Lumasiran: ILLUMINATE-B Study Overview

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SUMMARY

- ILLUMINATE-B (N=18) was a phase 3, open-label, single-arm study with a 6-month primary analysis period followed by an ongoing extension period of up to 54 months to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of lumasiran in infants and young children <6 years old with PH1 and an eGFR >45 mL/min/1.73m^2 (or normal serum creatinine for infants <12 months old).[1]
- The primary endpoint was the percent change in UOx, assessed with spot UOx:Cr levels, from baseline to month 6 (averaged across months 3 through 6), which resulted in a LS mean reduction of 72%.[2] At month 30 of the extension period, treatment with lumasiran resulted in a LS mean reduction of 75.8% from baseline.[1]
- Secondary endpoints evaluated in the primary analysis and extension periods included the change from baseline in additional measures of UOx excretion, POx, and eGFR.[1]
- At 30 months of the extension period, all 18 patients experienced an AE. Five patients (28%) experienced lumasiran-related AEs: ISRs, blood bilirubin increase, and headache. The majority of the lumasiran-related AEs were mild and transient ISRs. No AEs led to treatment discontinuations or death in the study.[1]

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STUDY DESIGN

ILLUMINATE-B (N=18) was a phase 3, open-label, single-arm study with a 6-month primary analysis period followed by an ongoing extension period of up to 54 months to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of lumasiran in infants and young children <6 years old with PH1 and an eGFR >45 mL/min/1.73m^2 (or normal serum creatinine for infants <12 months old). 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 spot UOx:Cr at 6 months.[1]

Patients received starting body weight-based doses of lumasiran once monthly for 3 doses, and then an ongoing dose once monthly or once every 3 months, as recommended by a weight-based regimen (**Table 1**).[1] The treatment arms were stratified utilizing weight-based dosing with dose adjustments for

interval weight gain. Continued weight-based dosing for patients weighing <20 kg was based on weight obtained 7 days prior to dosing and for patients weighing ≥20 kg, up to 4 months prior to dosing.[2,3]

Table 1. Lumasiran Weight-Based Dosing.[1]

Patient Weight	Starting Dose	Ongoing Dose
<10 kg	6.0 mg/kg qM × 3 doses	3.0 mg/kg qM
≥10 kg to <20 kg	6.0 mg/kg qM × 3 doses	6.0 mg/kg q3M
≥20 kg	3.0 mg/kg qM × 3 doses	3.0 mg/kg q3M

Abbreviations: qM = monthly; q3M = every 3 months.

The inclusion and exclusion criteria for ILLUMINATE-B are presented in **Table 2**.[2,3]

Table 2. ILLUMINATE-B Inclusion and Exclusion Criteria.[2,3]

Inclusion Criteria	Exclusion Criteria
• Full term infant to children age <6 years old • Genetically confirmed diagnosis of PH1 • eGFR >45 mL/min/1.73m^2 if aged ≥12 months or normal serum creatinine at screening if aged <12 months old • Elevated UOx:Cr >ULN based on age • For patients taking pyridoxine (vitamin B6) for treatment of PH1, regimen required to have been stable for at least 90 days before screening and willing to remain on regimen for at least 6 months[a]	• Clinical evidence of extrarenal systemic oxalosis • Clinically significant liver function test abnormalities • Known HIV, HCV, or HBV infection • Received an investigational agent within the last 30 days or 5 half-lives • History of kidney or liver transplant

Abbreviations: eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PH1 = primary hyperoxaluria type 1; ULN = upper limit of the normal; UOx:Cr = urinary oxalate:creatinine ratio.
[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 18 patients were enrolled and included in the 6-month analysis. Baseline demographics are shown below in **Table 3**.[1]

Table 3. Baseline Demographics and Disease Characteristics.[1,4]

