ILLUMINATE-C, a Single-Arm, Phase 3 Study of Lumasiran in Patients With Primary Hyperoxaluria Type 1 and CKD3b-5, Including Those on Hemodialysis

Mini Michael[1], Jaap W. Groothoff[2], Hadas Shasha-Lavsky[3], John C. Lieske[4], Yaacov Frishberg[5], Eva Simkova[6], Anne-Laure Sellier-Leclerc[7], Arnaud Devresse[8], Fitsum Guebre-Egziabher[9], Sevcan A. Bakkaloglu[10], Chebl Mourani[11], Rola Saqan[12], Richard Singer[13], Richard Willey[14], Bahru Habtemariam[14], Ishir Bhan[14], Tracy L. McGregor[14], Daniella Magen[15]

[1]Division of Nephrology, Department of Pediatrics, Texas Children's Hospital/Baylor College of Medicine, Houston, TX, USA; [2]Department of Pediatric Nephrology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands; [3]Pediatric Nephrology Unit, Galilee Medical Center, Nahariya, Israel; [4]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA; [5]Division of Pediatric Nephrology, Shaare Zedek Medical Center, Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel; [6]Al Jalila Children's Hospital, Dubai, United Arab Emirates; [7]Hôpital Femme Mère Enfant and Centre d'Investigation Clinique Inserm, Hospices Civils de Lyon, ERKnet, Bron, France; [8]Division of Nephrology, Cliniques Universitaires Saint-Luc, Brussels, Belgium; [9]Nephrology and Renal Function Unit, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon, France; [10]Department of Pediatric Nephrology, Faculty of Medicine, Gazi University, Ankara, Turkey; [11]Pediatrics, Hôtel-Dieu de France Hospital (HDF), Beirut, Lebanon; [12]Pharmaceutical Research Center - Jordan University of Science and Technology, Irbid, Jordan; [13]Canberra Health Services, Garran, ACT, Australia; [14]Alnylam Pharmaceuticals, Cambridge, MA, USA; [15]Pediatric Nephrology Institute, Rambam Health Care Campus, Haifa, Israel

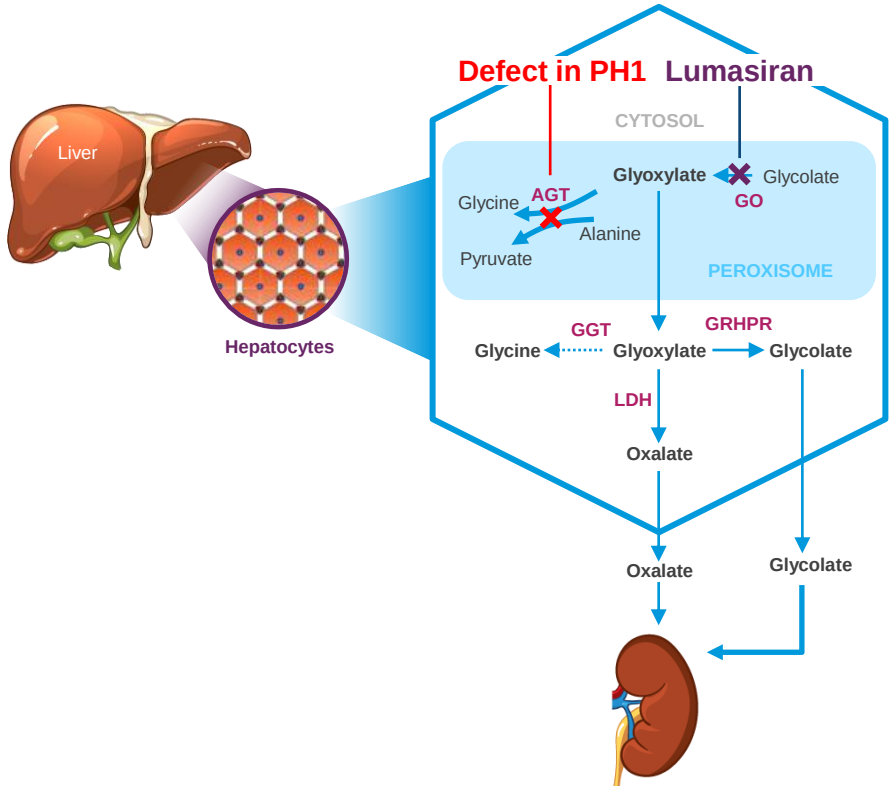
Presented at: ASN Kidney Week 2021; November 4–7, 2021; San Diego, CA

