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 a 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).[1]
- All 21 patients completed the 6-month primary analysis period and entered the extension period. At 60 months, 14 patients completed the study without protocol-defined censoring events.[2]
- 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]
- 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 60 months, all 21 patients experienced at least 1 AE. The most common treatment-related AEs were mild ISRs, which occurred in 5 patients (24%).[2]

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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 a 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]

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]

Select inclusion and exclusion criteria for ILLUMINATE-C are presented in **Table 1**.[1,3]

Table 1. ILLUMINATE-C Inclusion and Exclusion Criteria.[1,3]

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)

Baseline Characteristic	Cohort A (n=6)	Cohort B (n=15)	All Treated (N=21)
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)
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.

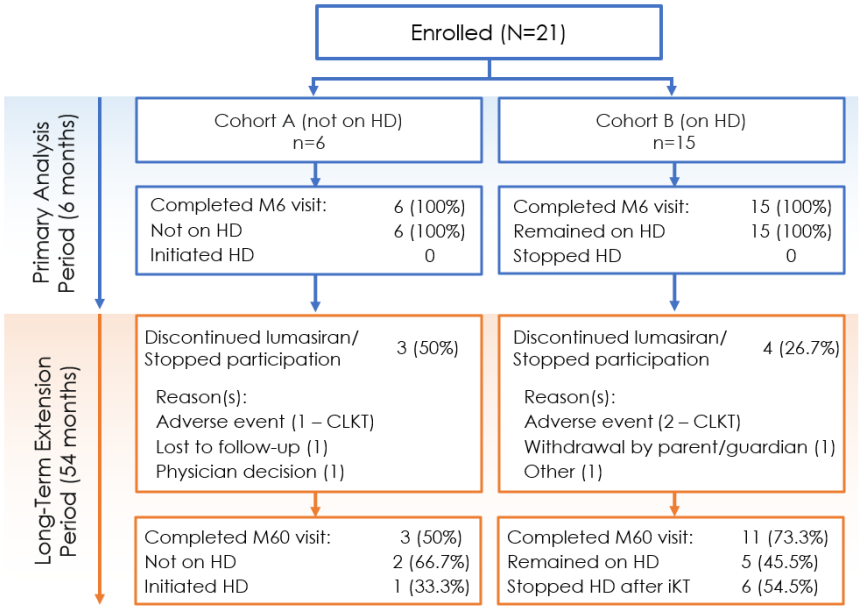
[e]eGFR was calculated only in patients ≥12 months.

[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.

Final Patient Disposition

Following the 6-month primary analysis period, all 21 patients entered the extension period. Age ranged from 0 to 59 years, and POx ranged from 22.7 to 167.0 µmol/L. By the end of the study at 60 months, a total of 14 patients completed the study without protocol-defined censoring events. A summary of the patient disposition by 60 months is shown in **Figure 1**.[2]

Figure 1. Final Patient Disposition in ILLUMINATE-C.[2]



Abbreviations: CLKT = combined liver-kidney liver transplant; HD = hemodialysis; M = month; iKT = isolated kidney transplant.
From Magen et al.[2]

