Lumasiran: Dialysis

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SUMMARY

- ILLUMINATE-C was a phase 3, open-label, single-arm study designed to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of lumasiran in full term infants to adult patients with advanced PH1. Patients enrolled in the study included those not receiving hemodialysis in Cohort A (N=6) and those receiving hemodialysis in Cohort B (N=15).[1]
  - The primary estimate of the LS mean percent reduction in POx from baseline to month 6 was 33.3% (95% CI: 15.2%, 81.8%) in Cohort A and 42.4% (95% CI: 34.2%, 50.7%) in Cohort B.[1]
  - At months 12 and 24, data from the interim analyses of the extension period showed sustained POx reductions in both cohorts.[2,3]
  - The majority of AEs were considered mild or moderate in severity. At month 24, the most frequently reported AEs were pyrexia (38%), diarrhea (29%), and ISRs (24%).[3]
- Case reports from published medical literature discuss the use of lumasiran in patients on dialysis.[4–7]
- In a consensus statement developed by OxalEurope and the European Rare Kidney Disease Reference Network, graded recommendations on the management of patients with (or suspected to have) PH are provided. The indication and rationale for each management recommendation is contained within the guidance, including recommendations for treatment with dialysis and RNAi therapy.[8] Clinical discretion should be used in the assessment of the information provided.

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CLINICAL DATA

Drug Product Information

After subcutaneous administration, lumasiran is primarily distributed to the liver. Due to its large molecular weight of 16,341 Da and linear conformation of the double-stranded siRNA (compared to small organic molecules), lumasiran is not expected to pass through commonly used hemodialysis membranes (1-2 nm in pore sizes) and less than 10% of the amount in plasma is likely to be removed via peritoneal dialysis.[9–13]

ILLUMINATE-C Study

ILLUMINATE-C was a phase 3, open-label, single-arm study with a 6-month primary analysis period followed by an ongoing 54-month extension period to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of lumasiran in full term infants to adult patients with advanced PH1 with an

eGFR ≤45 mL/min/1.73m^2 (or elevated serum creatinine if <12 months old) and POx ≥20 µmol/L. Patients enrolled in the study included those not receiving hemodialysis in Cohort A (N=6) and those receiving hemodialysis in Cohort B (N=15).[1]

In patients receiving hemodialysis, lumasiran was administered as soon as feasible following the end of dialysis, and no later than 120 minutes post-dialysis, under the supervision of the Investigator.[1]

All enrolled patients completed the 6 month primary analysis period and entered the 54-month extension period. Relevant baseline characteristics are detailed in **Table 1**.[1]

Table 1. Select ILLUMINATE-C Baseline Characteristics.[1]