Disclosures

MM: *principal investigator for Alnylam Pharmaceuticals.*
JWG: *consultancy fees from Alnylam Pharmaceuticals and study grants from Alnylam Pharmaceuticals, Dicerna Pharmaceuticals, and uniQure Pharmaceuticals.*
HS-L: *principal investigator for Alnylam Pharmaceuticals; travel and accommodation expenses from Alnylam Pharmaceuticals to attend international investigators' meetings.*
JCL: *grants from Alnylam Pharmaceuticals, Dicerna Pharmaceuticals, Retrophin, OxThera, and Siemens, as well as other from Novobiome and Orfan-Bridgebio, and grants and other from Allena and Synlogic.*
YF: *consultancy fees from Alnylam Pharmaceuticals and membership in the safety review committee.*
ES: *principal investigator for Alnylam Pharmaceuticals; travel and accommodation expenses from Alnylam Pharmaceuticals to attend international investigators' meeting.*
A-LS-L: *consultancy fees from Alnylam Pharmaceuticals and Dicerna Pharmaceuticals, and principal investigator for research funded by OxThera.*
AD: *principal investigator for Alnylam Pharmaceuticals; consultancy fees from Alnylam Pharmaceuticals.*
FG-E: *principal investigator for Alnylam Pharmaceuticals and Amgen.*
SAB: *no disclosures to report.*
CM: *no disclosures to report.*
R Saqan: *primary investigator for Alnylam Pharmaceuticals and secondary investigator for Novartis, institutional review board.*
R Singer: *no disclosures to report.*
RW and IB: *employees of Alnylam Pharmaceuticals and hold shares in Alnylam Pharmaceuticals.*
BH and TLM: *former employee of Alnylam Pharmaceuticals and holds shares in Alnylam Pharmaceuticals.*
DM: *research funding, consultancy fees, and non-financial support from Alnylam Pharmaceuticals.*

Primary Hyperoxaluria Type 1 and Lumasiran

- PH1 is characterized by excessive hepatic oxalate production due to a deficiency in the hepatic peroxisomal enzyme AGT[1,2]
- Excess oxalate results in recurrent kidney stones, nephrocalcinosis, progressive kidney disease, and ultimately kidney failure.[1,3] As kidney function declines, oxalate elimination is compromised and POx increases, leading to systemic oxalosis and multi-organ damage[1,2]
- Patients progressing to or presenting with kidney failure require intensive hemodialysis and liver or combined liver-kidney transplantation[1]
- Lumasiran is an RNAi therapeutic approved by the FDA for the treatment of PH1 to lower UOx levels in pediatric and adult patients[4]
  - Lumasiran decreases hepatic oxalate production by inhibiting the production of GO[4-6]
- In PH1 patients with CKD Stage 3b–5 (eGFR <45 mL/min/1.73m^2), elevated POx is directly related to the pathophysiology of oxalosis, making reduction of POx a suitable clinical target in this population[7]