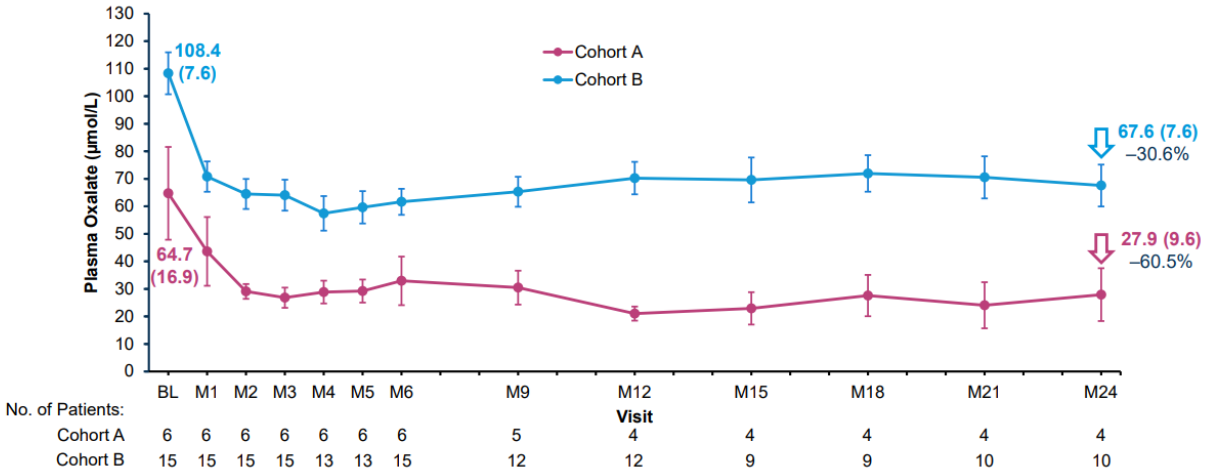
EFFICACY RESULTS

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 2**). 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.[4]

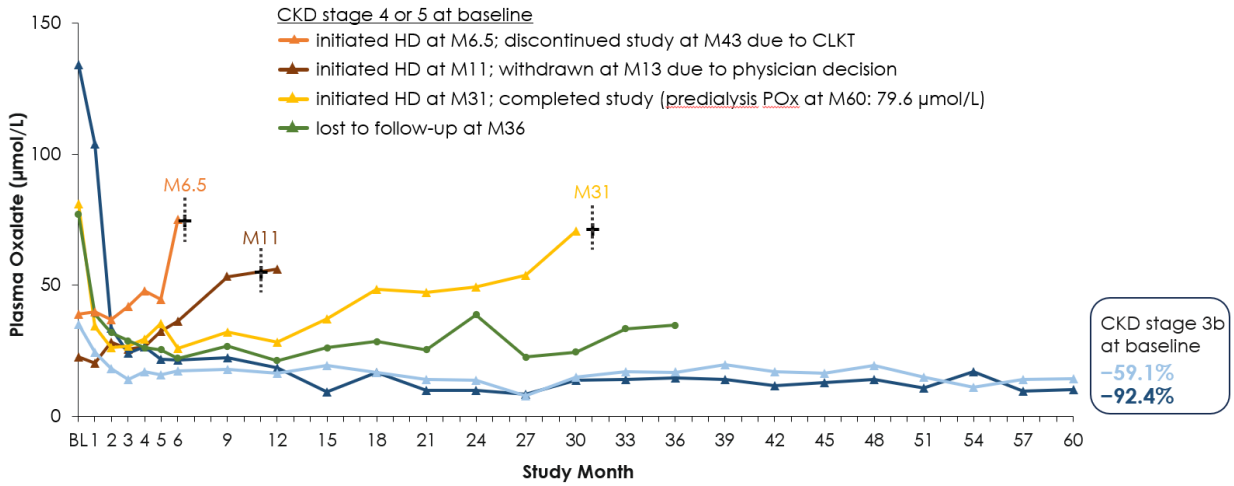
Figure 2. POx Mean (SEM) Actual Values Through Month 24.[4]



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.[4]

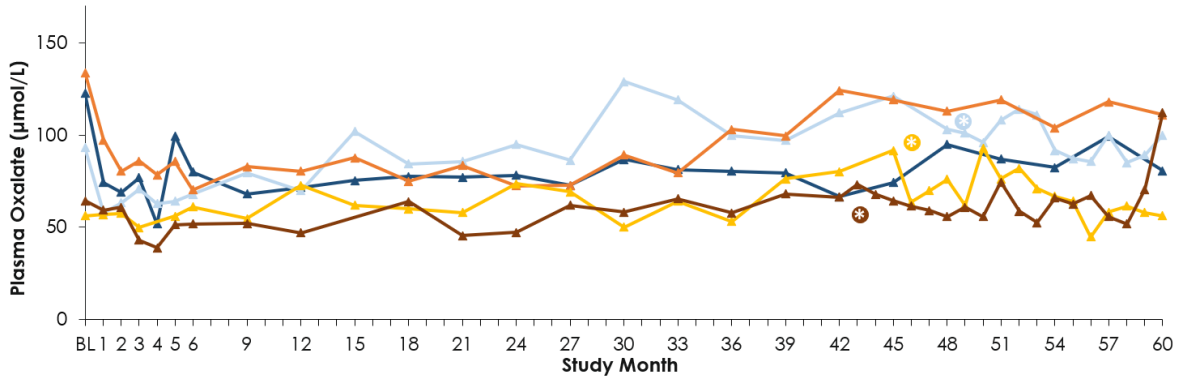
POx values for individual patients in Cohort A and Cohort B through 60 months are shown in **Figures 3 and 4**, respectively.[2]

