Lumasiran: ILLUMINATE-C Study Overview

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SUMMARY

- 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 PH1 and advanced kidney disease. Patients enrolled in the study included those not receiving hemodialysis in Cohort A and those receiving hemodialysis in Cohort B.[1]
- The primary endpoint was the percent change from baseline in POx at 6 months in Cohort A and percent change from baseline in predialysis POx at 6 months in Cohort B. At 6 months, the LS mean percent reductions in POx from baseline was 33.3% (95% CI, -15.2%, 81.8%) and 42.4% (95% CI, 34.2%, 50.7%) in Cohorts A and B, respectively.[1] POx reductions were sustained in both cohorts through 24 months of the extension period.[2]
- Secondary endpoints evaluated in the primary analysis and extension periods included the change from baseline in additional measures of POx, UOx, and kidney related outcomes, such as eGFR, rate of KSEs, and nephrocalcinosis.[1]
- At 24 months of the study extension period, all 21 patients experienced at least 1 AE. The most common treatment-related AEs were mild ISRs, which occurred in 5 patients (24%). There were no deaths or lumasiran-related severe or serious AEs, discontinuations, or study withdrawals.[2,3]

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STUDY DESIGN

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 PH1 and advanced kidney disease. Patients enrolled in the study included those not receiving hemodialysis in Cohort A (N=6) and those receiving hemodialysis in Cohort B (N=15). Patients received subcutaneous injections

of lumasiran as determined by a body weight-based dosing regimen. The primary endpoint was the percent change from baseline in POx at 6 months in Cohort A and percent change from baseline in predialysis POx at 6 months in Cohort B.[1]

Select inclusion and exclusion criteria for ILLUMINATE-C are presented in **Table 1**.[1,4]

Table 1. ILLUMINATE-C Inclusion and Exclusion Criteria.[1,4]

Inclusion Criteria	Exclusion Criteria
• Have reached at least 37 weeks estimated gestational age (full-term infant) at consent (or assent) • Genetically confirmed diagnosis of PH1 • POx ≥20 µmol/L • eGFR ≤45 mL/min/1.73m^2, or elevated serum creatinine if <12 months of age • For patients taking therapeutic pyridoxine (vitamin B6), must have been on stable regimen for at least 90 days before consent and willing to remain on a stable regimen until at least Month 6 visit.[a] • For patients in Cohort B, must have been on a stable hemodialysis regimen for at least 4 weeks prior to Screening POx assessment and willing to maintain on regimen through Month 6 visit, with changes to regimen permitted only when medically indicated.	• Receiving peritoneal dialysis alone or combined hemodialysis/peritoneal dialysis therapy, or plan to start dialysis replacement therapy in the next 6 months • Had any of the following laboratory assessments at Screening: ○ ALT or AST >2x ULN for age ○ Total bilirubin >1.5x ULN ○ INR >1.5 for patients not on anticoagulants; INR <3.5 for patients on anticoagulants ○ Hemoglobin <8.0 g/dL • Known HIV, HCV, or HBV infection • History of kidney or liver transplant • Received an investigational agent within the last 30 days or 5 half-lives prior to the first dose of study drug

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; PH1 = primary hyperoxaluria type 1; POx = plasma oxalate; ULN = upper limit of normal.

[a]Patients remained on background therapies, including hyperhydration, crystallization inhibitors, and/or pyridoxine therapy through the 6-month analysis period before adjustments were made to the regimen based on clinical discretion.

PATIENT DEMOGRAPHICS & BASELINE CHARACTERISTICS

A total of 21 patients were enrolled (6 in Cohort A and 15 in Cohort B). All patients completed the 6-month primary analysis period. Select baseline characteristics are detailed in **Table 2**.[1]

Table 2. Baseline Demographics and Disease Characteristics.[1]

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)
Female, n (%)	3 (50)	6 (40)	9 (43)
Genotype[a]			
PR/*	0	5 (33)	5 (24)
M/M or M/N	5 (83)	7 (47)	12 (57)
N/N	1 (17)	3 (20)	4 (19)
Pyridoxine use, n (%)	4 (67)	7 (47)	11 (52)
POx, median (range)[b], µmol/L	57.9 (22.7-134.0)	103.7 (56.3-167.0)	100.9 (22.7-167.0)

