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 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 the end of the study at month 60, treatment with lumasiran resulted in a LS mean reduction of 74% from baseline.[3]
- Secondary endpoints evaluated in the primary analysis and extension periods included the change from baseline in additional measures of UOx excretion, POx, and eGFR.[3]
- Change in nephrocalcinosis grade and kidney stone event was assessed as an exploratory endpoint.[3]
- At month 60, 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.[3]

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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 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.[2,4]

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**.[2,4]

Table 2. ILLUMINATE-B Inclusion and Exclusion Criteria.[2,4]

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**.[1,5]

Table 3. Baseline Demographics and Disease Characteristics.[1,5]

Baseline Characteristic	Initial Weight Group			All Treated (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)
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.Phe152Ile). M and N were defined based on publication by Mandrile et al.[6]

[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.

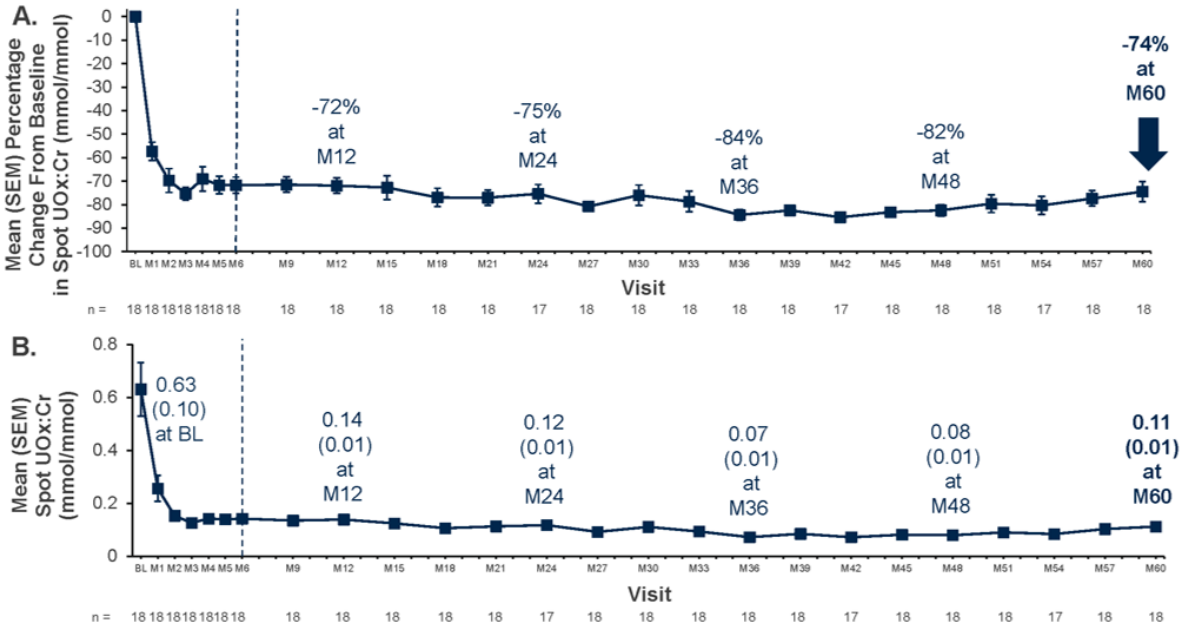
EFFICACY RESULTS

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. At month 60, the mean spot UOx:Cr decreased from 0.63 mmol/mmol at baseline to 0.11 mmol/mmol, with a mean percent reduction of 74% from baseline (**Figure 1**).[3]

Figure 1. Change in Spot UOx:Cr From Baseline Through Month 60.[3]



Abbreviations: BL = baseline; M = month; SEM = standard error of the mean; UOx:Cr = urinary oxalate:creatinine ratio.
Footnotes: The baseline value represents the mean of all assessments collected prior to the first dose of lumasiran; 1 mmol/mmol = 0.796 mg/mg; 1 mmol/mmol = 1000 mmol/mol. Labels on graph show mean (SEM) at baseline and at 12-month intervals. End of the primary analysis period is represented by the vertical dashed line; end-of-study appears in bold.
From Frishberg et al.[3]

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]1 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]

