary hyperoxaluria type 1 in infants and young children. Poster presented at: NKF Congress; April 10-13, 2025; Boston, MA.

ILLUMINATE-B: Secondary Endpoint

Reductions in POx from BL Were Observed at Month 6 and Sustained Through Month 60

Mean (SEM) Percentage Change in POx From BL* Through Month 60



POx

The **reduction in POx was sustained through Month 60** (25% reduction)

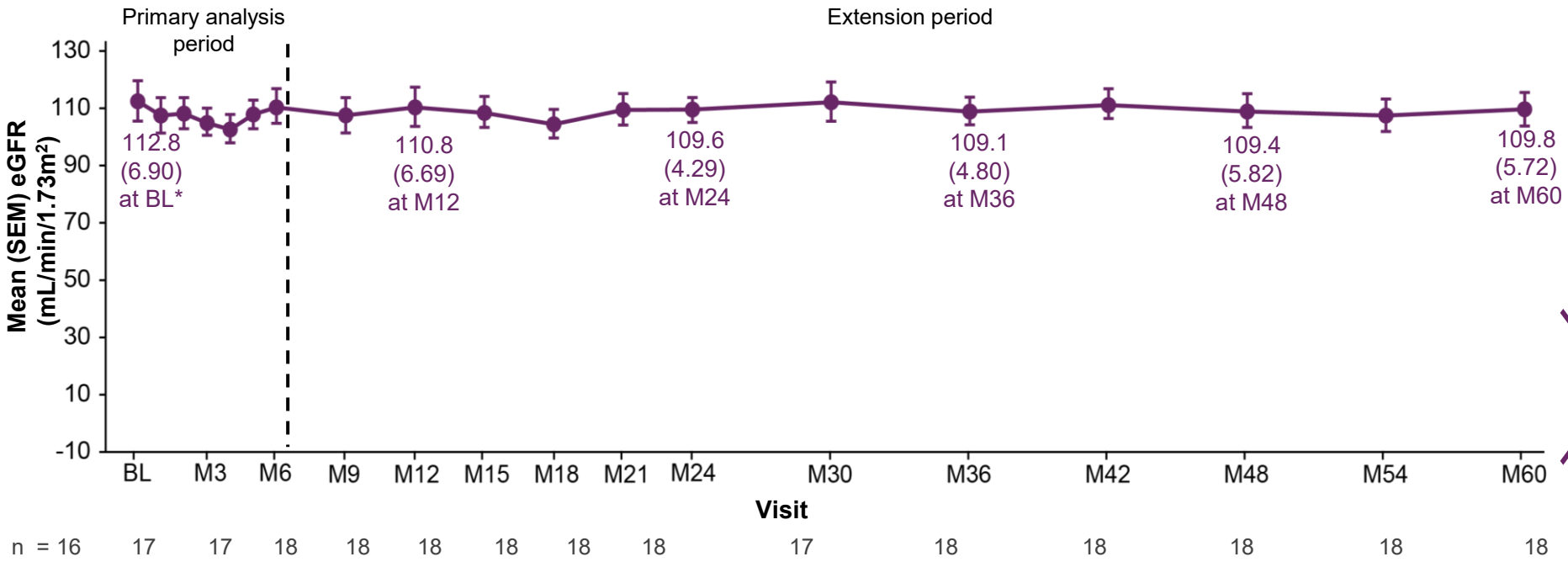
*BL value represents the mean of all assessments collected prior to the first dose of lumasiran. The lower limit of quantification = 5.55 µmol/L.
BL, baseline; M, Month; POx, plasma oxalate; SEM, standard error of the mean.

Frishberg Y, Hayes W, Ben-Shalom E, et al. Long-term efficacy and safety in the phase 3 ILLUMINATE-B trial of lumasiran for primary hyperoxaluria type 1 in infants and young children. Poster presented at: NKF Congress; April 10-13, 2025; Boston, MA.

ILLUMINATE-B: Secondary Endpoint

Stabilization of eGFR from BL was Observed Through Month 60[1]

Mean (SEM) eGFR From BL Through Month 60[1]



Month 60[1]

- **eGFR stability was observed through Month 60**
  - *Post hoc* analysis: The **annual change** in mean eGFR over 60 months was **+0.26 (SEM 0.8) mL/min/1.73m²/y**

*Baseline is the last non-missing value collected prior to the first dose of lumasiran. Labels on graph show mean (SEM) at baseline and at 12-month intervals. End of the primary analysis period is represented by the vertical dashed line; error bars show standard error of the mean (SEM)[1]. eGFR is calculated based on the Schwartz Bedside formula[2] in patients ≥ 12 months of age at the time of the assessment.[1] Baseline values are not available for two patients who were < 12 months of age at that time point[1].

BL, baseline; eGFR, estimated glomerular filtration rate; M, Month; SEM, standard error of the mean.

1. Frishberg Y, Hayes W, Ben-Shalom E, et al. Long-term efficacy and safety in the phase 3 ILLUMINATE-B trial of lumasiran for primary hyperoxaluria type 1 in infants and young children. Poster presented at: NKF Congress; April 10-13, 2025; Boston, MA; 2. Schwartz GJ, Muñoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol.* 2009;20:629-637.

ILLUMINATE-B: Secondary Endpoints

Reduced Urinary Oxalate and Plasma Oxalate Levels were Observed in Infants and Young Children With PH1 at Month 6 and Through Month 30

Secondary Endpoints, Including Additional Measures of UOx and POx

Endpoint	All Lumasiran Treated (N = 18)	
	Month 6[1]	Month 30[1]
Absolute change from BL in spot UOx:Cr, mmol/mmol, mean (SEM)*	−0.5 (0.1)	−0.5 (0.1)
Patients with spot UOx:Cr, n (%)		
≤ULN†	1 (6)	7 (39)
≤1.5 × ULN†	9 (50)	13 (72)
Change from BL corrected for BSA in 24-hour UOx, mean (SEM)‡		
Absolute change from BL, mmol/24 hours/1.73m^2	−1.4 (0.1)	−1.5 (0.4)
Percent change from BL, %	−68.4 (5.6)	−73.5 (8.8)
Absolute change from BL in POx, µmol/L, mean (SEM)§		
In efficacy analysis set	−5.0 (1.3)	−6.9 (1.6)
In POx analysis set¶	−6.5 (1.6)	−9.2 (1.8)

*1 mmol/mmol = 0.796 mg/mg; 1 mmol/mmol = 1000 mmol/mol; †Age-dependent ULN; ‡In patients with valid 24-hour UOx measurements; n = 2 at Month 6, n = 4 at Month 12, n = 2 at Month 18, n = 3 at Month 24, n = 4 at Month 30; §ULN = 12.11 µmol/L for POx, as determined based on data from healthy adult participants; ¶In patients with BL POx ≥1.5 × LLOQ (5.55 µmol/L [n = 13]; values below LLOQ were assigned a value of 5.55 µmol/L).

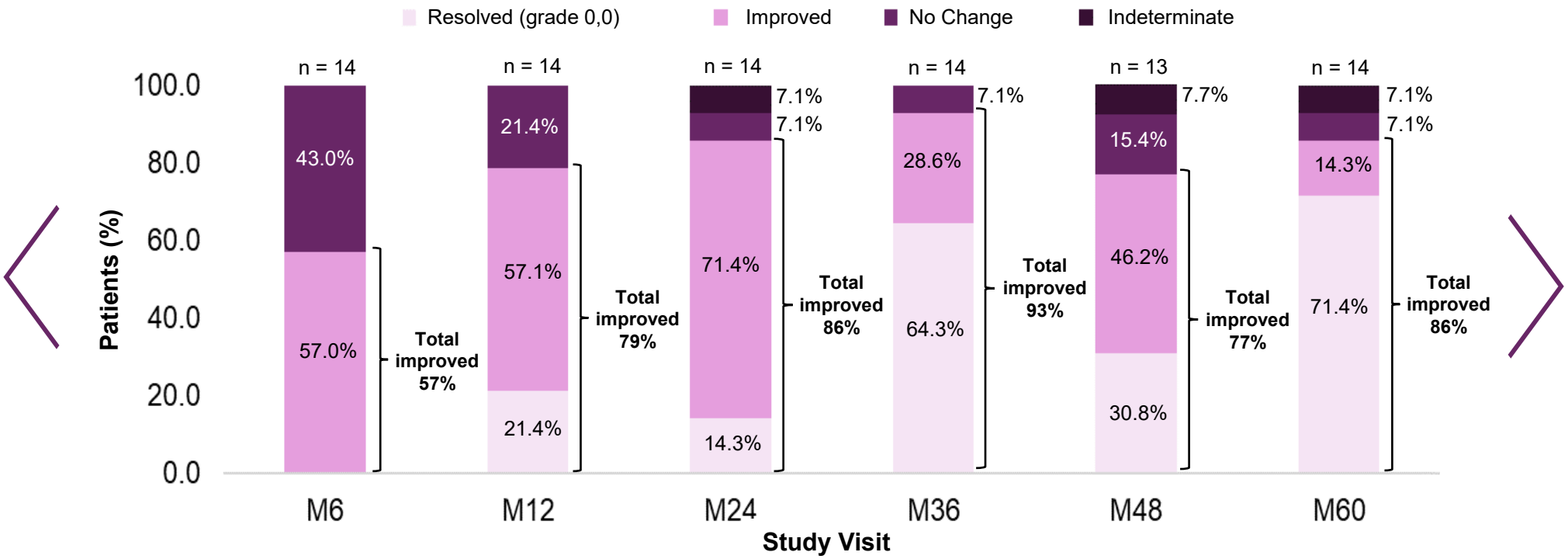
BL, baseline; BSA, body surface area; LLOQ, lower limit of quantification; PH1, primary hyperoxaluria type 1; POx, plasma oxalate; SEM, standard error of the mean; ULN, upper limit of normal; UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio.