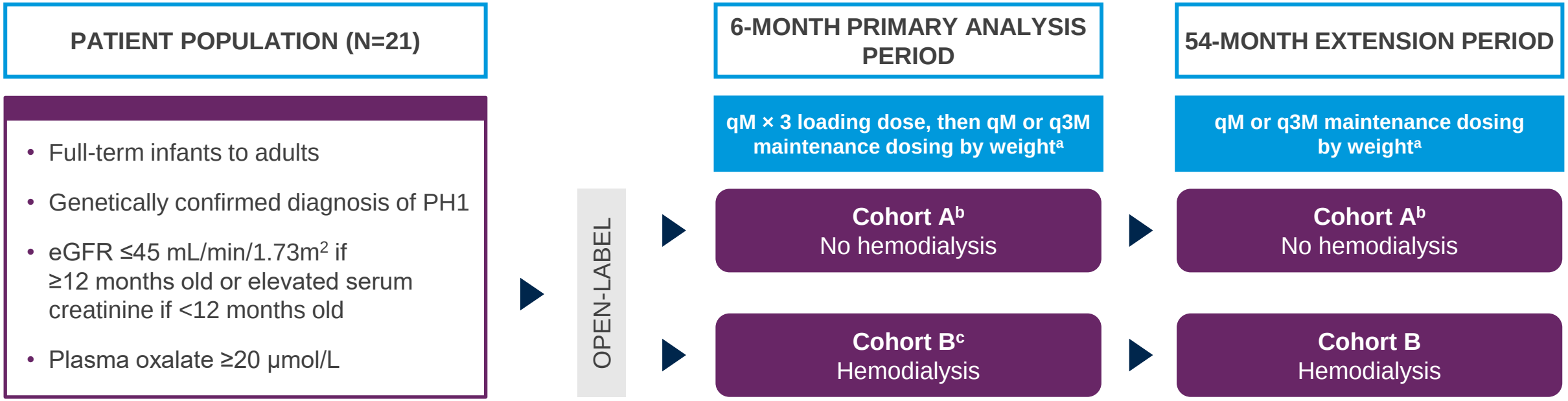


Here, we present 6-month primary analysis results from ILLUMINATE-C, a Phase 3 study designed to evaluate the efficacy and safety of lumasiran in patients with PH1 with impaired kidney function, including those on hemodialysis

AGT, alanine-glyoxylate aminotransferase; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FDA, US Food and Drug Administration; GO, glycolate oxidase; PH1, primary hyperoxaluria type 1; POx, plasma oxalate; RNAi, ribonucleic acid interference; UOx, urinary oxalate.

1. Cochat P, Rumsby G. *N Engl J Med*. 2013;369:649-58. 2. Danpure CJ. *The Online Metabolic and Molecular Bases of Inherited Disease*. New York, NY: The McGraw-Hill Companies, Inc.; 2019. 3. Lieske JC, et al. *Am J Nephrol*. 2005;25:290-6. 4. Oxlumo [package insert]. Cambridge, MA: Alnylam Pharmaceuticals; 2020. 5. Oxlumo [summary of product characteristics]. Amsterdam, Netherlands: Alnylam Netherlands; 2020. 6. Liebow A, et al. *J Am Soc Nephrol*. 2017;28:494-503. 7. Milliner DS, et al. *Clin J Am Soc Nephrol*. 2020;15:1056-65.

ILLUMINATE-C Study Design



- **Primary endpoint**
  - Cohort A: Percent change in POx from baseline to Month 6
  - Cohort B: Percent change in predialysis POx from baseline to Month 6
- **Secondary endpoints in the primary analysis period included:**
  - Percent change in POx AUC between dialysis sessions (Cohort B only)
  - Absolute change in POx
  - Percent and absolute change in spot UOx:Cr and 24-hour UOx corrected for BSA

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

[a]Lumasiran was administered subcutaneously using weight-based dosing. Patients <10 kg received loading doses of 6.0 mg/kg qM for 3 months and then maintenance doses of 3.0 mg/kg qM; patients ≥10 to <20 kg received loading doses of 6.0 mg/kg qM for 3 months and then maintenance doses of 6.0 mg/kg q3M; patients ≥20 kg received loading doses of 3.0 mg/kg qM for 3 months and then maintenance doses of 3.0 mg/kg q3M. Maintenance dosing was started 1 month after the last loading dose.
[b]Cohort A patients who experience progression of kidney impairment over time and begin to require hemodialysis therapy may cross over to Cohort B. No patient crossed over during the 6-month primary analysis period.
[c]No changes to dialysis regimen (except when medically necessary) or kidney transplantation were permitted during the primary analysis period.