Baseline Characteristic	Initial Weight Group[2]			All Treated[1] (N=18)
	<10 kg (N=3)	10 to <20 kg (N=12)	≥20 kg (N=3)	
Median age at informed consent, months (range)	10.1 (3-14)	50.1 (23-72)	62.2 (54-72)	50.1 (3-72)
Median age at diagnosis, months	0.8	22.7	27.0	16.3
Median time from diagnosis to first dose date, months	11.6	28.6	46.4	23.5
Genotype, n (%)				
PR/[a]	0	3 (25)	0	3 (17)
M/M or M/N	1 (33)	8 (67)	1 (33)	10 (56)
N/N	2 (67)	1 (8)	2 (67)	5 (28)
Pyridoxine (vitamin B6) use, n (%)	2 (67)	7 (58)	2 (67)	11 (61)
Median spot UOx:Cr (range), mmol/mmol[b]	1.253 (1.126-1.708)	0.453 (0.166-1.205)	0.350 (0.255-0.693)	0.469 (0.166-1.708)
24-hour UOx corrected for BSA (SEM), mmol/24h/1.73m^2	–	–	–	2.083 (0.3170)
Median plasma oxalate (range), µmol/L[c]	22.3 (17.2-30.6)	9.6 (6.6-19.9)	11.7 (7.2-18.7)	11.5 (6.6-30.6)

Baseline Characteristic	Initial Weight Group[2]			All Treated[1] (N=18)
	<10 kg (N=3)	10 to <20 kg (N=12)	≥20 kg (N=3)	
In plasma oxalate analysis set[d]	22.3 (17.2-30.6)	11.8 (8.7-19.9)	15.2 (11.7-18.7)	13.7 (8.7-30.6)
Median eGFR (range), mL/min/1.73m^2[e]	135 (135-135)	111 (76-174)	90 (65-135)	111 (65-174)
History of kidney stone events in past 12 months, n (%)	0	2 (17)	1 (33)	3 (17)
Presence of nephrocalcinosis at baseline, n (%)	3 (100)	10 (83)	1 (33)	14 (78)

Abbreviations: eGFR = estimated glomerular filtration rate; LLOQ = lower limit of quantitation; M = missense; N = nonsense; PR = pyridoxine-responsive; SEM = standard error of the mean; ULN = upper limit of normal; UOx:Cr = urinary oxalate:creatinine ratio.
[a]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 publication by Mandrile et al.[5]
[b]1 mmol/mmol = 0.796 mg/mg; 1 mmol/mmol = 1,000 mmol/mol.
[c]ULN = 12.11 µmol/L for plasma oxalate, as determined based on data from 75 healthy adults.
[d]In patients with baseline plasma oxalate ≥1.5×LLOQ (5.55 µmol/L; N (all treated)=13).
[e]eGFR (mL/min/1.73m^2) was calculated based on the Schwartz Bedside formula for patients ≥12 months; N (all treated)=16. eGFR was not calculated in 2 patients due to their age, which at baseline was <12 months.