Baseline Characteristic	Cohort A (n=6)	Cohort B (n=15)	All Treated (N=21)
Spot UOx:Cr[c], median (range), mmol/mmol	n=6 0.332 (0.075-1.380)	n=2 0.535 (0.451-0.618)	n=8 0.391 (0.075-1.380)
24-hour UOx excretion, median (range)[d], mmol/24h/1.73m^2	n=5 2.01 (0.56-2.47)	n=1 1.28 (1.28-1.28)	n=6 1.64 (0.56-2.47)
eGFR[e,f], median (range), mL/min/1.73 m^2	n=5 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: BSA = body surface area; eGFR = estimated glomerular filtration rate; NA = not applicable; POx = plasma oxalate; ULN = upper limit of normal; UOx = urinary oxalate; UOx:Cr = urinary oxalate:creatinine ratio.

[a]M = missense; N = nonsense; PR = pyridoxine-responsive; *= any genotype of PR, M, or N. PR was defined as NM_000030.3 (AGXT):c.508G>A (p. Gly170Arg) or NM+000030.3 (AGXT):c. 454T>A (p.Phe152lle). M and N were defined based on a publication by Mandrile et al.

[b]ULN=12.11 µmol/L (1.09 mg/mL) for POx, as determined based on data from 75 healthy adults.

[c]1 mmol/mmol = 0.796 mg/mg.

[d]ULN=0.514 mmol/24h/1.73m^2 for 24-hour UOx corrected for BSA.

[e]eGFR was calculated only in patients ≥12 months.

[f]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.

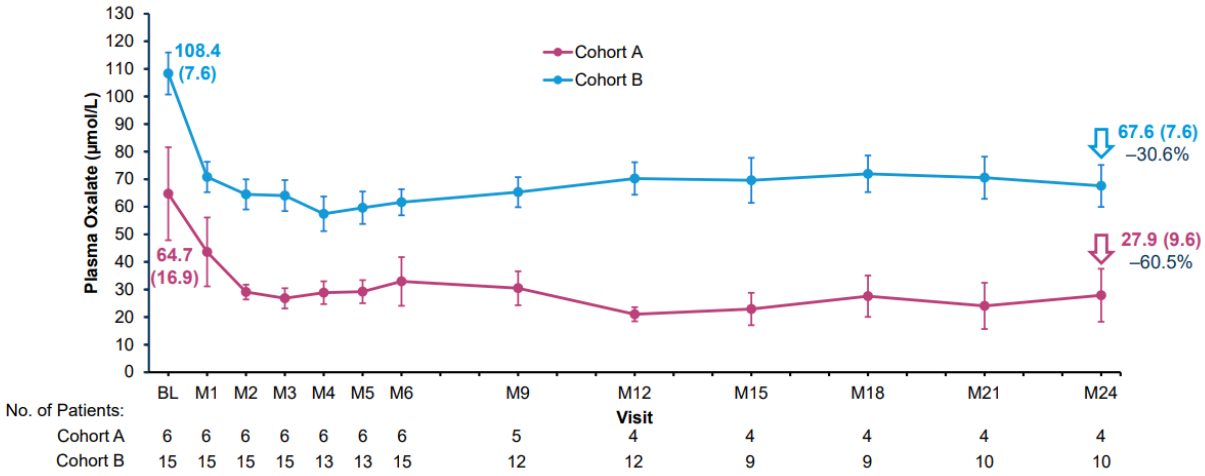
EFFICACY RESULTS

Plasma Oxalate

During the 6-month primary analysis period, the primary estimate of the LS mean percent reductions in POx from baseline was 33.3% (95% CI, -15.2%, 81.8%) and 42.4% (95% CI, 34.2%, 50.7%) in Cohorts A and B, respectively. A consistent treatment effect was observed across all prespecified subgroups in Cohort B. Trends were not available for assessment in Cohort A as treatment subgroups were too small.[1]

Data from the interim analysis through 24 months of the extension period showed sustained POx reductions in both cohorts (**Figure 1**). 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) at month 24, respectively. The mean percent reduction in POx from baseline was 60.5% for Cohort A and 30.6% for Cohort B.[2]