AUC, area under the curve; BSA, body surface area; eGFR, estimated glomerular filtration rate; PH1, primary hyperoxaluria type 1; POx, plasma oxalate; q3M, once every 3 months; qM, once monthly; qM × 3, once monthly for 3 consecutive months; UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio.

Patients

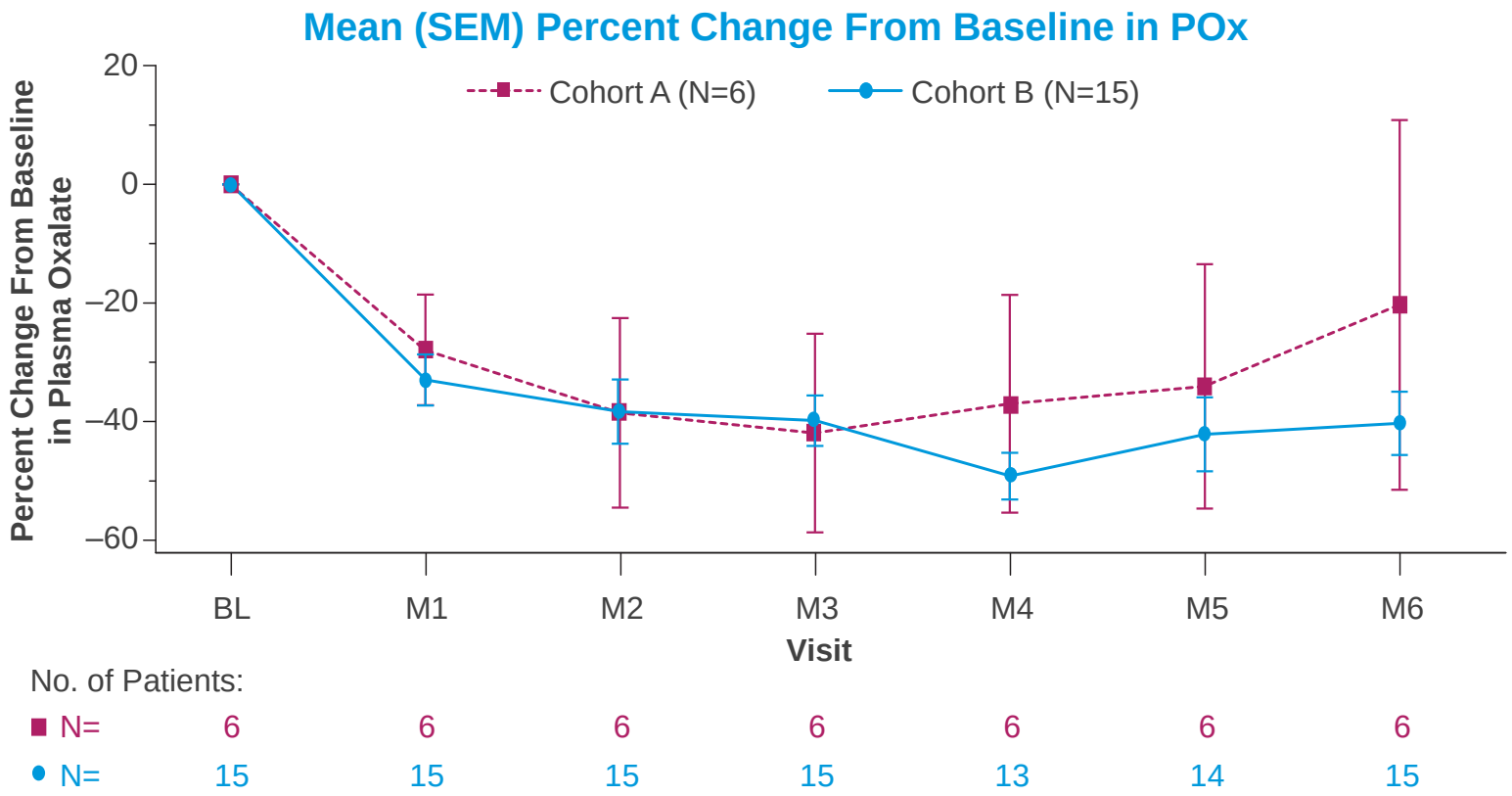
- From March through December 2020, 21 patients across 13 sites in 10 countries were enrolled in the study: 6 in Cohort A and 15 in Cohort B
  - All patients completed the 6-month primary analysis period