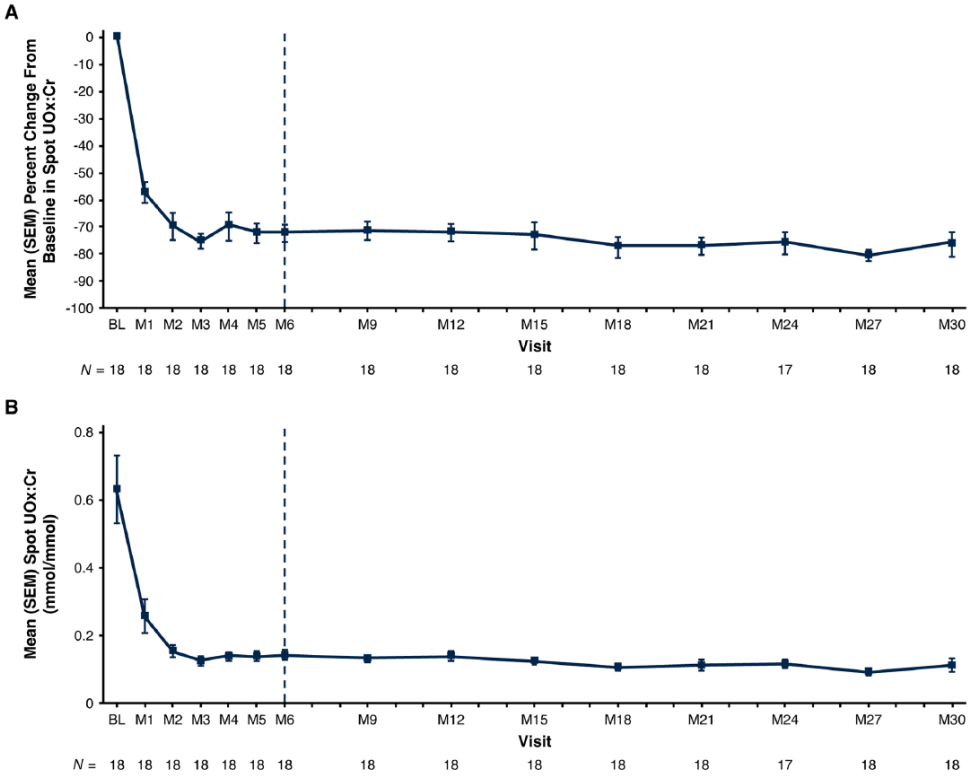
EFFICACY RESULTS

Urinary Oxalate

In the 6-month primary analysis period, the LS mean reduction in spot UOx:Cr from baseline to month 6 (averaged across months 3 through 6) was 72% (95% CI, 66.4%-77.5%). Spot UOx:Cr levels were also analyzed by weight category per a protocol specified subgroup analysis, in which mean spot UOx:Cr reductions were 84% in patients <10 kg, 69% in patients 10 to <20 kg, and 70% in patients ≥20 kg from baseline during the 6-month primary analysis period.[2]

In the extension period, the percent change from baseline in spot UOx:Cr was evaluated as a secondary endpoint. The mean spot UOx:Cr decreased from 0.63 mmol/mmol at baseline to 0.11 mmol/mmol at month 30, with a mean (SEM) percent decrease of 75.8% (4.5%) from baseline (**Table 4; Figure 1**).[1]

Figure 1. Mean (SEM) Spot UOx:Cr From Baseline Through Month 30.[1,a-e]



Abbreviations: BL = baseline; M = month; SEM = standard error of the mean; ULN = upper limit of normal; UOx:Cr = urinary oxalate:creatinine ratio.
(A) Percent change from baseline at each visit and (B) actual values at each visit.
[a]BL represents the baseline value; mean of all assessments collected prior to the first dose of lumasiran.
[b]1 mmol/mmol = 0.796 mg/mg; 1 mmol/mmol = 1,000 mmol/mol.
[c]Vertical dashed line represents the end of the primary analysis period.
[d]Non-quarterly visits from the extension period are not displayed.
[e]The ULN for spot UOx:Cr is age-dependent. 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.
From Frishberg et al.[1]

Secondary Endpoints

A summary of secondary efficacy endpoints, including additional measures of urinary and plasma oxalate, at months 6, 12, 18, 24, and 30 is presented in **Table 4**.[1]

Table 4. Secondary Efficacy Endpoints.[1]

Endpoint[a]	Lumasiran (N=18)				
	Month 6	Month 12	Month 18	Month 24	Month 30
Percent change from baseline in spot UOx:Cr	-71.7 (3.4)	-71.9 (3.2)	-76.9 (3.9)	-75.4 (4.0)	-75.8 (4.5)
Absolute change from baseline in spot UOx:Cr, mmol/mmol[b]	-0.5 (0.1)	-0.5 (0.1)	-0.5 (0.1)	-0.5 (0.1)	-0.5 (0.1)
Patients with spot UOx:Cr, n (%)					
≤ULN[c]	1 (6)	2 (11)	3 (17)	3 (18)	7 (39)
≤1.5× ULN[c]	9 (50)	10 (56)	11 (61)	7 (41)	13 (72)
Percent change from baseline corrected for BSA in 24h UOx, mmol/24h/1.73m^2[d]	-68.4 (5.6)	-63.2 (7.2)	-75.2 (4.3)	-72.9 (3.4)	-73.5 (8.8)