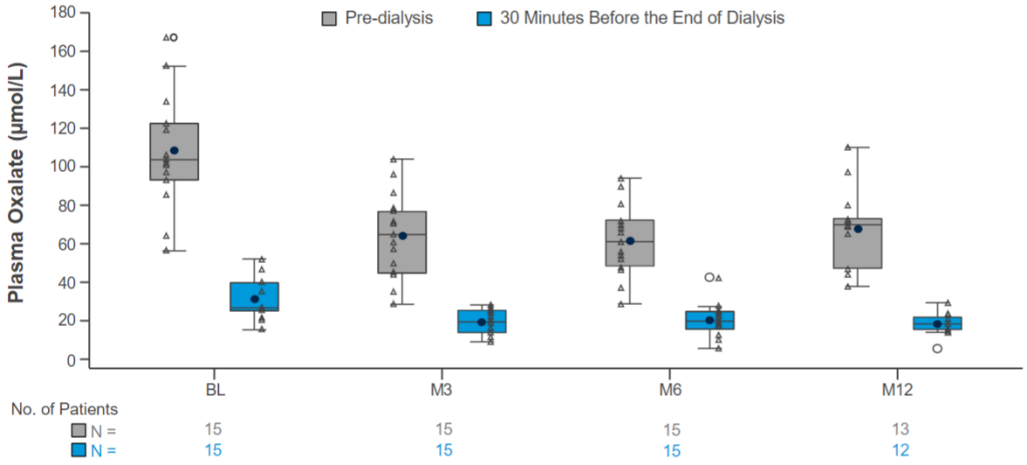
Figure 1. POx Mean (SEM) Actual Values Through Month 24.[2]



Abbreviations: BL = baseline; M = month; POx = plasma oxalate; SEM = standard error of the mean.
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. Observations occurring after a liver transplant, initiation of hemodialysis in Cohort A, or discontinuation of hemodialysis in Cohort B were censored.
From Sellier-Leclerc et al.[2]

The distribution of pre-dialysis and post-dialysis POx levels in Cohort B through 12 months of lumasiran treatment is presented in **Figure 2**.[5] 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]

Figure 2. Distribution of Pre- and Post-dialysis Plasma Oxalate Levels in Cohort B.[5]



Abbreviations: BL = baseline; M = month.
Filled circles represent means; horizontal lines represent medians; triangles represent observed values for individual patients; open circles represent outliers.
From Frishberg et al.[5]

Pharmacodynamic Secondary Endpoints

During the 6-month primary analysis period, reductions in additional measures of UOx and POx that were evaluated as secondary endpoints were observed (**Table 3**).[1]

Table 3. Change from Baseline in Pharmacodynamic Secondary Endpoints at Month 6.[1]

Secondary Endpoints[a]	Cohort A n=6	Cohort B n=15
Percent change in POx $AUC_{0\text{-}24h}$ between dialysis sessions[b]	NA	-41.4 ± 4.4 (-51.0, -31.8)
Absolute change in POx[c] (µmol/L)	-35.3 ± 7.4 (-56.3, -14.2)	-48.3 ± 3.6 (-55.9, -40.8)
Percent change in spot UOx:Cr	-39.5 ± 9.4 (-64.1, -14.9)	NA
Absolute change in spot UOx:Cr (mmol/mmol)[d]	-0.188 ± 0.016 (-0.229, -0.147)	NA
Percent change in 24-hour UOx corrected for BSA	n=5 -10.6 ±6.8 (-32.0, 10.9)	NA
Absolute change in 24-hour UOx corrected for BSA (mmol/24h/1.73m^2)	n=5 -0.53 ± 0.11 (-0.89, -0.18)	NA

Abbreviations: AUC = area under the curve; BSA = body surface area; CI = confidence interval; LS = least squares; M = month; MMRM = mixed-effect model for repeated measures; NA = not applicable; POx = plasma oxalate; SEM = standard error of the mean; ULN = upper limit of normal; UOx = urinary oxalate; UOx:Cr, = urinary oxalate:creatinine ratio.

[a]Values presented as LS mean ± SEM (95% CI). The change from baseline 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 REML-based MMRM model. The model included scheduled visits and baseline POx as fixed effects and patient as a random factor. Autoregressive (1) was used to model the within-patient variability.

[b] LS mean percent change from baseline in POx $AUC_{0\text{-}24h}$ at month 6 and its associated 95% CI were estimated using the REML-based MMRM model including data evaluated at months 3 and 6. The model included scheduled visits and baseline POx as fixed effects and patient as a random factor. Autoregressive (1) was used to model the within-patient variability.