Baseline Characteristic	Cohort A (N=6)	Cohort B (N=15)	All Treated (N=21)
Age at consent, median (range), years	9 (0–40)	6 (1–59)	8 (0–59)
Female, n (%)	3 (50)	6 (40)	9 (43)
POx, median (range)[a], µmol/L	57.9 (22.7–134.0)	103.7 (56.3–167.0)	100.9 (22.7–167.0)
Spot UOx:Cr[b], median (range), mmol/mmol	N=6 0.332 (0.075–1.380)	N=2[c] 0.535 (0.451–0.618)	N=8 0.391 (0.075–1.380)
24-hour UOx excretion corrected for BSA[d], median (range), mmol/24h/1.73m^2	N=5 2.01 (0.56–2.47)	N=1[c] 1.28 (1.28–1.28)	N=6 1.64 (0.56–2.47)
eGFR[e], median (range), mL/min/1.73m^2	N=5 17 (9–34)	Not applicable	Not applicable
Number of dialysis therapy sessions per week, median (range)	Not applicable	6 (3–7)	Not applicable

[a]ULN=12.11 µmol/L for POx, as determined based on data from healthy adults.
[b]1 mmol/mmol=0.796 mg/mg.
[c]Urinary measures of oxalate were collected in Cohort B for patients who were not anuric and able to supply an acceptable urine sample.
[d]ULN=0.514 mmol/24h/1.73m^2 for 24-hour UOx corrected for BSA.
[e]eGFR was calculated only in patients age ≥12 months. eGFR (mL/min/1.73m^2) was calculated from serum creatinine based on the Modification of Diet in Renal Disease formula for patients age ≥18 years and the Schwartz Bedside Formula for patients aged 1 to <18 years.
BSA, body surface area; eGFR, estimated glomerular filtration rate; POx, plasma oxalate; UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio; ULN, upper limit of normal.

Primary Efficacy Endpoint

- Percent change in POx from baseline to Month 6 (Cohort A): LS mean reduction of 33.33% (95% CI, −15.16 to 81.82)[a]
- Percent change in predialysis POx from baseline to Month 6 (Cohort B): LS mean reduction of 42.43% (95% CI, 34.15 to 50.71)[a]
- Reduction in POx was evident by Month 1 and persisted through the end of the 6-month primary analysis period