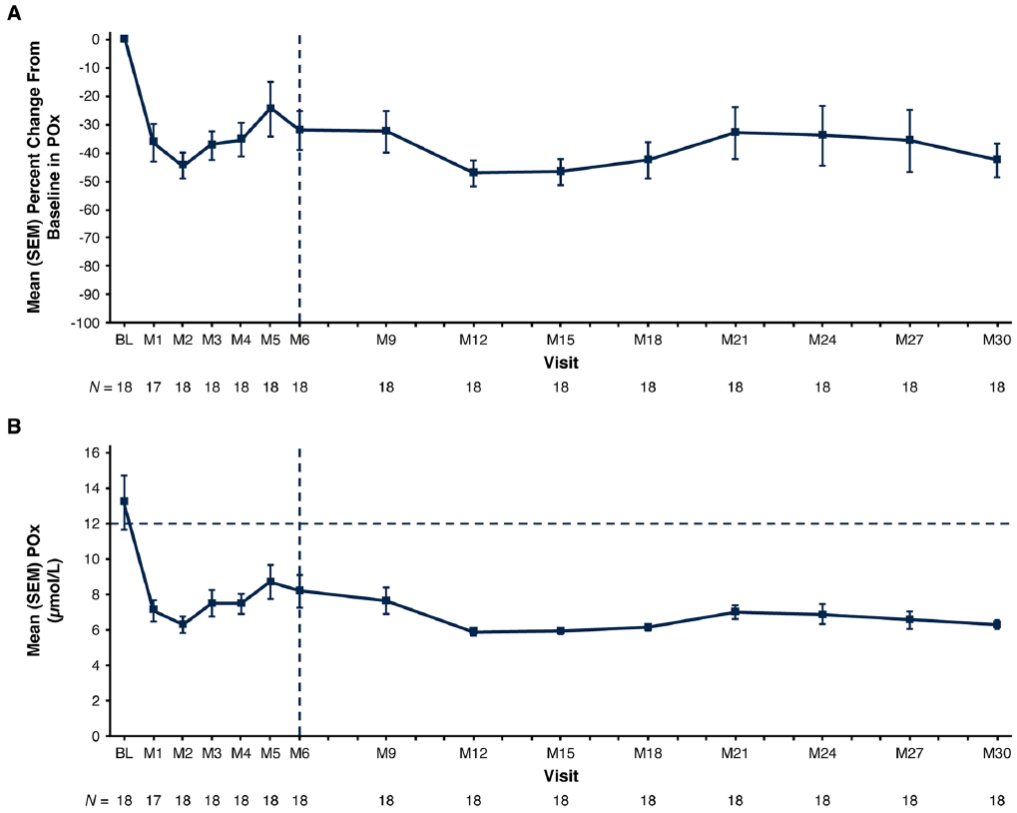
Absolute change from baseline corrected for BSA in 24h UOx, mmol/24h/1.73m^2[d]	-1.4 (0.1)	-1.2 (0.3)	-1.5 (0.1)	-1.6 (0.1)	-1.5 (0.4)
Percent change in POx from baseline[e]	-32.1 (6.7)	-47.1 (4.6)	-42.6 (6.4)	-33.9 (10.7)	-42.5 (6.0)
In POx analysis set[e]	-37.4 (8.8)	-56.4 (3.8)	-55.6 (4.7)	-51.0 (7.0)	-53.0 (5.4)
Absolute change in POx from baseline, µmol/L[e]	-5.0 (1.3)	-7.3 (1.5)	-7.1 (1.6)	-6.3 (1.8)	-6.9 (1.6)
In POx analysis set[e,f]	-6.5 (1.6)	-9.5 (1.7)	-9.5 (1.8)	-9.0 (1.9)	-9.2 (1.8)
Change from baseline in eGFR, mL/min/1.73m^2[g]	-0.3 (3.8)	-1.5 (4.4)	-8.9 (3.6)	-3.2 (4.8)	-2.0 (4.7)