[c]ULN=12.11 µmol/L (1.09 mg/mL) for POx, as determined based on data from 75 healthy adults.

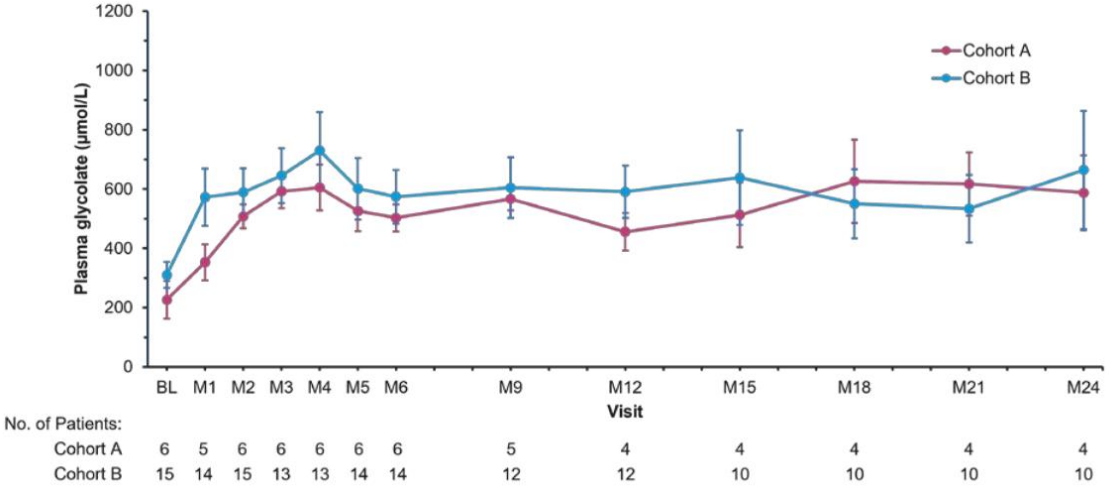
[d]1 mmol/mmol=0.796 mg/mg.

Pharmacodynamic Exploratory Endpoint

Plasma Glycolate

Plasma glycolate was assessed as a pharmacodynamic exploratory endpoint. In both cohorts, plasma glycolate levels initially increased through the 6-month primary analysis period, then remained relatively stable during the extension period through 24 months (**Figure 3**). The maximum measured plasma glycolate levels were 923 µmol/L in Cohort A and 2240 µmol/L in Cohort B.[1,3]

Figure 3. Plasma Glycolate Mean (SEM) Actual Values Through Month 24.[3]



Abbreviations: BL = baseline; M = month; SEM = standard error of the mean.

Baseline was defined as the mean of all plasma glycolate assessments prior to the first dose of lumasiran.

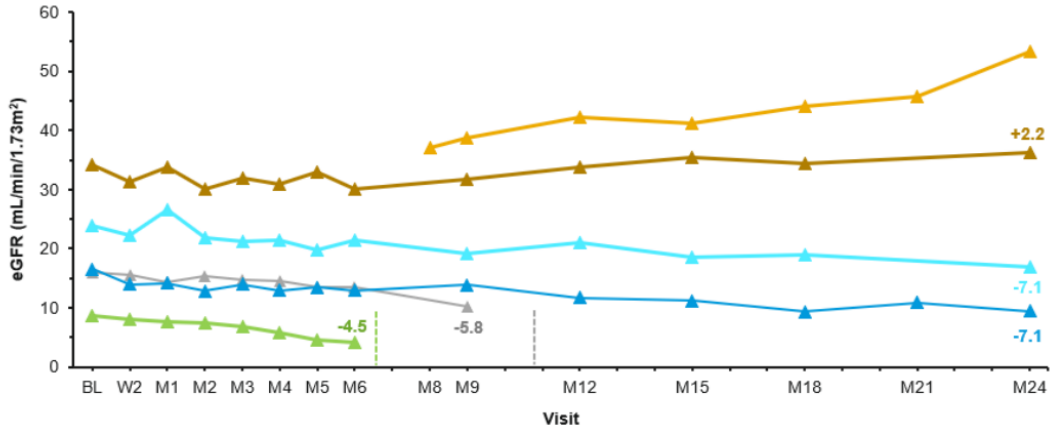
From Sellier-Leclerc et al.[3]