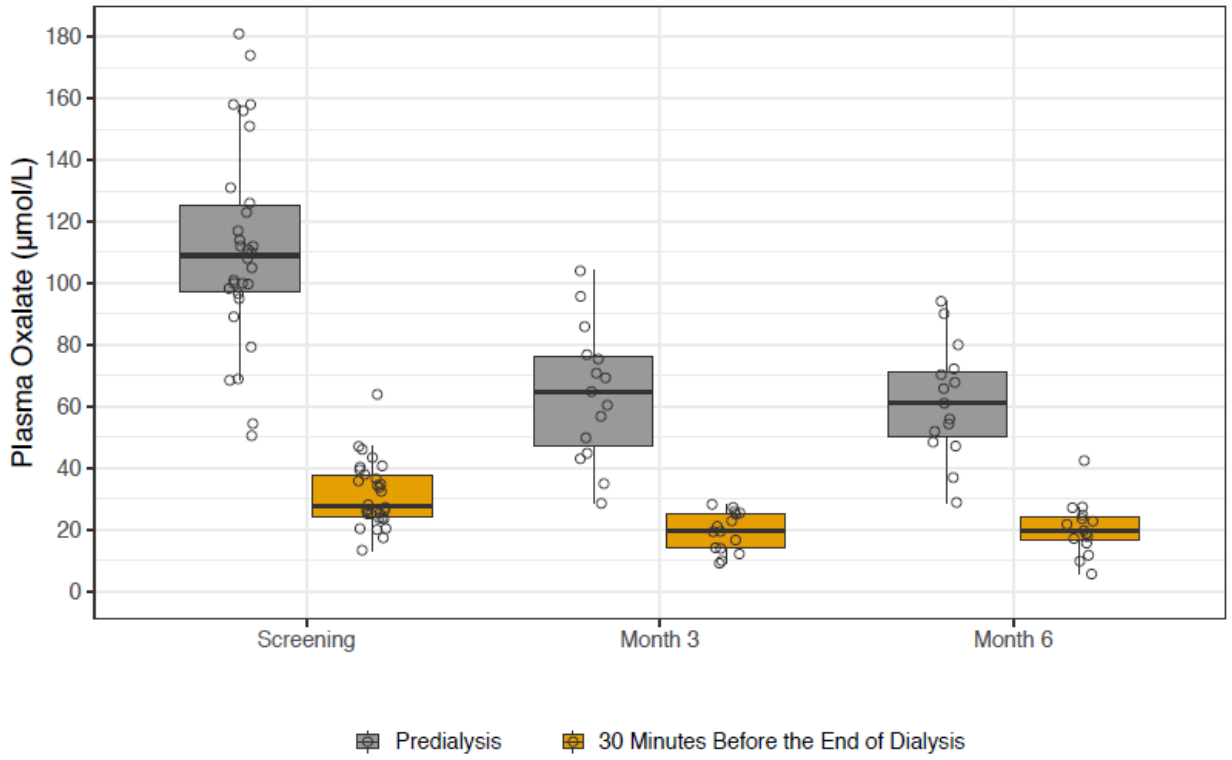


[a]The primary analysis of percent change from baseline in POx (Cohort A) and predialysis POx (Cohort B) was based on the MMRM model with the estimate calculated as the LS mean of the primary outcome variable averaged across Months 3 to 6 and presented with corresponding SEM and 95% CI.
Baseline value was the mean of the last 4 POx values (predialysis in Cohort B) collected prior to the first dose of lumasiran.
ULN=12.11 µmol/L for POx, as determined based on data from healthy adults.
BL, baseline; LS, least squares; M, month; POx, plasma oxalate; SEM, standard error of the mean; ULN, upper limit of normal.

Secondary Efficacy Endpoints

Secondary Endpoints, LS mean (95% CI)[a]	Cohort A (N=6)	Cohort B (N=15)
Absolute change in POx from baseline to Month 6 (µmol/L)	-35.28 (-56.32, -14.24)	-48.33 (-55.85, -40.80)
Percent change in POx $AUC_{0\text{-}24h}$ between dialysis sessions from baseline to Month 6	Not applicable	-41.4 (-51.0, -31.8)
Percent change in 24-hour UOx corrected for BSA from baseline to Month 6	N=5 -10.557 (-31.986, 10.871)	Not applicable
Absolute change in 24-hour UOx corrected for BSA from baseline to Month 6 (mmol/24h/1.73m²)	N=5 -0.533 (-0.888, -0.179)	Not applicable
Percent change in spot UOx:Cr from baseline to Month 6	-39.51 (-64.13, -14.90)	Not applicable
Absolute change in spot UOx:Cr from baseline to Month 6 (mmol/mmol)	-0.188 (-0.229, -0.147)	Not applicable