Frishberg Y, Hayes W, Shasha-Lavsky H, et al. Efficacy and safety of lumasiran for infants and young children with primary hyperoxaluria type 1: 30-month analysis of the phase 3 ILLUMINATE-B trial. *Front Pediatr.* 2024;12:1392644. doi:10.3389/fped.2024.1392644.

ILLUMINATE-B: Exploratory Endpoints

Changes in Medullary Nephrocalcinosis Grade Were Observed in Infants and Young Children With PH1 with Long-Term Lumasiran Use Through Month 60[1,2]

Post Hoc Analysis: Change in Medullary Nephrocalcinosis Grade Through Month 60 in Patients with Nephrocalcinosis at BL[1,2,*,†,‡]



*Patients who had no nephrocalcinosis at BL (n = 4) remained stable, with no nephrocalcinosis at Month 60; these patients are not depicted.[1,2] †Resolved (grade 0,0) denotes bilateral grade of '0,0' (both kidneys); Improved indicates grade lower than BL; stable indicates grade the same as BL; Indeterminate indicates one side improved and the other side worsened; Worsened denotes grade higher than BL (no patients worsened).[1] ‡Medullary nephrocalcinosis was determined via renal ultrasound, performed by a central radiologist.[2]

BL, baseline; M, Month; PH1, primary hyperoxaluria type 1.

1. Frishberg Y, Hayes W, Ben-Shalom E, et al. Long-term efficacy and safety in the phase 3 ILLUMINATE-B trial of lumasiran for primary hyperoxaluria type 1 in infants and young children. Poster presented at: NKF Congress; April 10-13, 2025; Boston, MA; 2. Frishberg Y, Hayes W, Shasha-Lavsky H, et al. Efficacy and safety of lumasiran for infants and young children with primary hyperoxaluria type 1: 30-month analysis of the phase 3 ILLUMINATE-B trial. *Front Pediatr.* 2024;12:1392644. doi:10.3389/fped.2024.1392644.

ILLUMINATE-B: Exploratory Endpoint

Post Hoc Analysis: Low Rates of Kidney Stone Events Were Observed Through Month 60[1]

Kidney Stone Event Rates*[1-4]

Kidney stone events per person-year, rate (95% CI)	All Lumasiran Treated (N = 18)
12-month period prior to informed consent[2,3]	0.24† (0.09-0.63)
Primary analysis period (Month 6)[2,3]	0.24 (0.06-0.96)
Extension period (Month 30)[4]	≤ 0.25
Extension period (Month 60)[1]	0.11 (0.06-0.21)

Month 60

- **Nine kidney stone events** occurred in a total of **four patients** from BL **through Month 60**[1]
- All events were either **mild or moderate**[1]
- **77.8% of patients** (n = 14) **had no kidney stone events** during ILLUMINATE-B[1]

*Kidney stone events included at least 1 of the following: visit to a healthcare professional because of a kidney stone, medication for renal colic, stone passage, or macroscopic hematuria caused by a kidney stone. Events were adjudicated by the investigator.[2] †Historical patient-reported history of kidney stone events. An annualized rate was not calculated for patients < 6 months old.[4]

BL, baseline; CI, confidence interval.

1. Frishberg Y, Hayes W, Ben-Shalom E, et al. Long-term efficacy and safety in the phase 3 ILLUMINATE-B trial of lumasiran for primary hyperoxaluria type 1 in infants and young children. Poster presented at: NKF Congress; April 10-13, 2025; Boston, MA; 2. Sas DJ, Magen D, Hayes W, et al. Phase 3 trial of lumasiran for primary hyperoxaluria type 1: a new RNAi therapeutic in infants and young children. *Genet Med.* 2022;24(3):654-662. doi:10.1016/j.gim.2021.10.024; 3. Sas DJ, Magen D, Hayes W, et al. Phase 3 trial of lumasiran for primary hyperoxaluria type 1: a new RNAi therapeutic in infants and young children. *Genet Med.* 2022;24(3):654-662. doi:10.1016/j.gim.2021.10.024 (supplementary appendix); 4. Frishberg Y, Hayes W, Shasha-Lavsky H, et al. Efficacy and safety of lumasiran for infants and young children with primary hyperoxaluria type 1: 30-month analysis of the phase 3 ILLUMINATE-B trial. *Front Pediatr.* 2024;12:1392644. doi:10.3389/fped.2024.1392644.

ILLUMINATE-B: Safety Data

Safety Profile Up to Month 60 in Infants and Young Children With PH1

Safety Summary in Infants and Young Children With PH1

Event, n (%)	All Treated (N = 18)
AEs	18 (100)
Treatment-related AEs*	5 (28)
Severe treatment-related AEs	0
AEs leading to treatment discontinuation	0
AEs leading to study withdrawal	0
Serious AEs	2 (11)†
Deaths	0

Month 60

- The **most common AEs** with lumasiran were **mild, transient ISRs**, reported in **17% of patients** (n = 3) at **Month 60**
  - Symptoms included erythema, hematoma, pain at the injection site, and urticaria
- There were **no clinically relevant changes** in laboratory measures, vital signs, or electrocardiograms related to lumasiran
- Data suggest **no unexpected safety concerns**

*Treatment-related AEs included ISR, transient blood bilirubin increase, and headache.
†One patient had a serious AE of viral infection (moderate in severity; considered unrelated to lumasiran by the investigator) during the 6-month primary analysis period, which was reported previously. The other patient had a serious AE of ear pain and ear hemorrhage (severe; considered unrelated to lumasiran by the investigator) during the extension period. In both patients, lumasiran dosing was not changed.
AE, adverse event; BL, baseline; ISR, injection site reaction; PH1, primary hyperoxaluria type 1.

Frishberg Y, Hayes W, Ben-Shalom E, et al. Long-term efficacy and safety in the phase 3 ILLUMINATE-B trial of lumasiran for primary hyperoxaluria type 1 in infants and young children. Poster presented at: NKF Congress; April 10-13, 2025; Boston, MA.

ILLUMINATE-C: Study Design

ILLUMINATE-C was a Multinational, Single-Arm, Open-Label Phase 3 Trial That Evaluated the Efficacy and Safety of Lumasiran in Patients With PH1 With Impaired Kidney Function[1]

Patients were enrolled into one of two cohorts based on whether they were receiving hemodialysis (Cohort A) or not receiving hemodialysis (Cohort B) at study entry:[1,2]

Patient Population (N = 21)

6-Month Primary Analysis Period

54-Month Extension Period

Patients

Open label

Lumasiran SC
QM × 3 loading dose, then QM or Q3M maintenance dosing by weight*[1,2]

- Cohort A (no HD)† (n = 6)[1]
- Cohort B (HD) (n = 15)[1]

Lumasiran SC
QM or Q3M maintenance dosing by weight*[2]

- Cohort A (no HD) (n = 6)[1]
- Cohort B (HD) (n = 15)[1]

Selected eligibility criteria[1]

- All ages
- Diagnosis of PH1 confirmed by genetic analysis
- POx ≥ 20 µmol/L (ULN 12.11 µmol/L)
- eGFR ≤45 mL/min/1.73 m^2 if aged ≥ 12 months or increased serum creatinine if aged < 12 months

! Patients with a history of kidney transplant and receiving immunosuppressants were excluded from the study at enrollment. Over the course of the study, at the discretion of the investigators, patients could receive a transplant during the study[3,4]

*Patients weighing <10 kg received loading doses 6.0 mg/kg QM for 3 months and then maintenance doses of 3.0 mg/kg QM; patients weighing ≥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 weighing ≥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 last loading dose[1]; †Cohort A patients who experience progression of kidney impairment over time and begin to require dialysis therapy will cross over to Cohort B.[1]

BL, baseline; eGFR, estimated glomerular filtration rate; HD, hemodialysis; PH1, primary hyperoxaluria type 1; POx, plasma oxalate; QM, every month; Q3M, every 3 months; SC, subcutaneous; ULN, upper limit of normal.