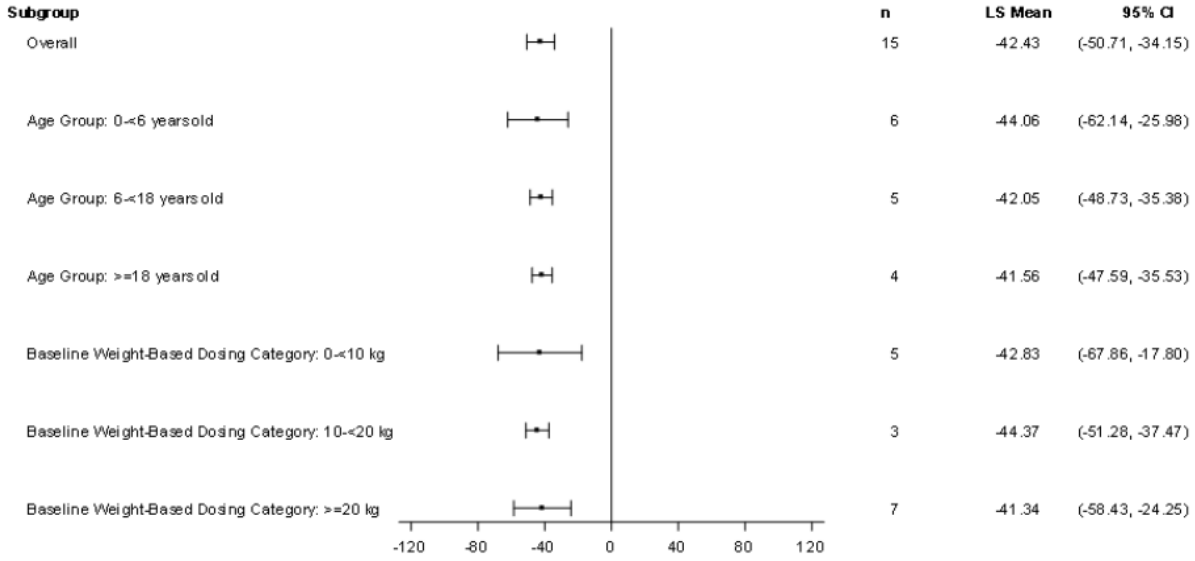
Select Baseline Characteristic	Cohort A (N=6)	Cohort B (N=15)	All Treated (N=21)
Age at consent, median (range), years	9 (0-40)	6 (1-59)	8 (0-59)
Time from diagnosis to first dose, median (range), months	72.2 (4-350)	16.6 (6-440)	21.6 (4-440)
Pyridoxine use, n (%)	4 (67)	7 (47)	11 (52)
POx, median (range)[a], µmol/L	57.9 (22.7-134.0)	103.7 (56.3-167.0)	100.9 (22.7-167.0)
eGFR[b], median (range), mL/min/1.73 m^2	N=5[b] 16.5 (8.6-34.1)	NA	N=5 16.5 (8.6-34.1)
Number of dialysis therapy sessions per week, median (range)	NA	6 (3-7)	NA

Abbreviations: eGFR = estimated glomerular filtration rate; NA = not applicable; POx = plasma oxalate.
[a]Upper limit of normal = 12.11 µmol/L (1.09 mg/mL) for plasma oxalate, as determined based on data from 75 healthy adults.
[b]eGFR was calculated only in patients ≥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. eGFR value available for 5 patients in Cohort A.

Efficacy Results: Plasma Oxalate

In ILLUMINATE-C, POx was evaluated as a primary endpoint: the percent change in POx from baseline to month 6 was assessed in Cohort A and the percent change in predialysis POx from baseline to month 6 was assessed in Cohort B. Data from the 6-month primary analysis period showed that patients in both cohorts had significant reductions in POx, with POx reduction observed as early as month 1. The primary estimate of the LS mean percent reduction in POx from baseline to month 6 was 33.3% (95% CI: 15.2%, 81.8%) in Cohort A and 42.4% (95% CI: 34.2%, 50.7%) in Cohort B.1 Subgroup analyses by age and weight-based dosing in Cohort B demonstrated a consistent treatment effect, as shown in **Figure 1**.[14]

Figure 1. Percent Change in POx in Prespecified Subgroups in Cohort B.[14]

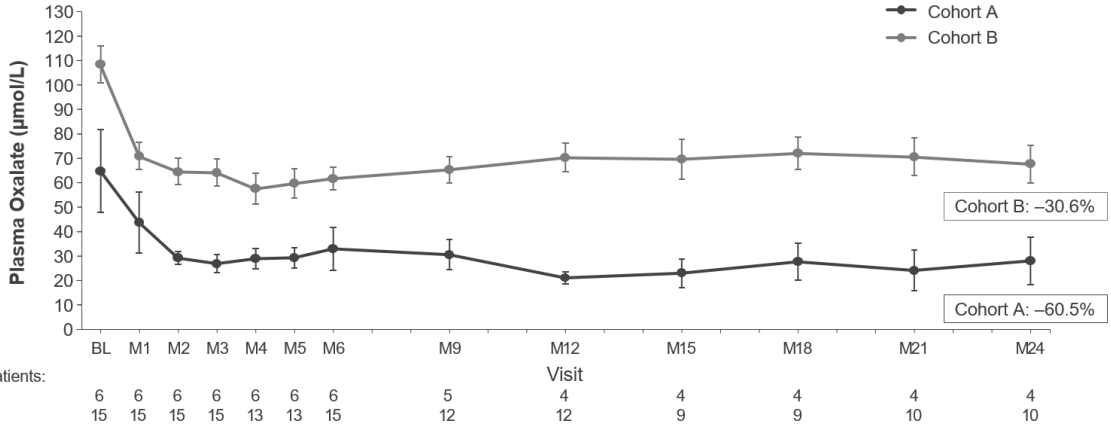


Abbreviations: CI = confidence interval; LS = least squares; POx = plasma oxalate.