Kidney Related Outcomes

eGFR

The change from baseline in eGFR was evaluated in Cohort A as a secondary endpoint in the extension period to assess kidney function during the study. For Cohort A, the mean (SD) eGFR was 19.8 ± 9.6 mL/min/1.73 m^2 at baseline and 16.4 ± 9.8 mL/min/1.73 m^2 at 6 months. The eGFR values for each patient in Cohort A from baseline to 24 months are presented in **Figure 4**.[1,3]

Figure 4. eGFR values from Baseline to Month 24 in Cohort A.[3]



Abbreviations: BL = baseline; eGFR = estimated glomerular filtration rate; M = month; W = week.
eGFR was only calculated in patients aged ≥12 months at time of assessment. The measurement of eGFR in 1 patient (yellow) did not begin until Month 8, after reaching 12 months of age. Pre-dialysis eGFR values are shown for 2 patients who initiated dialysis, through Month 9 (gray) and M6 (green). Dashed green and gray lines indicate when dialysis was initiated in these patients. Data labels show actual eGFR change from baseline at Month 24 (brown, light blue, blue), Month 9 (gray), and Month 6 (green) in the 5 patients with baseline eGFR data.
From Sellier-Leclerc et al.[3]

As of 36 months of the extension period, 5 of the 6 patients in Cohort A remained in the study and 3 patients, who had the lowest baseline eGFR ranging from 8.6 to 16.5 mL/min/1.73 m^2, began hemodialysis. The remaining two patients, with a baseline eGFR of 24.0 and 34.1 mL/min/1.73 m^2, had annual rates of decline in eGFR of -2.3 and -0.9 mL/min/1.73 m^2 per year, respectively, over 36 months.[6]

Kidney Stone Events

The change from baseline in KSE rates was evaluated as a secondary endpoint in the extension period. A KSE was defined as ≥1 of the following (as adjudicated by the Investigator): visit to healthcare provider because of a kidney stone; medication for renal colic; stone passage; or macroscopic hematuria due to a kidney stone.[1,4]

For patients enrolled in Cohort A, the rate of KSEs per person-year was 3.20 (95% CI, 1.96, 5.22) in the 12 months prior to informed consent and 1.48 (95% CI, 0.55, 3.92) in the 6-month primary analysis period. For patients enrolled in Cohort B, the rate of KSEs per person-year was 0.07 (95% CI, 0.01, 0.71) in the 12-months prior to informed consent and 0.00 (95% CI, 0.00, 0.53) in the 6-month primary analysis period.[1]

In the extension period as of a data cutoff date of October 17, 2022 (beyond Month 24), the KSE rates were 0.32 (95% CI, 0.08, 1.27) and 0.00 (95% CI, 0.00, 0.19) in Cohorts A and B, respectively.[3]

Nephrocalcinosis

The change from baseline in nephrocalcinosis was evaluated as a secondary endpoint in the extension period. Nephrocalcinosis grade was assessed at baseline and month 6 by kidney ultrasound scans. Each kidney was assessed for the degree of medullary nephrocalcinosis by a radiologist, and the central reads were completed using a validated, semi-quantitative scale of 0 to 3, with a higher grade indicating greater severity. Changes in nephrocalcinosis grade were grouped into 4 categories of overall change (for both kidneys): no change, improving, worsening, and indeterminate (1 kidney improving and 1 kidney worsening).[1,7]

In Cohort A, medullary nephrocalcinosis was present at baseline in 5 patients (83%). Of those 5 patients, medullary nephrocalcinosis remained stable in 2 patients, worsened in no patients, and improved in 3 patients (2 patients had unilateral and 1 patient had bilateral improvement) at 6 months. In Cohort B, medullary nephrocalcinosis was present at baseline in 2 of the 11 patients (18%) with kidney ultrasound scan results. Of these 2 patients, nephrocalcinosis improved in both (1 patient has unilateral improvement and 1 patient had bilateral improvement) at 6 months. In patients without nephrocalcinosis at baseline (1 patient in Cohort A, 9 patients in Cohort B), bilateral worsening was observed in the patient in Cohort A, and nephrocalcinosis remained stable in the 9 patients in Cohort B.[1]

SAFETY RESULTS

Through 24 months of the extension period, 21 patients (100%) experienced at least 1 AE (**Table 4**).[3] The serious AEs reported in the 6-month primary analysis period were primarily associated with dialysis procedural complications and may be attributed to the advanced kidney disease in the ILLUMINATE-C patient population.[1]