1. Michael M, Groothoff JW, Shasha-Lavsky H, et al. Lumasiran for advanced primary hyperoxaluria type 1: phase 3 ILLUMINATE-C trial. *Am J Kidney Dis*. 2023;81(2):145-155.e1. doi:10.1053/j.ajkd.2022.05.012;
2. Michael M, Groothoff JW, Shasha-Lavsky H, et al. Lumasiran for advanced primary hyperoxaluria type 1: phase 3 ILLUMINATE-C trial. *Am J Kidney Dis*. 2023;81(2):145-155.e1. doi:10.1053/j.ajkd.2022.05.012 (supplementary appendix); 3. Somers MJ, Devresse A, Willey R, et al. Kidney function and isolated kidney transplant outcomes in primary hyperoxaluria type 1 treated with long-term lumasiran. Poster presented at: ASN Kidney Week; October 24-27, 2024; San Diego, CA; 4. ClinicalTrials.gov identifier: NCT04152200. Updated February 13, 2025. Accessed August 1, 2025. https://clinicaltrials.gov/study/NCT04152200.

ILLUMINATE-C: Study Design

Patients With PH1 With Impaired Kidney Function, Including Those Receiving HD, Were Enrolled in ILLUMINATE-C[1,2]

Inclusion Criteria[1-3]

- All ages
- Diagnosis of PH1 confirmed by genetic analysis
- POx ≥ 20 µmol/L (ULN 12.11 µmol/L)
- CKD with eGFR ≤ 45 mL/min/1.73 m^2 if aged ≥ 12M or increased SCr if aged < 12M months
- For patients receiving SoC, treatment must be stable*
- Stable HD regimen for ≥ 4weeks, to be continued through to Month 6 (cohort B)

Exclusion Criteria[3]

- Receiving peritoneal dialysis
- History of kidney transplant and currently receiving immunosuppressants
- History of liver transplant
- Undergoing combined hemodialysis/peritoneal dialysis therapy

*Patients receiving pyridoxine therapy were required to have been receiving a stable regimen for at least 90 days before providing informed consent and to continue to receive this regimen through the month-6 visit.[1]

BL, baseline; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HD, hemodialysis; M, Month; PH1, primary hyperoxaluria type 1; POx, plasma oxalate; SCr, serum creatinine; SoC, standard of care; ULN, upper limit of normal.

1. Michael M, Groothoff JW, Shasha-Lavsky H, et al. Lumasiran for advanced primary hyperoxaluria type 1: phase 3 ILLUMINATE-C trial. *Am J Kidney Dis*. 2023;81(2):145-155.e1. doi:10.1053/j.ajkd.2022.05.012;
2. Sellier-Leclerc AL, Magen D, Shasha-Lavsky H, et al. Efficacy and safety of lumasiran for advanced primary hyperoxaluria type 1: 24-month follow-up of the phase 3 ILLUMINATE-C trial. *Am J Kidney Dis*. Published online March 13, 2025. doi:10.1053/j.ajkd.2025.01.016; 3. ClinicalTrials.gov identifier: NCT04152200. Updated February 13, 2025. Accessed August 1, 2025. https://clinicaltrials.gov/study/NCT04152200

ILLUMINATE-C: Endpoints

Primary Endpoint Assessed Percentage Change in Predialysis POx or POx up to Month 6 While Secondary and Exploratory Endpoints Further Assessed Efficacy Through the Extension Period

Primary*,[1,2]

- Percentage change in predialysis POx (**Cohort B**) or POx from BL (**Cohort A**) to Month 6

Secondary*,[1,2]

- Percentage and absolute change in POx from BL through extension period
- Frequency of kidney stone event rate through extension period
- Percentage change in POx AUC between dialysis sessions (**Cohort B only**) from BL to Month 6 and through extension period
- Percentage and absolute change in 24-hour UOx and spot UOx:Cr from BL to Month 6 and through extension period
- Change in cardiac measures of systemic oxalosis from BL through extension period

Exploratory[2]

- Change in plasma glycolate from BL through extension period

This is not inclusive of all available endpoints or data, please refer to the study protocol linked above.
*Primary endpoint and pharmacodynamic secondary endpoints at M6 were an average of measurements from M3 to M6.[1]
AUC, area under the curve; BL, baseline; M, month; POx, plasma oxalate; UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio.

1. Michael M, Groothoff JW, Shasha-Lavsky H, et al. Lumasiran for advanced primary hyperoxaluria type 1: phase 3 ILLUMINATE-C trial. *Am J Kidney Dis*. 2023;81(2):145-155.e1. doi:10.1053/j.ajkd.2022.05.012;
2. ClinicalTrials.gov identifier: NCT04152200. Study protocol. Accessed August 1, 2025. https://clinicaltrials.gov/study/NCT04152200.

ILLUMINATE-C: BL Characteristics

Baseline Characteristics Were Generally Balanced Between Cohorts in ILLUMINATE-C[1,2]

Patient Characteristics for ILLUMINATE-C

BL Characteristic	Cohort A (n = 6)	Cohort B (n = 15)	All Treated (N = 21)
Age at consent, median (range), years[1,2]	9.0 (0-40)	6.0 (1-59)	8.0 (0-59)
Time from diagnosis to first dose, median (range), months[1]	72.2 (4-350)	16.6 (6-440)	21.6 (4-440)
Female sex, n (%)[1,2]	3 (50)	6 (40)	9 (43)
Race, n (%)[1]			
White	4 (67)	12 (80)	16 (76)
Asian	1 (17)	3 (20)	4 (19)
Other	1 (17)	0	1 (5)
Geographic region, n (%)[1]			
Europe	0	8 (53)	8 (38)
North America	1 (17)	2 (13)	3 (14)
Israel	1 (17)	2 (13)	3 (14)
United Arab Emirates	0	3 (20)	3 (14)
Other*	4 (67)	0	4 (19)
Genotype, n (%)†[1,2]			
PR/any genotype	0	5 (33)	5 (24)
Missense/Missense or Missense/Nonsense	5 (83)	7 (47)	12 (57)
Nonsense/Nonsense	1 (17)	3 (20)	4 (19)

Month 6

All 21 patients completed the 6-month primary analysis period and **entered the 54-month** extension period[2]

*Australia, Jordan, Lebanon, and Turkey; †Pyridoxine-responsive was defined as NM_000030.3(*AGXT*):c.508G>A (p.Gly170Arg) or NM_000030.3(AGXT):c.454T>A (p.Phe152Ile). Missense and nonsense were defined based on Mandrile et al.[3]

AGXT, alanine-glyoxylate aminotransferase [gene]; BL, baseline; PR, pyridoxine-responsive.

1. Michael M, Groothoff JW, Shasha-Lavsky H, et al. Lumasiran for advanced primary hyperoxaluria type 1: phase 3 ILLUMINATE-C trial. *Am J Kidney Dis*. 2023;81(2):145-155.e1. doi:10.1053/j.ajkd.2022.05.012;
2. Sellier-Leclerc AL, Magen D, Shasha-Lavsky H, et al. Efficacy and safety of lumasiran for advanced primary hyperoxaluria type 1: 24-month follow-up of the phase 3 ILLUMINATE-C trial. *Am J Kidney Dis*. Published online March 13, 2025. doi:10.1053/j.ajkd.2025.01.016 (supplementary appendix); 3. Mandrile G, van Woerden CS, Berchialla P, et al. Data from a large European study indicate that the outcome of primary hyperoxaluria type 1 correlates with the AGXT mutation type. *Kidney Int*. 2014;86(6):1197-1204. doi:10.1038/ki.2014.222.