Abbreviations: BSA = body surface area; eGFR = estimated glomerular filtration rate; LLOQ = lower limit of quantitation; 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 are mean (SEM) unless otherwise noted.
[b]One mmol/mmol = 0.796 mg/mg; 1 mmol/mmol = 1,000 mmol/mol.
[c]Age-dependent ULN.
[d]In patients with valid 24h UOx measurements; N=2 at month 6, N=4 at month 12, N=2 at month 18; N=3 at month 24, and N=4 at month 30.
[e]ULN = 12.11 µmol/L for POx, as determined based on data from healthy adults.
[f]In patients with baseline POx ≥1.5×LLOQ (5.55 µmol/L [N=13]; values below LLOQ were assigned a value of 5.55 µmol/L)
[g]eGFR (mL/min/1.73m^2) was calculated based on the Schwartz Bedside formula for patients ≥12 months; N=16 at month 6, N=16 at month 12, N=16 at month 18, N=16 at month 24, and N=15 at Month 30.

Plasma Oxalate

In the 6-month primary analysis period, POx reductions were observed in all patients with an LS mean reduction of 31.7% (95% CI, 23.9%-39.5%) or 5.2 µmol/L (95% CI, 4.2-6.2 µmol/L).[2] In the extension period, the mean POx decreased from 13.2 µmol/L at baseline to 6.3 µmol/L at month 30 (ULN = 12.11 µmol/L), with a mean (SEM) percent decrease of 42.5% (6.0%) from baseline. In patients with baseline POx ≥1.5 × LLOQ, the mean POx decreased from 15.6 µmol/L at baseline to 6.4 µmol/L at month 30, with a mean (SEM) percent decrease of 53.0% (5.4%) (**Table 4; Figure 2**).[1]

Figure 2. Mean (SEM) in POx Levels From Baseline Through Month 30.[1,a-d]



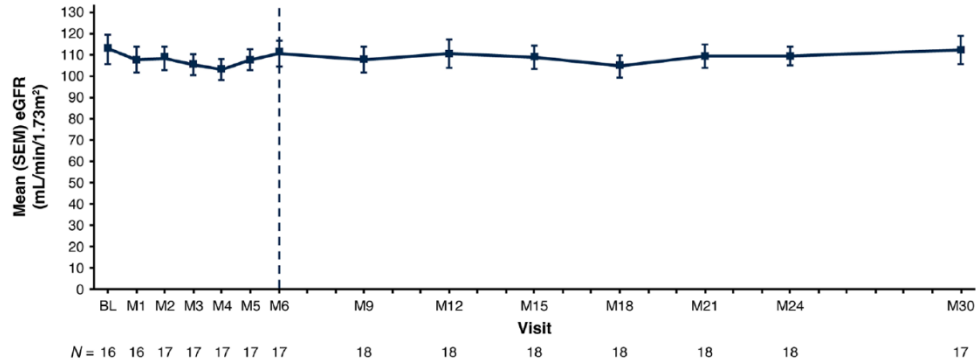
Abbreviations: BL = baseline; LLOQ = lower limit of quantitation; M = month; POx = plasma oxalate; SEM = standard error of the mean.
[a]BL represents the baseline value; mean of all assessments collected prior to the first dose of lumasiran.
[b]Vertical dashed line represents the end of the primary analysis period.
[c]Horizontal dashed line in panel B represents the ULN for POx of 12.11µmol/L (determined based on data from 75 healthy adults).
[d]LLOQ is 5.55 µmol/L. Reductions in POx below the LLOQ were conservatively imputed as 5.55 µmol/L.
From Frishberg et al.[1]

Kidney Function Measures

eGFR

Mean (SEM) eGFR remained stable from baseline through month 6 of the primary analysis period and through month 30 of the extension period (**Table 4; Figure 3**).[1,2] The mean (SEM) was 112.8 (6.9) ml/min/1.73m^2 at baseline and 112.5 (6.7) ml/min/1.73m^2 at month 30.[1]

Figure 3. Mean (SEM) eGFR from Baseline Through Month 30.[1,a-e]