The most frequently reported AEs were pyrexia (38%), diarrhea (29%), and ISRs (24%). Mild ISRs were the most common AE related to lumasiran, which occurred in 5 patients (6 events). There were no deaths or lumasiran-related severe or serious AEs, discontinuations, or withdrawals that occurred through 24 months.[2,3]

Table 4. Lumasiran Safety Overview Through Month 24.[3,a]

Treatment-emergent Event, n (%)	Original Assignment		After Dialysis Change		All Treated N=21 (PY 39.9)
	Cohort A (not on dialysis) n=6 (PY 9.0)	Cohort B (on dialysis) n=15 (PY 26.2)	Cohort A (on dialysis) n=2 (PY 1.4)	Cohort B (not on dialysis) n=5 (PY 3.3)	
Patients with ≥1 AE	6 (100)	15 (100)	1 (50)	5 (100)	21 (100)
AEs occurring in ≥3 patients in either cohort					
Pyrexia	1 (17)	7 (47)	0 (0)	0 (0)	8 (38)
Injection site reaction	1 (17)	4 (27)	0 (0)	0 (0)	5 (24)
Diarrhea	1 (17)	3 (20)	0 (0)	2 (40)	6 (29)
Anemia	1 (17)	2 (13)	1 (50)	0 (0)	4 (19)
Vomiting	2 (33)	1 (7)	0 (0)	1 (20)	4 (19)
Kidney transplant	0 (0)	3 (20)	0 (0)	1 (20)	4 (19)[b]
COVID-19 infection	0 (0)	2 (13)	1 (50)	1 (20)	4 (19)
Cough	1 (17)	1 (7)	1 (50)	0 (0)	3 (14)

Treatment-emergent Event, n (%)	Original Assignment		After Dialysis Change		All Treated N=21 (PY 39.9)
	Cohort A (not on dialysis) n=6 (PY 9.0)	Cohort B (on dialysis) n=15 (PY 26.2)	Cohort A (on dialysis) n=2 (PY 1.4)	Cohort B (not on dialysis) n=5 (PY 3.3)	
Upper respiratory tract infection	1 (17)	1 (7)	1 (50)	0 (0)	3 (14)
Gastroenteritis	1 (17)	1 (7)	0(0)	1 (20)	3 (14)
AEs leading to treatment discontinuation and study withdrawal[c]	0 (0)	2 (13)	0 (0)	0 (0)	2 (10)
Severe AEs[d]	3 (50)	8 (53)	0 (0)	0 (0)	11 (52)
Serious AEs[e]	3 (50)	11 (73)	0(0)	4 (80)	15 (71)
Death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviations: AE = adverse event; PY = patient year.

[a]Safety anaylses during the extension period include all available data through the data cutoff date of October 17, 2022 (beyond Month 24). "Original Assignment" columns display AEs prior to any change in dialysus status, ie, while not on dialysis for Cohort A/while on dialysis for Cohort B. "After Dialysis Change" columns display AEs reported after patients in Cohort A initiated dialysis (n=2), and after patients in Cohort B went off dialysis (n=5). "All Treated" column displays total patients reporting AEs, regardless of cohort/dialysis status.

[b]Two patients underwent kidney transplantation before Month 24, and 2 patients underwent kidney transplantation after Month 24.

[c]AEs led to both treatment discontinuation and study withdrawal in 2 patients; both were due to liver-kidney transplant.

[d]Severe AEs that occurred in 2 patients included liver/kidney transplant and kidney transplant. Other severe AEs affected no more than 1 patient. 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. Other serious AEs affected no more than 1 patient. No serious AEs were determined to be related to lumasiran.

ABBREVIATIONS

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUC = area under the curve; BL = baseline; BSA = body surface area; CI = confidence interval; eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; ISR = injection site reaction; KSE = kidney stone event; LS = least squares; M = month; MMRM = mixed-effect model for repeated measures; NA = not applicable; PH1 = primary hyperoxaluria type 1; POx = plasma oxalate; QoL= Quality of Life; PY = patient year; SC = subcutaneous; SD = standard deviation; SEM = standard error of the mean; ULN = upper limit of normal; UOx = urinary oxalate; UOx:Cr = urinary oxalate:creatinine ratio; W = week.

Updated 16 October 2025

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