ILLUMINATE-C: BL Characteristics

Baseline Characteristics Were Generally Balanced Between Cohorts in ILLUMINATE-C[1,2]

Patient Characteristics for ILLUMINATE-C

BL Characteristic	Cohort A (n = 6)	Cohort B (n = 15)	All Treated (N = 21)
Pyridoxine use, n (%)[2]	5 (83)	7 (47)	12 (57)
POx, median (range),* µmol/L[1,2]	57.9 (22.7-134.0)	103.7 (56.3-167.0)	100.9 (22.7-167.0)
Spot UOx:Cr†[1,2]			
Patients with measurement, n	6	2	8
Value, median (range), mmol/mmol	0.332 (0.075-1.380)	0.535 (0.451-0.618)	0.391 (0.075-1.380)
24-h UOx excretion‡[1,2]			
Patients with measurement, n	5	1	6
Value, median (range), mmol/24 hours/1.73 m^2	2.01 (0.56-2.47)	1.28 (1.28-1.28)	1.64 (0.56-2.47)
eGFR§[1,2]			
Patients with measurement, n	5	NA	5
Value (range), mL/min/1.73 m^2	16.5 (8.6-34.1)	-	16.5 (8.6-34.1)
Dialysis sessions per week, median (range)[1,2]	NA	6 (3-7)	NA

Month 24

Of the 21 patients who completed the 6-month analysis, **83% in Cohort A (no HD)** and **80% in Cohort B (HD)** completed the **Month 24 visit**[2]

*ULN = 12.11 µmol/L (1.09 mg/mL) as determined based on data from 75 healthy adult participants;[1] †1 mmol/mmol = 0.796 mg/mg;[1] ‡Upper limit of normal = 0.514 mmol/24 hours/1.73 m^2 for BSA-adjusted 24-hour UOx;[1] §eGFR was calculated only in patients aged ≥12 months; calculated according to the Modification of Diet in Renal Disease Study equation for those aged ≥ 18 years and the Schwartz bedside formula for those aged 1 to < 18 years.[1]

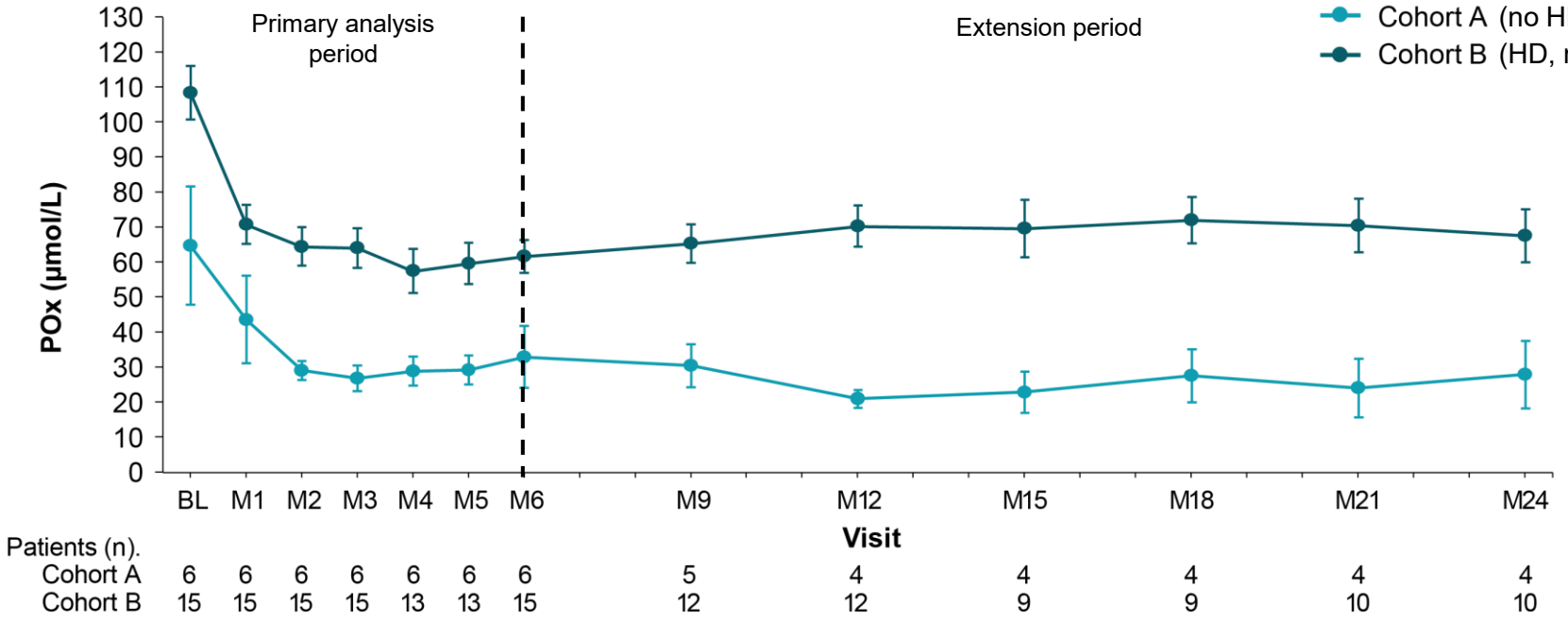
BL, baseline; BSA, body surface area; eGFR, estimated glomerular filtration rate; HD, hemodialysis; NA, not applicable; POx, plasma oxalate; UOx, urinary oxalate; ULN, upper limit of normal; UOx:Cr, urinary oxalate:creatinine ratio.

1. Michael M, Groothoff JW, Shasha-Lavsky H, et al. Lumasiran for advanced primary hyperoxaluria type 1: phase 3 ILLUMINATE-C trial. *Am J Kidney Dis*. 2023;81(2):145-155.e1. doi:10.1053/j.ajkd.2022.05.012;
2. Sellier-Leclerc AL, Magen D, Shasha-Lavsky H, et al. Efficacy and safety of lumasiran for advanced primary hyperoxaluria type 1: 24-month follow-up of the phase 3 ILLUMINATE-C trial. *Am J Kidney Dis*. Published online March 13, 2025. doi:10.1053/j.ajkd.2025.01.016 (supplementary appendix).

ILLUMINATE-C: Primary and Secondary Endpoints

Reductions in POx Were Observed at Month 6 and Sustained Through Month 24[1,2]

Change in Mean (SEM) POx or Predialysis POx Levels Through to Month 24*†,1



Primary endpoint

Cohort A
−33.3%‡ LS mean percent change in **POx** from BL to Month 6[2]

Cohort B
−42.4%§ LS mean percent change in **predialysis POx** from BL to Month 6[2]

Cohort A
−60.5% LS mean percent change in **POx** from BL to Month 24[1]

Cohort B
−30.6% LS mean percent change in **predialysis POx** from BL to Month 24[1]

Secondary endpoint

*In Cohort A, BL was defined as the mean of all POx samples (µmol/L) collected prior to the first dose of lumasiran. In Cohort B, BL was defined as the mean of the last four predialysis POx samples (µmol/L) collected prior to the first dose of lumasiran. Observations occurring after a liver transplant, initiation of hemodialysis in Cohort A, or discontinuation of hemodialysis in Cohort B were censored;[1]†The primary estimate is the least squares mean of the percent change in POx from baseline to month 3 through month 6 averaged over these time points.[2] ‡ (95% CI, -15.2-81.8%);2 § (95% CI, 34.2-50.7%).[2]

BL, baseline; CI, confidence interval; HD, hemodialysis; LS, least squares; M, Month; PH1, primary hyperoxaluria type 1; POx, plasma oxalate; SEM, standard error of the mean.

1. Sellier-Leclerc AL, Magen D, Shasha-Lavsky H, et al. Efficacy and safety of lumasiran for advanced primary hyperoxaluria type 1: 24-month follow-up of the phase 3 ILLUMINATE-C trial. *Am J Kidney Dis.* Published online March 13, 2025. doi:10.1053/j.ajkd.2025.01.016; 2. Michael M, Groothoff JW, Shasha-Lavsky H, et al. Lumasiran for advanced primary hyperoxaluria type 1: phase 3 ILLUMINATE-C trial. *Am J Kidney Dis.* 2023;81(2):145-155.e1. doi:10.1053/j.ajkd.2022.05.012

ILLUMINATE-C: Secondary Endpoint

Post Hoc Analysis: Reductions in Kidney Stone Events from Pre-Study Rates Were Observed in Cohort A During the 6-month Primary Analysis Period and were Sustained Through Month 24[1]

Kidney Stone Event Rates*,[1]

Kidney stone events per person-year, rate (95% CI)	Cohort A (N = 6)	Cohort B (N = 15)
12-month period prior to informed consent	3.20 (1.96-5.22)	0.07 (0.01-0.71)
Primary analysis period	1.48 (0.55-3.92)	0.00 (0.00-0.53)
Extension period†	0.32 (0.08-1.27)	0.00 (0.00-0.19)

Kidney stone event

- **Kidney stone event rates declined from pre-study rates in Cohort A** during the 6-month primary analysis period and extension period[1]
- **In Cohort B, no patients had a kidney stone event** during the treatment period[1]

*Kidney stone events during the extension period include all available data through the data cutoff date (October 17, 2022). A kidney stone event is defined as an event that includes ≥1 of the following: visit to healthcare professional because of a kidney stone, medication for kidney colic, stone passage, and macroscopic hematuria due to a kidney stone.[1] †Patient-reported history of KSEs. An annualized rate was not calculated for patients < 6 months old.[2,3]

BL, baseline; CI, confidence interval; KSE, kidney stone event.