At months 12 and 24, data from the interim analyses of the extension period showed sustained POx reductions in both cohorts (**Figure 2**).[2,3] At month 12, the mean (SEM) percent change from baseline for Cohorts A and B were 69.3% (6.9%) and 34.3% (6.9%), respectively.[2]

At month 24, the mean (SEM) POx decreased from baseline values of 64.7 (16.9) µmol/L for Cohort A and 108.4 (7.6) µmol/L for Cohort B to 27.9 (9.6) and 67.6 (7.6), respectively. The percent reduction in mean POx actual values from baseline were 60.5% for Cohort A and 30.6% for Cohort B.[3]

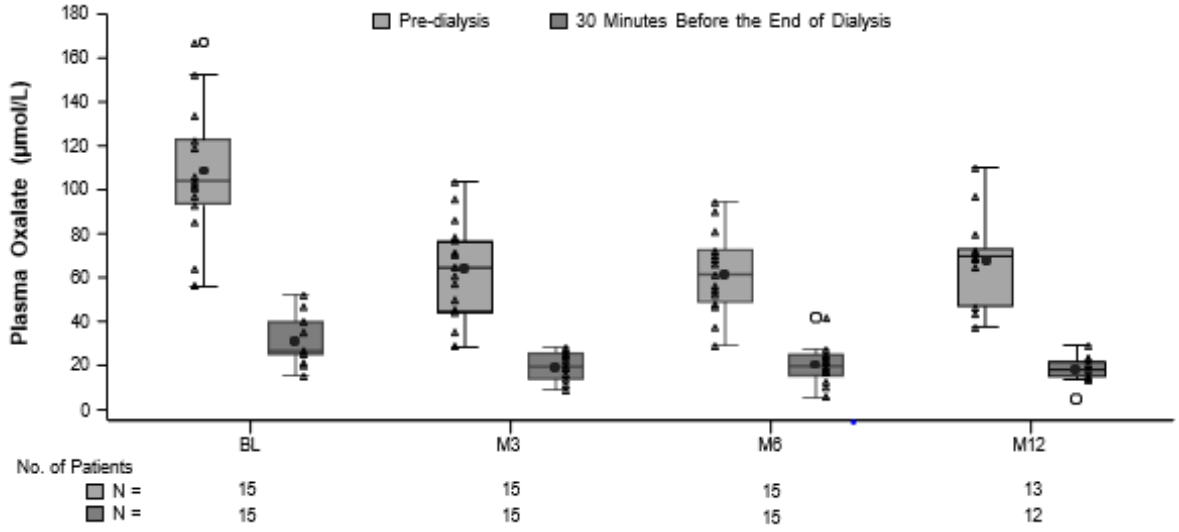
Figure 2. POx Mean Actual Values at Each Visit through Month 24.[3,a]



Adapted from Lieske et al[3]
Abbreviations: BL = baseline; POx = plasma oxalate.
[a]In Cohort A, baseline was defined as the mean of all POx samples (µmol/L) collected prior to the first dose of lumasiran. In Cohort B, baseline was defined as the mean of the last 4 predialysis POx samples (µmol/L) collected prior to the first dose of lumasiran.