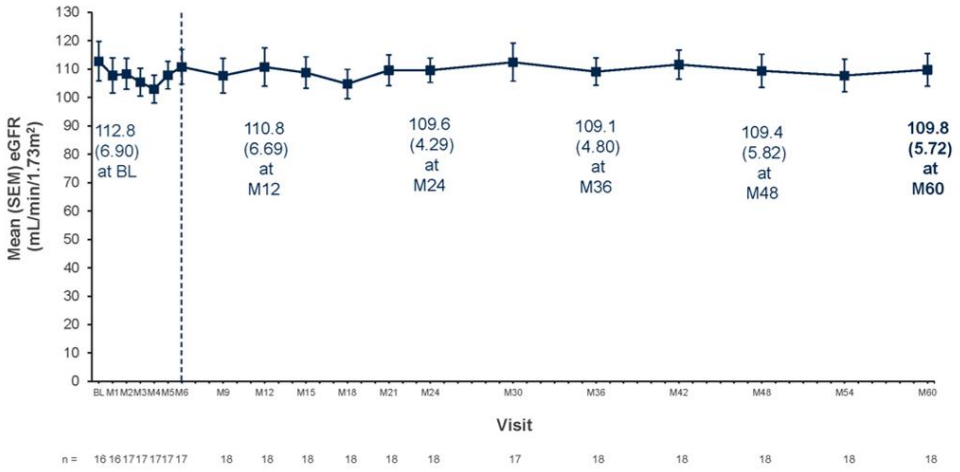
At month 60, the mean POx decreased from 13.2 µmol/L at baseline (ULN = 12.11 µmol/L) to 8.2 µmol/L, with a mean percent reduction of 25% from baseline.[3]

Kidney Related Outcomes

eGFR

Mean (SEM) eGFR remained stable from baseline through month 60 (**Figure 2**).[2,3] The mean (SEM) eGFR was 112.8 (6.9) ml/min/1.73m^2 at baseline and 109.8 (5.72) ml/min/1.73m^2 at month 60. In a post-hoc analysis, the annual change in mean (SEM) eGFR over 60 months was +0.26 (0.8) mL/min/1.73m^2 per year.[3]

Figure 2. Mean (SEM) eGFR from Baseline Through Month 60.[3]



Abbreviations: BL = baseline; eGFR = estimated glomerular filtration rate; M = month; SEM = standard error of the mean.
Footnotes: eGFR is calculated based on the Schwartz Bedside formula in patients ≥12 months of age at the time of the assessment. Baseline values are not available for 2 patients who were <12 months of age at that time point.
From Frishberg et al.[3]

Nephrocalcinosis

Change in nephrocalcinosis grade was assessed as an exploratory endpoint. Medullary nephrocalcinosis was assessed by ultrasound by a single central radiologist and graded per kidney on a scale of 0 to 3, with 0 indicating absence of nephrocalcinosis and higher grades indicating greater severity. Changes in the grade of nephrocalcinosis were grouped into 4 categories of overall change: no change, improving, worsening, and indeterminate (1 kidney improving and 1 worsening).[2] In a post-hoc analysis, nephrocalcinosis was present in 14 out of 18 patients at baseline. Among these 14 patients, nephrocalcinosis grade was indeterminate in 1 patient (7.1%), had no change in 1 patient (7.1%), and total improved (comprised improved and resolved grade) in 12 patients (86%) at 60 months. Of those who improved (defined as grade lower than baseline and considered unilateral improvement if one side improved and other side did not change), 10 patients (71.4%) improved to a bilateral grade of 0 in both kidneys. The 4 patients without nephrocalcinosis at baseline remained without nephrocalcinosis at month 60.[3]

Kidney Stone Events

Changes in kidney stone events were evaluated as an exploratory endpoint. 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] KSE rates were 0.11/person-year (95% CI, 0.06-0.21) through month 60 of lumasiran treatment. Overall, 9 KSEs in 4 patients were reported, and all events were mild or moderate in severity. Fourteen patients (77.8%) had no KSEs during the study.[3]

SAFETY RESULTS

The total median (range) exposure to lumasiran was 55.5 (54.5-56.1) months. A summary of the safety results from ILLUMINATE-B is 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%]; symptoms included erythema, discoloration, pain at injection site, and urticaria). There were no clinically relevant changes in laboratory measures, vital signs, or electrocardiograms related to lumasiran.[3] 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 in ILLUMINATE-B.[3]

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	2 (11)[b]
Severe treatment-related AEs	0
Death	0

Abbreviations: AE = adverse event; ISR = injection site reaction.

[a]Treatment-related AEs included 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. One patient had a serious AE of ear pain and ear hemorrhage during the extension period. AEs were considered unrelated to lumasiran by the investigator, and lumasiran dosing was not changed in both patients.

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.

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