1. Sellier-Leclerc AL, Magen D, Shasha-Lavsky H, et al. Efficacy and safety of lumasiran for advanced primary hyperoxaluria type 1: 24-month follow-up of the phase 3 ILLUMINATE-C trial. *Am J Kidney Dis*. Published online March 13, 2025. doi:10.1053/j.ajkd.2025.01.016 (supplementary appendix); 2. Michael M, Groothoff JW, Shasha-Lavsky H, et al. Lumasiran for advanced primary hyperoxaluria type 1: phase 3 ILLUMINATE-C trial. *Am J Kidney Dis*. 2023;81(2):145-155.e1. doi:10.1053/j.ajkd.2022.05.012; 3. Frishberg Y, Hayes W, Shasha-Lavsky H, et al. Efficacy and safety of lumasiran for infants and young children with primary hyperoxaluria type 1: 30-month analysis of the phase 3 ILLUMINATE-B trial. *Front Pediatr*. 2024;12:1392644. doi:10.3389/fped.2024.1392644

ILLUMINATE-C: Secondary Endpoints

Lumasiran Treatment Was Associated With Improvements in Secondary Endpoints at Month 6 in Patients With PH1 With Impaired Kidney Function or on Hemodialysis

Secondary Endpoints

Endpoint Values given as LS mean ± SEM (95% CI)	Cohort A (n = 6)	Cohort B (n = 15)
Percentage change in POx $AUC_{0\text{-}24h}$ between dialysis sessions from BL to Month 6*	NA	−41.4 ± 4.4 (−51.0, −31.8)
Absolute change in POx from BL to Month 6, µmol/L†,‡	−35.3 ± 7.4 (−56.3, −14.2)	−48.3 ± 3.6 (−55.9, −40.8)
Percentage change in spot UOx:Cr from BL to Month 6‡	−39.5 ± 9.4 (−64.1, −14.9)	NA
Absolute change in spot UOx:Cr from BL to Month 6, mmol/mmol§,‡	−0.188 ± 0.016 (−0.229, −0.147)	NA
Percentage change in BSA-adjusted 24-hour UOx from BL to Month 6‡	−10.6 ± 6.8 (−32.0, 10.9)¶	NA
Absolute change in BSA-adjusted 24-hour UOx from BL to Month 6, mmol/24 hours/1.73 m^2‡	−0.53 ± 0.11 (−0.89, −0.18)¶	NA

Values given as LS mean ± SEM (95% CI). *LS mean percent change from BL in POx $AUC_{0\text{-}24h}$ at Month 6 and its associated 95% CI were estimated using the restricted maximum likelihood-based mixed model for repeated measures approach including data evaluated at Months 3 and 6. The model included scheduled visits and BL POx as fixed effects, and patients as a random factor. Autoregressive(1) was used to model the within-patient variability; † ULN = 12.11 µmol/L (1.09 mg/mL), as determined based on data from 75 healthy adult participants; ‡Change from BL to Month 6 was calculated as the change across Months 3 through 6. The LS mean with corresponding SEM and 95% CI were derived using the restricted maximum likelihood-based mixed model for repeated measures model. The model included scheduled visits and BL POx as fixed effects, and patients as a random factor. Autoregressive(1) was used to model the within-patient variability; §1 mmol/mmol = 0.796 mg/mg; ¶n = 5.

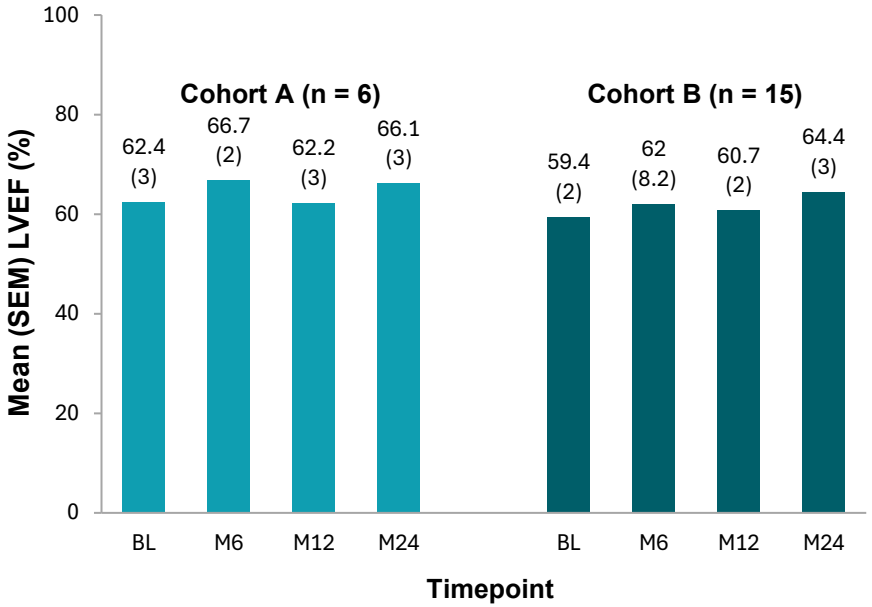
$AUC_{0\text{-}24h}$, area under the curve from 0 to 24 hours; BL, baseline; BSA, body surface area; CI, confidence interval; LS, least squares; NA, not applicable; PH1, primary hyperoxaluria type 1; POx, plasma oxalate; SEM, standard error of the mean; UOx, urinary oxalate; ULN, upper limit of normal; UOx:Cr, urinary oxalate:creatinine ratio.

Michael M, Groothoff JW, Shasha-Lavsky H, et al. Lumasiran for advanced primary hyperoxaluria type 1: phase 3 ILLUMINATE-C trial. *Am J Kidney Dis*. 2023;81(2):145-155.e1. doi:10.1053/j.ajkd.2022.05.012

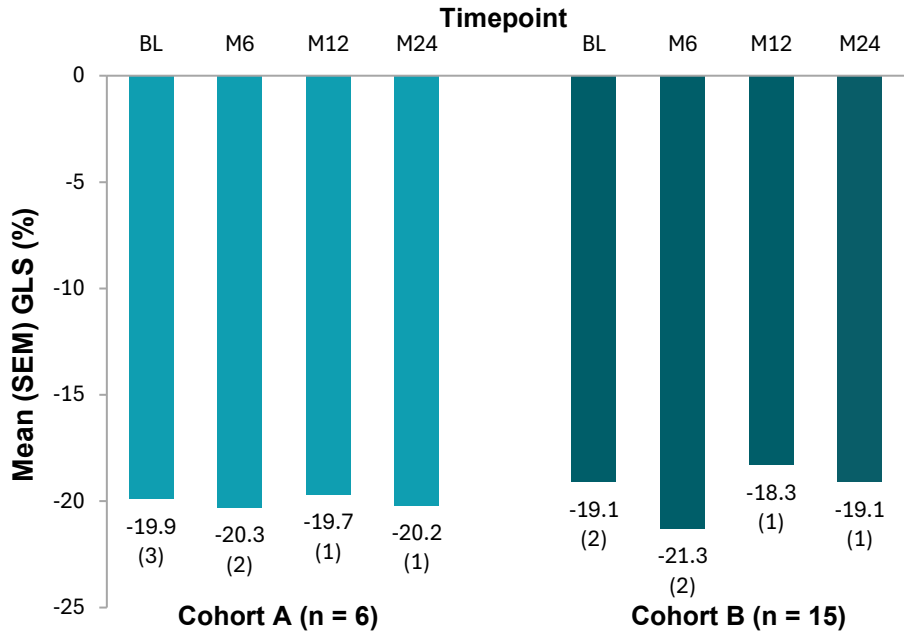
ILLUMINATE-C: Secondary Endpoints

Measures of Cardiac Systemic Oxalosis* Were Observed to be Stable from Baseline† Through Month 24[1]

Mean (SEM) Percentage Change in LVEF[1]



Mean (SEM) Percentage Change in GLS[1]



Month 24[1]

- **No patients in cohort A remaining in the study met the criteria for worsening LVEF‡ through Month 24[2]**
- Three patients in Cohort B had abnormal GLS at BL§. It was observed **all three of these patients showed a 2% improvement in GLS at Month 24¶[1]**
- Of the three patients in cohort B with an abnormal LVEF at BL, **two met criteria for important improvement by Month 24,** while one patient did not **[1]**
- One patient in Cohort A without GLS abnormality at BL met the criteria for GLS worsening†† at Month 24[1]