The distribution of pre-dialysis and post-dialysis POx levels in Cohort B through 12 months of lumasiran treatment is presented in **Figure 3**.[2] In patients receiving hemodialysis, lumasiran was administered as soon as feasible following the end of dialysis, and no later than 120 minutes post-dialysis, under the supervision of the Investigator.[1,2]

Figure 3. Distribution of Pre- and Post-dialysis POx Levels in Cohort B.[2]



Adapted from Frishberg et al[2]
Abbreviation: POx = plasma oxalate.
Filled circles represent means; horizontal lines represent medians; triangles represent observed values for individual patients; open circles represent outliers.

Safety Results

The majority of AEs were considered mild or moderate in severity. Serious AEs reported during the 6-month primary analysis period were primarily associated with dialysis procedural complications and may be attributed to the underlying advanced kidney disease in the ILLUMINATE-C patient population.[1]

An overview of AEs reported through month 24 is summarized in **Table 2**. The most frequently reported AEs were pyrexia (38%), diarrhea (29%), and ISRs (24%). There were no lumasiran-related deaths or lumasiran-related serious or severe AEs, discontinuations, or withdrawals.[3]

Table 2. Lumasiran Safety Overview through Month 24.[3]

Treatment-Emergent Event, n (%)	Original Assignment[a]		After HD Change[b]		All Treated N=21 (PY 39.9)
	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)	
Patients with ≥1 AE	6 (100)	15 (100)	1 (50)	5 (100)	21 (100)
AEs leading to treatment discontinuation and study withdrawal	0 (0)	2 (13)	0 (0)	0 (0)	2 (10)[c]
Severe AEs	3 (50)	8 (53)	0 (0)	0 (0)	11 (52)[d]
Serious AEs	3 (50)	11 (73)	0(0)	4 (80)	15 (71)[e]
Death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviations: AE = adverse event; HD = hemodialysis; PY = patient year.
[a]"Original Assignment" columns display AEs prior to any change in HD status, ie, while not on HD for Cohort A/while on HD for Cohort B.
[b]"After HD Change" columns display AEs reported after patients in Cohort A initiated HD (N=2), and after patients in Cohort B went off HD (N=5).
[c]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.
[d]No severe AEs were determined to be related to lumasiran.
[e]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.

CASE REPORTS

The following information provides an overview of published case reports regarding patients with PH1 who received dialysis while being treated with lumasiran. It is not intended to be an all-inclusive list or summary of relevant publications, abstracts, and manuscripts.

Taroni F, et al. Lumasiran treatment in pediatric patients with PH1: real-world data within a compassionate use program in Italy. *Clin Kidney J*. 2024;17(5). doi:10.1093/ckj/sfae090[4]

- A case report detailed the treatment outcomes of 9 pediatric patients with PH1 who received lumasiran therapy in a compassionate use setting across various centers in Italy.
- One patient was diagnosed with PH1 at half a year old and received peritoneal dialysis due to the severity of kidney impairment. Lumasiran treatment was initiated at 1.7-years-old.
- Before treatment with lumasiran, the patient's POx was 116 mmol/L. At months 3, 6, and 12 of follow up, POx was 86, 79, and 90 mmol/L, respectively.
- Patients enrolled in the study did not report any major clinical or laboratory AEs. The most frequently reported AE was erythema at the injection site.

Martin-Higueras C, et al. Multicenter long-term real world data on treatment with lumasiran in patients with primary hyperoxaluria type 1. *Kidney Int Rep*. 2024;9(1):114-133. doi:10.1016/j.ekir.2023.10.004[5]

- A case report detailed the treatment outcomes of 33 patients with PH1 who received lumasiran therapy outside of clinical trials from 12 European centers. Of the 13 patients who received dialysis, 6 adults and 5 pediatric patients received hemodialysis, 1 adult received peritoneal dialysis, and 1 child received hemodialysis and peritoneal dialysis.
- Data were analyzed for patients grouped either in preserved kidney function or hemodialysis, with consideration of those with the same dose regimen and according to vitamin B6 medication.
- Median follow up of the 13 patients on dialysis was 15 months. Among the 9 patients who were treated with 3 mg/kg monthly (or 6 mg/kg monthly according to age) of lumasiran for the first 4 months and then quarterly, mean POx (SD) decreased from 78 µmol/L (40.2) to 37.2 µmol/L (16.9) at month 3, then increased to 43.1 µmol/L (16.3) at month 12, and to 59.3 µmol/L (23.8) at month 18.
- Additional details regarding the treatment outcomes of individual patients are provided in the publication.