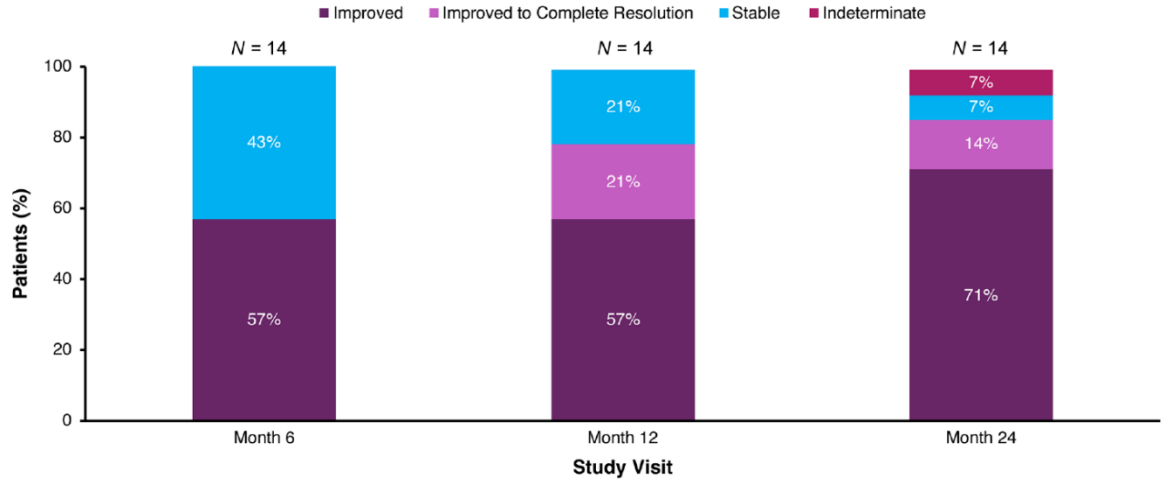


Abbreviations: BL = baseline; eGFR = estimated glomerular filtration rate; M = month; SEM = standard error of the mean.
[a]BL value was the last non-missing value collected prior to the first dose of lumasiran.
[b]Non-quarterly visits from the extension period are not displayed.
[c]Vertical dashed line represents the end of the primary analysis period.
[d]eGFR was calculated in patients ≥12 months old at assessment, based on the Schwartz Bedside formula.
[e]eGFR was not calculated for 2 patients, as their age at baseline was <12 months during that time point.
From Frishberg et al.[1]

Nephrocalcinosis

Change in nephrocalcinosis grade was assessed as an exploratory endpoint. Nephrocalcinosis was present in 14 out of 18 patients at baseline. Among these 14 patients, nephrocalcinosis grade was indeterminate in 1 patient (7%), remained stable in 1 patient (7%), and improved in 12 patients (86%), of whom 2 patients (14%) improved to complete resolution. The 4 patients without nephrocalcinosis at baseline remained stable and without nephrocalcinosis at month 24 (**Figure 4**).[1]

Figure 4. Change in Medullary Nephrocalcinosis Grade in Patients with Nephrocalcinosis at Baseline.[1,a-e]