Figure 3. POx Values of Patients in Cohort A Through 60 Months.[2,a]



Abbreviations: BL = baseline; CKD = chronic kidney disease; CLKT = combined liver-kidney transplant; HD = hemodialysis; iKT = isolated kidney transplant; M = month; POx = plasma oxalate.
[a]Dashed line indicates data censoring due to initiating HD. POx observations occurring after a liver transplant, iKT, initiation of HD for a patient in Cohort A, or discontinuation of HD for a patient in Cohort B were censored per the protocol.
From Magen et al.[2]

Figure 4. POx Values of Patients in Cohort B Through 60 Months.[2,a]



[a]POx observations occurring after a liver transplant, iKT, initiation of HD for a patient in Cohort A, or discontinuation of HD for a patient in Cohort B were censored per the protocol. In Cohort B, POx values are from samples collected predialysis; 4 patients withdrew from the trial prior to Month 60. Circled stars indicate the change in maintenance dosing regimen.
From Magen et al.[2]

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

Secondary Endpoints[a]	Cohort A n=6	Cohort B n=15
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.

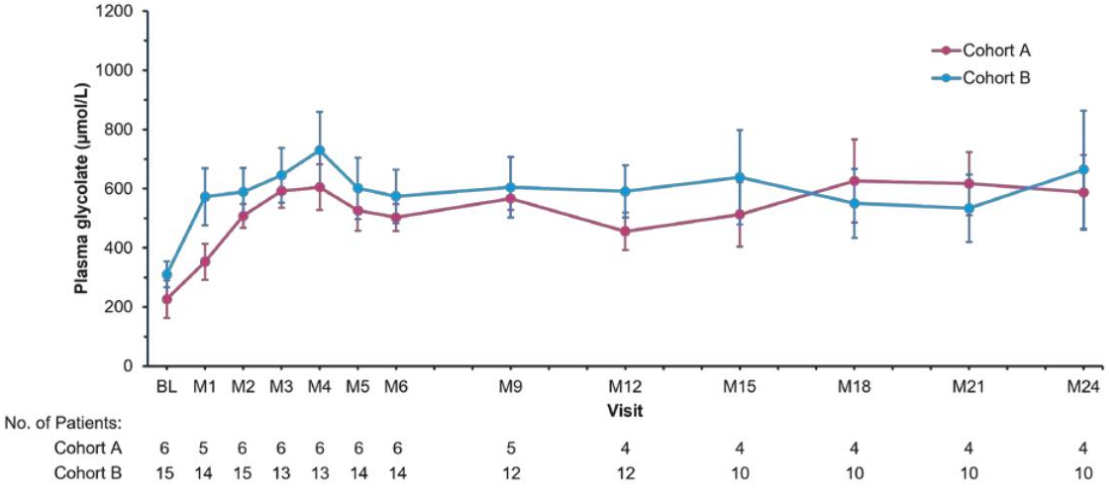
[d]1 mmol/mmol=0.796 mg/mg.

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 5**). The maximum measured plasma glycolate levels were 923 µmol/L in Cohort A and 2240 µmol/L in Cohort B.[1,5]

Figure 5. Plasma Glycolate Mean (SEM) Actual Values Through Month 24.[5]



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.