Distribution of Pre- and Post-dialysis Plasma Oxalate Levels in Cohort B



[a]The POx $AUC_{0\text{-}24h}$ (Cohort B) was calculated using the linear-trapezoidal method and the LS mean percent change from baseline at Month 6 was estimated using the MMRM model including data evaluated at Months 3 and 6. Analyses of other secondary endpoints were also performed using the MMRM model. The change from baseline to Month 6 was calculated as the change across Months 3 through 6.

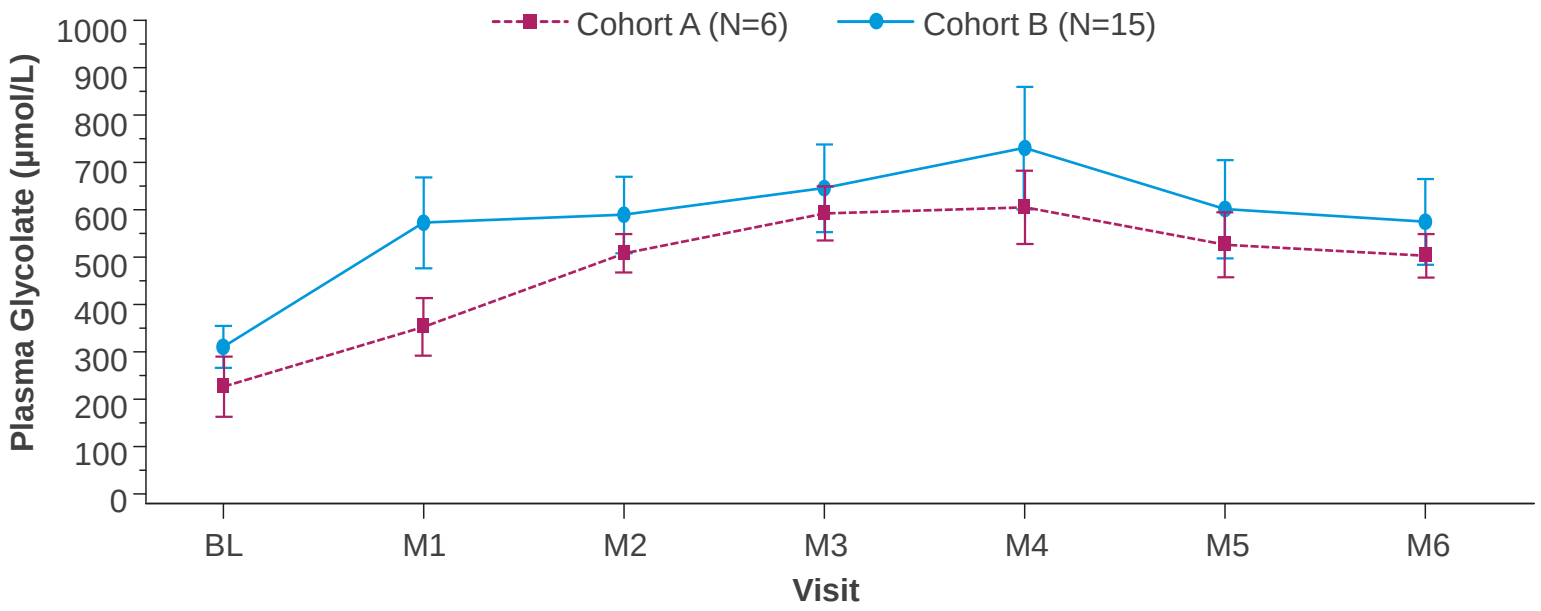
ULN=12.11 µmol/L for plasma oxalate, as determined based on data from healthy adults. 1 mmol/mmol=0.796 mg/mg.