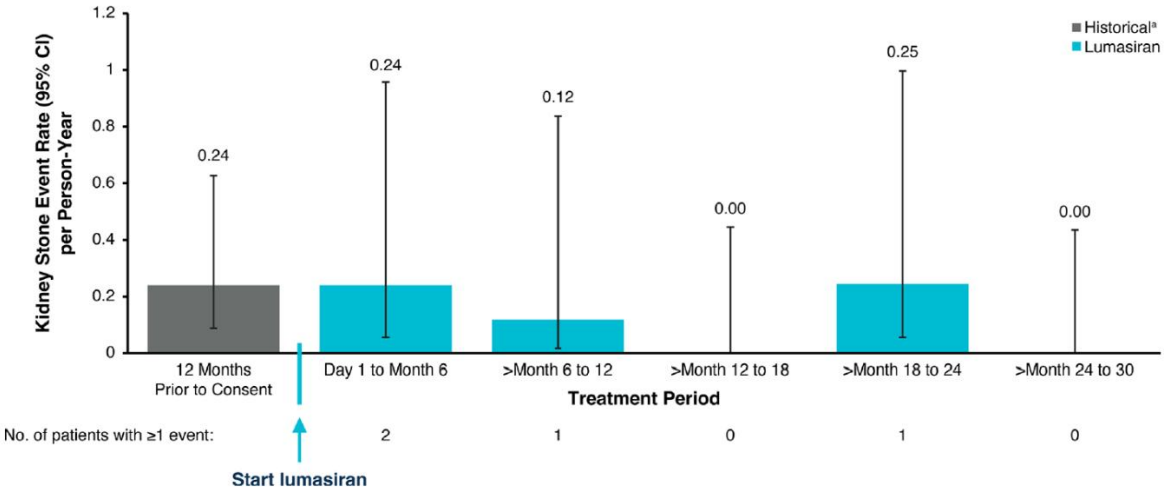
[a]Worsened = grade higher than baseline; stable = grade same as baseline; improved = grade lower than baseline; indeterminate = one kidney improved and the other kidney worsened.
[b]There were no patients with worsening nephrocalcinosis grade.
[c]Change in nephrocalcinosis grade was indeterminate in 1 patient.
[d]The 4 patients without nephrocalcinosis at baseline, who remained stable and without nephrocalcinosis at month 24, are not depicted.
[e]Renal ultrasound was performed at baseline and months 6, 12, and 24, but not month 30.
From Frishberg et al.[1]

Kidney Stone Events

A kidney stone event 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] Historical KSE rates (patient reported) were ≤0.25/person-year through month 30 of lumasiran treatment (**Figure 5**).[1]

Figure 5. Kidney Stone Event Rates from Historical Recall Through Month 30.[1,a-b]



Abbreviations: CI = confidence interval.
[a]Historical group: patient-reported history of kidney stone events; annualized rate was not calculated for patients age <6 months.
[b]Rate is calculated as total number of kidney stone events divided by total person-years during respective period. The 95% CI for the event rate was obtained using a generalized linear model for a Poisson distribution unless the rate was 0, in which case the upper bound of the 95% CI was calculated using the exact Poisson method.
From Frishberg et al.[1]

SAFETY RESULTS

The safety profile of lumasiran was evaluated in the 6-month primary analysis and at month 30 of the extension period, with a total median (range) exposure to lumasiran of 32.6 (27.5-35.3) months, being presented in **Table 5**. Five patients (28%) experienced lumasiran-related AEs: ISRs, transient blood bilirubin increase, and headache. The majority of the lumasiran-related AEs were mild, transient ISRs (3 patients [17%] experienced symptoms of erythema, discoloration, and pain at injection site). There were no clinically relevant changes in laboratory measures, vital signs, or electrocardiograms related to lumasiran. At baseline, no patients tested positive for anti-drug antibodies. Three patients (17%) developed transient, low-titer (1:50) anti-drug antibodies with no observed impact on safety or efficacy.[1]

Table 5. Lumasiran Safety Profile.[1]

Event, n (%)	All Lumasiran Treated (N=18)
AEs	18 (100)
Treatment-related AEs[a]	5 (28)
AEs leading to treatment discontinuation	0
AEs leading to study withdrawal	0
Serious AEs	1 (6)[b]
Severe AEs	0
Death	0

Abbreviations: AE = adverse event.
[a]Treatment-related AEs include ISRs, transient blood bilirubin increase, and headache.
[b]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.

ABBREVIATIONS

AE = adverse event; 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; ISR = injection site reaction; KSE = kidney stone event; LLOQ = lower limit of quantitation; LS = least-squares; M = missense; N = nonsense; PH1 = primary hyperoxaluria type 1; POx = plasma oxalate; PR = pyridoxine-responsive; q3M = every 3 months; qM = monthly; SEM = standard error of the mean; ULN = upper limit of normal; UOx = urinary oxalate; UOx:Cr = urinary oxalate:creatinine ratio.

Updated 2 October 2024

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