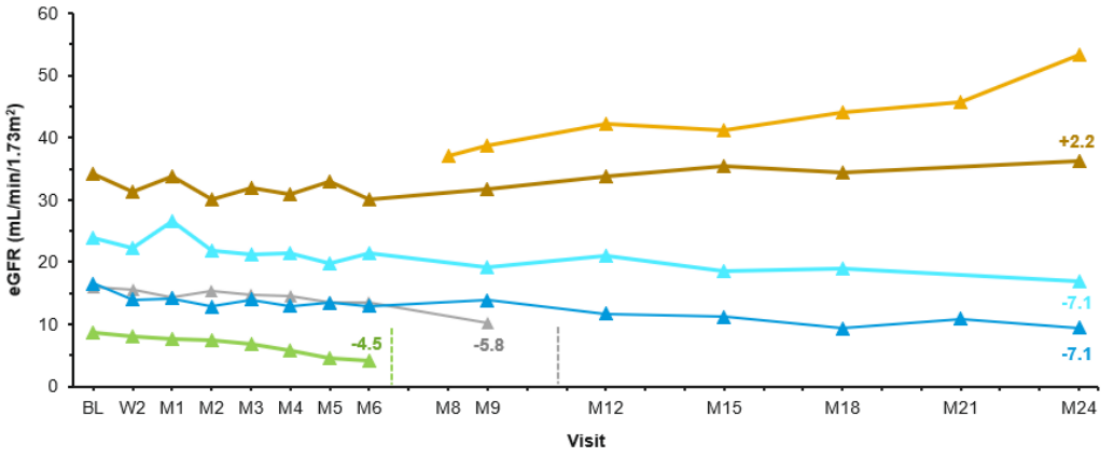
From Sellier-Leclerc et al.[5]

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 6**.[1,5]

Figure 6. eGFR values from Baseline to Month 24 in Cohort A.[5]



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.[5]

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.[1,3]

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.[5]

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

At 60 months, 21 patients (100%) experienced at least 1 AE (**Table 4**). ISRs occurred in 5 patients (24%). The rate of ISRs was 1.4% of 486 total lumasiran doses administered. No ADAs were detected at baseline or at any time post-dose, and no treatment-related AEs of metabolic acidosis were reported in patients receiving hemodialysis.[2]

Table 4. Lumasiran Safety Overview Through Month 60.[2,a]

Treatment-emergent Event, n (%)	Original Assignment		After Dialysis Change		All Treated N=21 (PY 76.9)
	Cohort A (not on dialysis) n=6 (PY 15.9)	Cohort B (on dialysis) n=15 (PY 40.3)	Cohort A (on dialysis) n=3 (PY 5.3)	Cohort B (not on dialysis) n=7 (PY 15.4)	
Patients with ≥1 AE	6 (100)	15 (100)	2 (67)	6 (86)	21 (100)
Treatment-related AEs	2 (33)	5 (33)	0	1 (14)	7 (33)
Injection site reaction	1 (17)	4 (27)	0 (0)	0 (0)	5 (24)
AEs leading to treatment discontinuation and study withdrawal	0 (0)	2 (13)	1 (33)	0 (0)	3 (14)[b]
Severe AEs	4 (67)	11 (73)	2 (67)	3 (43)	15 (71)
Serious AEs	4 (67)	13 (87)	2 (67)	5 (71)	19 (91)
Death	0 (0)	1 (7)	0 (0)	0 (0)	1 (5)

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

[a]"Original Assignment" columns display AEs prior to any change in dialysis 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, and after patients in Cohort B went off dialysis. "All Treated" column displays total patients reporting AEs, regardless of cohort/dialysis status.

[b]All AEs leading to treatment discontinuation and study withdrawal were due to patients receiving a combined liver-kidney transplant.

ABBREVIATIONS

ADA = antidrug antibody; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUC = area under the curve; BL = baseline; BSA = body surface area; CI = confidence interval; CKLT = combined kidney-liver transplant; eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HD = hemodialysis; HIV = human immunodeficiency virus; iKT = isolated kidney transplant; 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; PY = patient year; QoL = Quality of Life; 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.

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