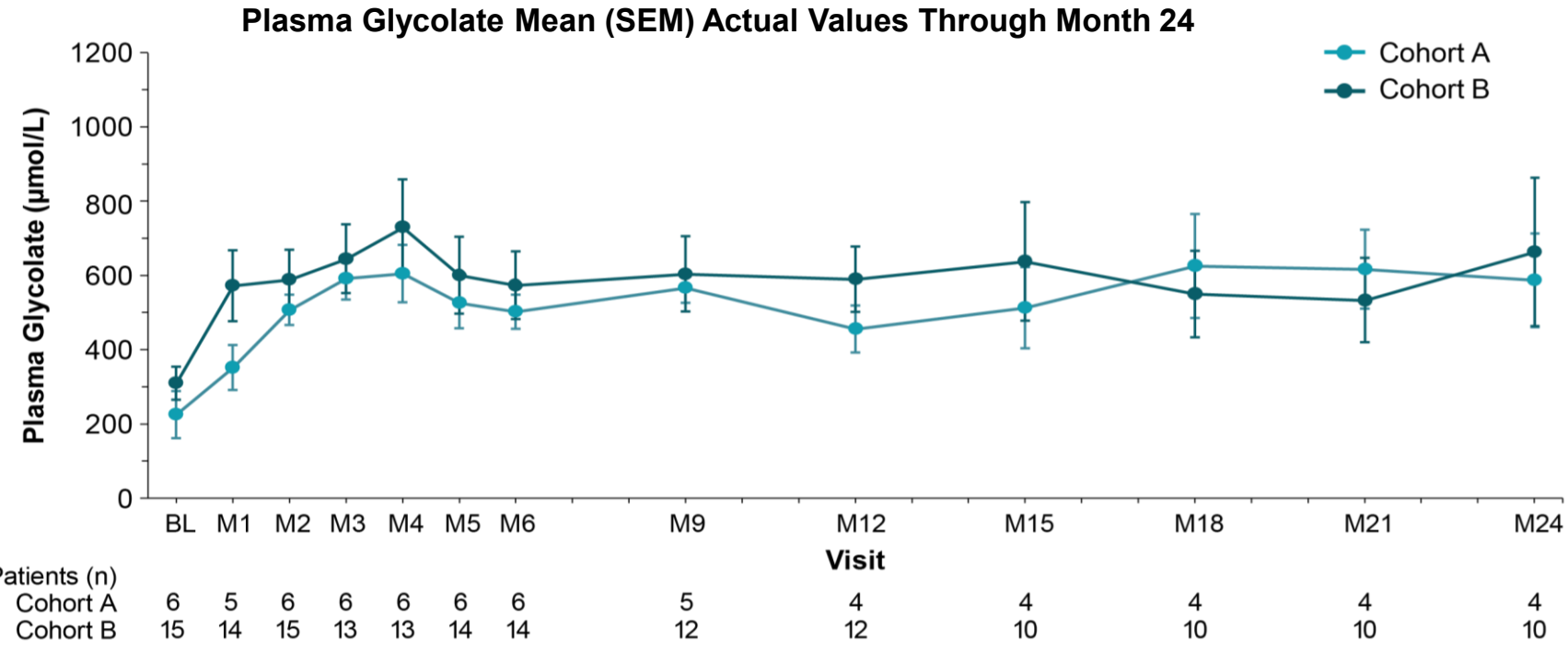
*There was insufficient follow-up time for interpretation of oxalosis data[2]; †BL was defined as last non-missing value collected prior to the first dose of lumasiran. ‡Worsening from BL in LVEF was defined as a >10% decline from BL to a value of < 50%. §Definition of abnormality = absolute value of GLS <15%; ¶ Definition of important improvement from BL was increase from BL of > 2% in GLS absolute value; ** Definition of LVEF abnormality was <55% and important improvement from BL was an increase of ≥5% if <55% at BL; ††Definition of GLS worsening from BL was a > 15% decline form BL to an absolute value of < 16% in patients aged ≥ 18 years, and an absolute value of < 19.5% in patients aged < 18 years.

BL, baseline; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; M, Month.

1. Sellier-Leclerc AL, Magen D, Shasha-Lavsky H, et al. Efficacy and safety of lumasiran for advanced primary hyperoxaluria type 1: 24-month follow-up of the phase 3 ILLUMINATE-C trial. *Am J Kidney Dis.* Published online March 13, 2025. doi:10.1053/j.ajkd.2025.01.016 (supplementary appendix); 2. Sellier-Leclerc AL, Magen D, Shasha-Lavsky H, et al. Efficacy and safety of lumasiran for advanced primary hyperoxaluria type 1: 24-month follow-up of the phase 3 ILLUMINATE-C trial. *Am J Kidney Dis.* Published online March 13, 2025. doi:10.1053/j.ajkd.2025.01.016.

ILLUMINATE-C: Exploratory Endpoints

Stable Levels of Plasma Glycolate Were Observed During the Extension Period Through Month 24 in Patients With PH1 With Impaired Kidney Function



Month 24

Plasma glycolate levels increased during the primary analysis period (through Month 6), then were **relatively stable** during the extension period through Month 24

BL was defined as the mean of all plasma glycolate assessments prior to the first dose of lumasiran.[1]
BL, baseline; M, Month; PH1, primary hyperoxaluria 1; SEM, standard error of the mean.

Sellier-Leclerc AL, Magen D, Shasha-Lavsky H, et al. Efficacy and safety of lumasiran for advanced primary hyperoxaluria type 1: 24-month follow-up of the phase 3 ILLUMINATE-C trial. *Am J Kidney Dis*. Published online March 13, 2025. doi:10.1053/j.ajkd.2025.01.016 (supplementary appendix).

ILLUMINATE-C: Safety Data

Safety Profile Up to 24 Months of Treatment in Patients With PH1 With Impaired Kidney Function, Including Those Undergoing Hemodialysis

Safety Summary of Patients Enrolled in ILLUMINATE-C*

Treatment-Emergent Event, n (%)	Original Assignment		After HD Change		All Treated
	Cohort A n = 6 (PY 9.0)	Cohort B n = 15 (PY 26.2)	Cohort A (On HD) n = 2 (PY 1.4)	Cohort B (Off HD) n = 5 (PY 3.3)	N = 21 (PY 39.9)
Patients with ≥1 AE	6 (100)	15 (100)	1 (50)	5 (100)	21 (100)
AEs occurring in ≥ 5 patients in either cohort					
Pyrexia	1 (17)	7 (47)	0	0	8 (38)
ISR	1 (17)	4 (27)	0	0	5 (24)
Diarrhea	1 (17)	3 (20)	0	2 (40)	6 (29)
AEs leading to treatment discontinuation and study withdrawal†	0	2 (13)	0	0 (0)	2 (10)
Severe AEs‡	3 (50)	8 (53)	0	0 (0)	11 (52)
Serious AEs§	3 (50)	11 (73)	0	4 (80)	15 (71)
Death	0	0	0	0	0

Month 24

- The most common treatment-related AEs were **mild ISRs**, experienced by 24% of patients
- There were **no lumasiran-related severe or serious AEs, discontinuations, or withdrawals**

*Safety data during the extension period include all available data through the data cutoff date. "Original Assignment" columns display AEs prior to any change in HD status, i.e., while not on HD for Cohort A/while on HD for Cohort B. "After HD Change" columns display AEs reported after patients in Cohort A initiated HD (n = 2), and after patients in Cohort B discontinued HD (n = 5). "All Treated" column displays total patients reporting AEs, regardless of cohort/HD status; †AEs led to both treatment discontinuation and study withdrawal in 2 patients; both were due to liver-kidney transplant and were not related to lumasiran; ‡No severe AEs were determined to be related to lumasiran; §Serious AEs of pyrexia occurred in 6 patients; serious AEs of renal transplant occurred in 4 patients; and serious AEs of liver-kidney transplant occurred in 2 patients. No serious AEs were determined to be related to lumasiran.

AE, adverse event; BL, baseline; HD, hemodialysis; ISR, injection site reaction; PH1, primary hyperoxaluria 1; PY, patient-years.

Sellier-Leclerc AL, Magen D, Shasha-Lavsky H, et al. Efficacy and safety of lumasiran for advanced primary hyperoxaluria type 1: 24-month follow-up of the phase 3 ILLUMINATE-C trial. *Am J Kidney Dis*. Published online March 13, 2025. doi:10.1053/j.ajkd.2025.01.016 (supplementary appendix).

ILLUMINATE-C: Patient Case Summaries of Isolated Kidney Transplantations

Due to Natural Disease Progression, 5 of the 15 Patients in Cohort B Received Isolated Kidney Transplantation at the Discretion of Investigators as of Month 36 of the Study[1]

Patients with prior kidney transplants were not enrolled in this study[2]

Prior to transplantation, these 5 patients were receiving lumasiran and **demonstrated reductions in POx levels[1]**

BL POx values ranged from **84.6 to 152.3 µmol/L[1]**

POx values immediately prior to kidney transplants were **<70 µmol/L[1,3]**

All 5 patients who underwent kidney transplantation **remained dialysis-free**, had **no oxalate nephropathy**, and **continued lumasiran treatment[1]**

These patient case summaries were descriptive in nature and occurred after the protocol-specified final analysis. No statistical conclusions can be drawn since formal statistical tests were not conducted.[2]

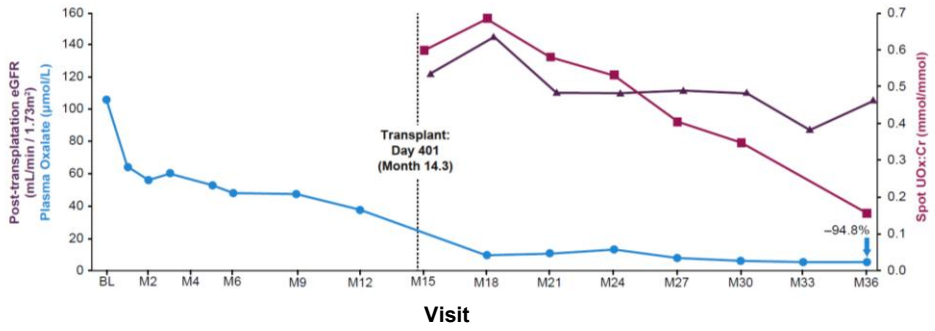
BL, baseline; ESKD, end-stage kidney disease; POx, plasma oxalate.