Poyah P, et al. Primary hyperoxaluria type 1 (PH1) presenting with end-stage kidney disease and cutaneous manifestations in adulthood: A case report. *Can J Kidney Health Dis*. 2021;8. doi:10.1177/20543581211058931[6]

- A case report detailed a 40-year-old female patient with a history of nephrolithiasis at age 19 and 33 who presented with ESRD and cutaneous symptoms. The patient was diagnosed with PH1, and genetic testing confirmed a homozygous splice donor mutation (AGXT c.680+IG>A).
- The patient was maintained on oral pyridoxine and high-intensity hemodialysis. She developed bilaterial swan-neck deformities of the fingers and limited grasp, and lumasiran 1 mg/kg monthly for 3 months, then every 3 months was initiated 11 months after presentation on a compassionate use basis.
- After 3 months of lumasiran treatment, there were no AEs reported and the patient remained dialysis dependent. Predialysis POx decreased by 36%, from 98.2 µmol/L prior to lumasiran treatment to 62.8 µmol/L after lumasiran treatment.
- After 14 months of high-intensity hemodialysis and 3 months of lumasiran treatment, extrarenal involvement increased, with progressive swan-neck deformities, reduced cardiac systolic function, and pulmonary hypertension. The patient was waitlisted for kidney-liver transplantation.

Stone HK, et al. Primary hyperoxaluria diagnosed after kidney transplant: A review of the literature and case report of aggressive renal replacement therapy and lumasiran to prevent allograft loss. *Am J Transplant*. 2021;21(12):4061-4067. doi:10.1111/ajt.16762[7]

- A case report detailed a 7-year-old pediatric patient who was diagnosed with PH1 following kidney transplantation. Due to early post-transplant complications, PH1 was clinically suspected and confirmed with genetic testing, which resulted with two AGXT variants: c.33dup (p.Lys12Glnfs*156) and c.454T>A (p.Phe152Ile).
- Following the diagnosis of PH1, the patient received aggressive renal replacement therapy and lumasiran was initiated on day 34 post-transplant. The hemodialysis regimen was slowly weaned while following oxalate levels and discontinued at approximately 4 months post-transplant. In the first 5 months of lumasiran treatment, UOx decreased by 65.9%. UOx continued to decline since discontinuing hemodialysis, although levels remained above the upper limit of normal. The patient was also prescribed high fluid intake, pyridoxine, and potassium citrate.
- The patient was closely monitored for any AEs associated with treatment; overall, lumasiran was well tolerated.

OXLUMO PRESCRIBING INFORMATION – RELEVANT CONTENT

For relevant labeling information, please refer to the following sections of the OXLUMO Prescribing Information[9]:

- DOSAGE AND ADMINISTRATION Section 2.1 Recommended Dosage
- USE IN SPECIFIC POPULATIONS Section 8.7 Renal Impairment
- CLINICAL PHARMACOLOGY Section 12.3 Pharmacokinetics

ABBREVIATIONS

AE = adverse event; AGXT = alanine-glyoxylate aminotransferase; BL = baseline; CI = confidence interval; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; ISR = injection site reaction; LS = least squares; NA = not applicable; PH = primary hyperoxaluria; PH1 = primary hyperoxaluria type 1; POx = plasma oxalate; RNAi = ribonucleic acid interference; SD = standard deviation; SEM = standard error of the mean; siRNA = small interfering ribonucleic acid; UOx = urinary oxalate.

Updated 14 May 2024

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2. Frishberg Y, Michael M, Groothoff JW, et al. Lumasiran for patients with primary hyperoxaluria type 1 and impaired kidney function: 12-month analysis of the phase 3 ILLUMINATE-C trial. Presented at: American Society of Nephrology (ASN) Kidney Week; November 3-6, 2022; Orlando, FL, USA.
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