AUC, area under the curve; BSA, body surface area; CI, confidence interval; LS, least squares; M, month; MMRM, mixed-effect model for repeated measures; POx, plasma oxalate; ULN, upper limit of normal; UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio.

Exploratory Endpoint: Plasma Glycolate

- Plasma glycolate levels initially increased and then plateaued, consistent with a reduction in hepatic GO activity mediated by lumasiran
- Results demonstrate comparable target engagement between Cohorts A and B

Mean (SEM) of Actual Plasma Glycolate Values



No. of Patients:							
N=	6	5	6	6	6	6	6
N=	15	14	15	13	13	14	14

Baseline value was the mean of two assessments collected prior to the first dose of lumasiran.
BL, baseline; GO, glycolate oxidase; M, month; SEM, standard error of the mean.

Safety

- The majority of AEs were mild or moderate in severity
- There were no serious or severe AEs related to lumasiran and no deaths of patients who received lumasiran
- There were no treatment discontinuations or study withdrawals
- The most frequently reported AEs were pyrexia (28.6%) and injection-site reactions (23.8%)
- The most common AE related to lumasiran was injection-site reaction (23.8% [5/21] of patients)
  - All injection-site reactions were mild and transient, and the most common symptoms included erythema, discoloration, and injection-site hematoma
- There were no clinically relevant trends in laboratory measures (including hematology, blood chemistries, liver function tests), vital signs, physical examinations, or electrocardiograms related to lumasiran

Event	Number of Patients (%)		
	Cohort A (N=6)	Cohort B (N=15)	All Treated (N=21)
AEs	5 (83.3)	12 (80.0)	17 (81.0)
AEs occurring in ≥10% of patients in either cohort			
Pyrexia	1 (16.7)	5 (33.3)	6 (28.6)
Injection-site reaction	1 (16.7)	4 (26.7)	5 (23.8)
Device-related infection	0	2 (13.3)	2 (9.5)
Diarrhea	0	2 (13.3)	2 (9.5)
AEs leading to discontinuation of study treatment	0	0	0
AEs leading to withdrawal from the study	0	0	0
Death	0	0	0
Serious AEs	1 (16.7)	5 (33.3)	6 (28.6)
Severe AEs	0	3 (20.0)	3 (14.3)

Data presented for the 6-month primary analysis period.
AE, adverse event.

Conclusions

- Data from the 6-month primary analysis period of the ILLUMINATE-C study showed substantial reductions in POx in both cohorts of patients with PH1 and CKD Stage 3b–5, with an acceptable safety profile
  - In patients on hemodialysis (Cohort B), substantial reductions in POx $AUC_{0\text{-}24h}$ between dialysis sessions were observed from baseline to Month 6
  - Injection-site reaction was the most common drug-related AE
- Changes of this magnitude in POx may impact long-term clinical outcomes, including those related to systemic oxalosis, which will be further evaluated in the extension period of the study
- All measures of UOx showed concordant findings in Cohort A
- Similar magnitude of plasma glycolate increase in Cohorts A and B and previously completed studies in patients with relatively preserved kidney function (ILLUMINATE-A and ILLUMINATE-B)[1,2] suggest similar pharmacodynamics of lumasiran regardless of kidney function

Acknowledgments

Thank you to the patients, investigators, and study staff who participated in the ILLUMINATE-C study. Editorial assistance was provided by Peloton Advantage, LLC, an OPEN Health company, in accordance with Good Publication Practice (GPP3) guidelines and funded by Alnylam Pharmaceuticals. This study was funded by Alnylam Pharmaceuticals.

AE, adverse event; AUC, area under the curve; CKD, chronic kidney disease; PH1, primary hyperoxaluria type 1; POx, plasma oxalate; UOx, urinary oxalate.

1. Garrelfs SF, et al. *N Eng J Med.* 2021;384:1216-26. 2. Deschênes G, et al. Presented at: Annual Meeting of the American Society of Nephrology; October 22-25, 2020