1. Somers MJ, Devresse A, Willey R, et al. Kidney function and isolated kidney transplant outcomes in primary hyperoxaluria type 1 treated with long-term lumasiran. Poster presented at: ASN Kidney Week; October 24-27, 2024; San Diego, CA; 2. ClinicalTrials.gov identifier: NCT04152200. Study protocol. Accessed August 1, 2025. https://clinicaltrials.gov/study/NCT04152200; 3. Lieske JC, Sellier-Leclerc AL, Shasha-Lavsky H, et al. Lumasiran for primary hyperoxaluria type 1 and impaired kidney function: 24-month analysis of the phase 3 ILLUMINATE-C trial. Poster presented at: ASN Kidney Week; November 2-5, 2023; Philadelphia, PA.

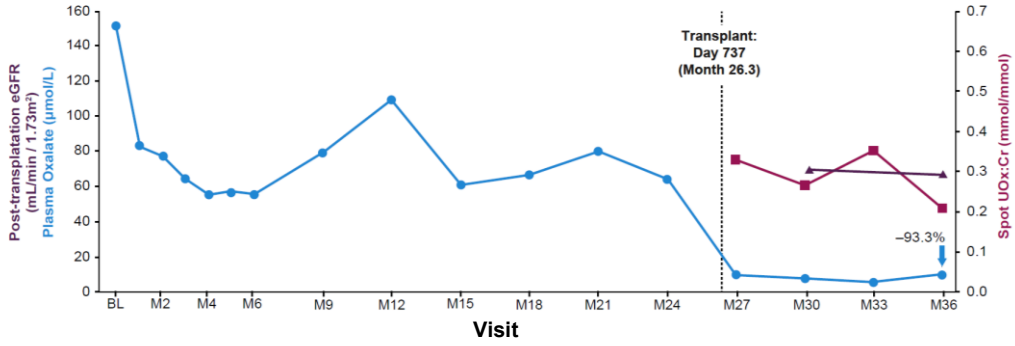
ILLUMINATE-C: Patient Case Summaries

Isolated Kidney Transplant in Four Pediatric Patients in Cohort B With ESKD by Month 36

Patient 1 (age 2 years at study entry; non-pyridoxine-responsive genotype)

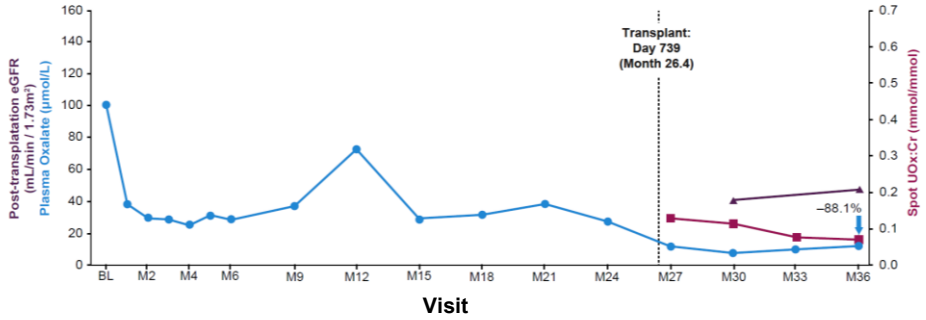


Patient 2 (age 0.9 years at study entry; non-pyridoxine-responsive genotype)

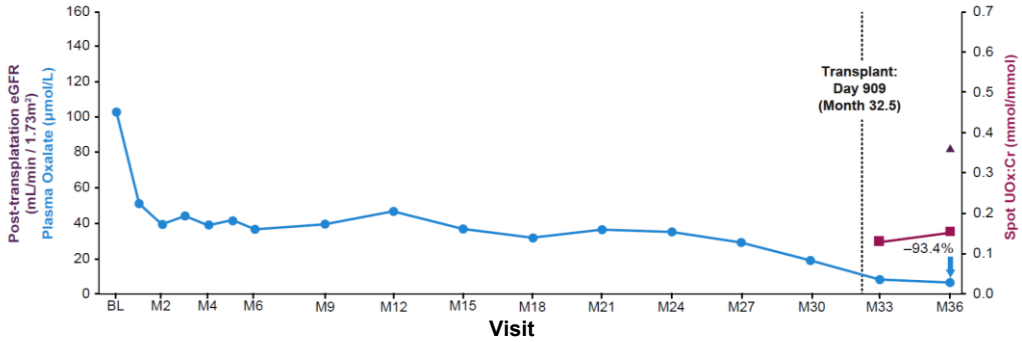


eGFR (mL/min/1.73m²) | POx (µmol/L) | % changes from baseline | Spot UOx:Cr (mmol/mmol)

Patient 3 (age 18 years at study entry; non-pyridoxine-responsive genotype)



Patient 4 (age 1 year at study entry; pyridoxine-responsive genotype)



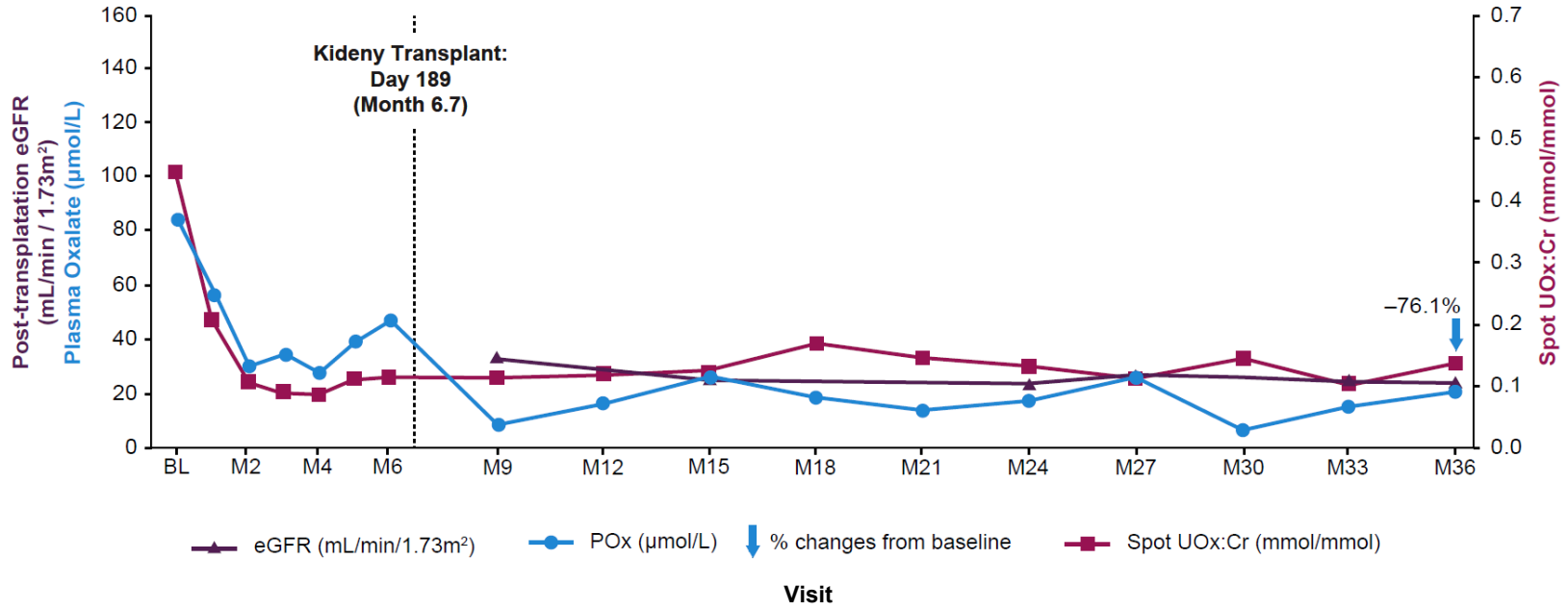
These patient case summaries were descriptive in nature and occurred after the protocol-specified final analysis. No statistical conclusions can be drawn since formal statistical tests were not conducted.
BL, baseline; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; M, Month; POx, plasma oxalate; UOx:Cr, urinary oxalate:creatinine ratio.

Somers MJ, Devresse A, Willey R, et al. Kidney function and isolated kidney transplant outcomes in primary hyperoxaluria type 1 treated with long-term lumasiran. Poster presented at: ASN Kidney Week; October 24-27, 2024; San Diego, CA.

ILLUMINATE-C: Patient Case Summaries

Isolated Kidney Transplant in One Adult Patient in Cohort B With ESKD by Month 36

Patient 5 (age 44 years at study entry; pyridoxine-responsive genotype)



These patient case summaries were descriptive in nature and occurred after the protocol-specified final analysis. No statistical conclusions can be drawn since formal statistical tests were not conducted.
BL, baseline; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; M, Month; POx, plasma oxalate; UOx:Cr, urinary oxalate:creatinine ratio.

Somers MJ, Devresse A, Willey R, et al. Kidney function and isolated kidney transplant outcomes in primary hyperoxaluria type 1 treated with long-term lumasiran. Poster presented at: ASN Kidney Week; October 24-27, 2024; San Diego, CA.

ILLUMINATE-C: Patient Case Summaries – Safety

Post-Transplant AEs Were Frequent and Included Transplant-Related Complications (Not Related to Lumasiran)

Summary of AEs among patients receiving isolated kidney transplant

Patient	Age at study entry, years	Post-transplant AEs
Patient 1	2	• The patient's hemodialysis was stopped 36 days after transplant; the reason for the continuation of dialysis after transplantation was not reported • Within the first month after transplant, the patient experienced several AEs (severe, not related to the study drug) of pyrexia 13 days after the transplant; graft complication, urinoma, and acute kidney injury 14 days after the transplant; and herpes simplex infection 21 days after the transplant
Patient 2	0.9	• The patient experienced urinary tract infection (mild, not related to the study drug) 14 days after the transplant and recovered from the event • Other complications that occurred within 3 months to 1 year after the transplant and required hospitalization included hypogammaglobulinemia (moderate); gastroenteritis, pneumonia, and post-transplant lymphoproliferative disorder (all severe); and ear infection
Patient 3	18	• The patient experienced two moderate AEs (diarrhea and BK virus infection), which were both not related to the study drug, within the first month post-transplantation; both events were not resolved at time of the datacut
Patient 4	1	• The patient experienced two moderate AEs (*Clostridium difficile* infection and incision site discharge) within the first month post-transplantation, from which the patient recovered, along with one mild AE (perinephric collection, which was not resolved); all three AEs were not related to the study drug
Patient 5	44	• The patient experienced a post-transplantation AE of graft failure which resolved • A renal graft biopsy performed 6 weeks after transplantation associated with this AE showed evidence of BK virus nephropathy without calcium oxalate nephropathy

These patient case summaries were descriptive in nature and occurred after the protocol-specified final analysis. No statistical conclusions can be drawn since formal statistical tests were not conducted.
AE, adverse event; BL, baseline.

Somers MJ, Devresse A, Willey R, et al. Kidney function and isolated kidney transplant outcomes in primary hyperoxaluria type 1 treated with long-term lumasiran. Poster presented at: ASN Kidney Week; October 24-27, 2024; San Diego, CA.

US PI

LUMASIRAN IMPORTANT SAFETY INFORMATION

Indication

Lumasiran is an RNAi therapeutic indicated for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary and plasma oxalate levels in pediatric and adult patients

Important Safety Information

Adverse Reactions

- The most common (≥ 20%) adverse reaction reported in patients treated with lumasiran was injection site reaction. Injection site reactions included erythema, swelling, pain, hematoma, pruritus, and discoloration

Pregnancy and Lactation

- No data are available on the use of lumasiran in pregnant women. No data are available on the presence of lumasiran in human milk or its effects on breastfed infants or milk production. Consider the developmental and health benefits of breastfeeding along with the mother's clinical need for lumasiran and any potential adverse effects on the breastfed child from lumasiran or the underlying maternal condition

For additional information on lumasiran, please see full Prescribing Information at https://www.alnylam.com/oxlumo-us-prescribing-information

Phase 2 OLE: Primary Endpoint

Safety Summary for Patients in the Phase 2 OLE Study

Category/Event, n (%) [n events/exposure-adjusted rate per 100 PY]	All Treated* (N = 20; PY = 80.5)
≥ 1 AE	20 (100) [227/282.1]
AE reported by ≥ 3 patients	
COVID-19	9 (45) [9/11.2]
ISR	8 (40) [13/16.2]
Vomiting	6 (30) [9/11.2]
Headache	4 (20) [6/7.5]
Back pain	3 (15) [6/7.5]
Increased blood bilirubin	3 (15) [3/3.7]
Cough	3 (15) [6/7.5]
Limb injury	3 (15) [3/3.7]
Nasopharyngitis	3 (15) [3/3.7]
Nephrolithiasis	3 (15) [8/9.9]
Oropharyngeal pain	3 (15) [3/3.7]
Rhinitis	3 (15) [4/5.0]
Positive SARS-CoV-2 test result	3 (15) [3/3.7]
Ureterolithiasis	3 (15) [3/3.7]
Vitamin D deficiency	3 (15) [7/8.7]
≥ 1 treatment-related AE†	11 (55) [21/26.1]
AE leading to treatment discontinuation or study withdrawal	0
≥ 1 severe AE‡	2 (10) [4/5.0]
≥ 1 serious AE§	7 (35) [13/16.2]
Death	0

*Data shown as n (%) [n events/exposure-adjusted rate per 100 PY]; †Treatment-related AEs included ISRs (n = 8; 40%, all mild in severity); increased blood bilirubin (n = 3; 15%, two mild and one moderate in severity); increased conjugated bilirubin (n = 1; 5%, moderate in severity); headache (n = 1; 5%, moderate in severity); prolonged electrocardiogram QRS complex (n = 1; 5%, mild in severity); and increased glycolic acid (n = 1; 5%, mild in severity); ‡Severe AEs included tibia fracture, flank pain, nephrolithiasis, and ureterolithiasis (each n = 1; 5%); §Serious AEs included ureterolithiasis (n = 3; 15%) and bone contusion, craniocerebral injury, decreased glomerular filtration rate, nephrolithiasis, pyelonephritis, renal colic, renal stone removal, thyroid mass, and thyroid operation (each n = 1; 5%).

AE, adverse event; BL, baseline; ISR, injection site reaction; OLE, open-label extension; PH1, primary hyperoxaluria type 1; PY, patient-years.

Frishberg Y, Groothoff JW, Hulton SA, et al. Long-term treatment with lumasiran: final results from the phase 2 open-label extension study. Poster presented at: 61st ERA Congress, May 23-26, 2024; Stockholm, Sweden.

Phase 2 OLE: Secondary Endpoints

Mean UOx change

At Month 54, **mean absolute change** in 24-hour UOx from BL was **−1.5 mmol/24h/1.73m²** and the **mean percent change** in 24-hour UOx from BL was **−68%**

Normalization

Through Month 54, **80% of patients had normalization of 24-hour UOx** at ≥ 1 post-BL visit

≤ 1.5 × ULN

≥89% of patients had a 24-hour UOx ≤ 1.5 × ULN from Month 42 through Month 54

BL, baseline; OLE, open-label extension; PH1, primary hyperoxaluria type 1; ULN, upper limit of normal; UOx, urinary oxalate.

Frishberg Y, Groothoff JW, Hulton SA, et al. Long-term treatment with lumasiran: final results from the phase 2 open-label extension study. Poster presented at: 61st ERA Congress, May 23-26, 2024; Stockholm, Sweden.

Phase 2 OLE: Secondary and Exploratory Endpoints

Stable eGFR

Over 48 months of follow-up, the annualized mean (SEM) **rate of eGFR change was −0.6 (0.7) mL/min/1.73m²** for the 20 patients

Phase 2 secondary endpoint

POx

Reductions in mean POx levels from BL were sustained within normal levels through Month 54

Glycolate

Plasma glycolate levels increased and subsequently plateaued through Month 54, consistent with the **mechanism of action of lumasiran**

ADAs

ADAs were detected in **one patient (5%)** at Month 6, but this **did not impact the UOx response,** and the patient had **no ADA-related AEs**

Phase 2 exploratory endpoints

ADA, antidrug antibody; AE, adverse event; BL, baseline; eGFR, estimated glomerular filtration rate; OLE, open-label extension; POx, plasma oxalate; SEM, standard error of the mean; UOx, urinary oxalate.

Frishberg Y, Groothoff JW, Hulton SA, et al. Long-term treatment with lumasiran: final results from the phase 2 open-label extension study. Poster presented at: 61st ERA Congress, May 23-26, 2024; Stockholm, Sweden.