Lumasiran: ILLUMINATE-A Study Overview

The following information is provided in response to your unsolicited inquiry. It is intended to provide you with a review of the available scientific literature and to assist you in forming your own conclusions in order to make healthcare decisions. This document is not for further dissemination or publication without authorization.

The full Prescribing Information for OXLUMO® (lumasiran) is provided here. Alnylam Pharmaceuticals does not recommend the use of its products in any manner that is inconsistent with the approved Prescribing Information. This resource may contain information that is not in the approved Prescribing Information.

If you are seeking additional scientific information related to Alnylam medicines, you may visit the Alnylam US Medical Affairs website at RNAiScience.com.

SUMMARY

- ILLUMINATE-A was a phase 3, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of lumasiran in adults and children ≥6 years old with PH1 and an eGFR ≥30 mL/min/1.73m^2. After the 6-month double-blind treatment period, all patients received lumasiran in an optional ongoing 54-month OLE.[1]
- The study met the primary endpoint of percent change from baseline in 24-hr UOx excretion corrected for BSA at 6 months. The LS mean percent change from baseline in 24-hr UOx in the lumasiran group was -65.4% compared with -11.8% in the placebo group, resulting in a between-group LS mean difference of -53.5% (95% CI: -62.3 to -44.8; P<0.001).[1] Treatment with lumasiran for up to 36 months resulted in sustained UOx reduction.[2]
- The study met all secondary endpoints that were tested hierarchically, including a significant reduction in POx levels in patients treated with lumasiran compared to placebo at 6 months.[1]
- At 36 months of the study, 36 patients (92%) experienced an AE. The most common treatment-related AEs were ISRs, which occurred in 19 patients (49%) and were mild in severity. 4 patients (10%) experienced a serious AE and 2 patients (5%) experienced a severe AE, none of which were considered related to lumasiran.[2]

INDEX

STUDY DESIGN

ILLUMINATE-A was a phase 3, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of lumasiran in adults and children ≥6 years old with PH1. Patients were randomized (2:1) to receive subcutaneous injections of lumasiran 3 mg/kg (N=26) or placebo (N=13) once monthly for 3 loading doses, followed by maintenance doses once every 3 months beginning 1 month after the last loading dose. The primary endpoint was the percent change from baseline in 24-hr UOx excretion corrected for BSA at 6 months (average of visits from month 3 through 6). After the 6-month double-blind treatment period, all patients received lumasiran in an optional ongoing 54-month OLE.[1] The inclusion and exclusion criteria for ILLUMINATE-A are presented in **Table 1**.[1,3]

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

Inclusion Criteria	Exclusion Criteria
• Age ≥6 years old • Diagnosis of PH1 confirmed by genetic analysis • eGFR ≥30 mL/min/1.73 m^2 • Mean UOx ≥0.7 mmol/24 hr/1.73 m^2 • For patients taking pyridoxine (vitamin B6) for treatment of PH1, regimen required to have been stable for at least 90 days before randomization and willing to remain on regimen for 12 months from first study drug administration	• 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; hr = hour; PH1 = primary hyperoxaluria type 1; UOx = urinary oxalate.

PATIENT DEMOGRAPHICS & BASELINE CHARACTERISTICS

Baseline characteristics were generally comparable between the lumasiran and placebo arms, as shown in **Table 2**.[1]

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

Baseline Characteristic[a]	Lumasiran (N=26)	Placebo (N=13)	Overall (N=39)
Median age (range), years	16.5 (6-47)	11.0 (6-60)	14.0 (6-60)
Age category, n (%)			
6 to <18 years	14 (54)	8 (62)	22 (56)
18 to <65 years	12 (46)	5 (38)	17 (44)
Female sex, n (%)	8 (31)	5 (38)	13 (33)
Race, n (%)			
Asian	3 (12)	3 (23)	6 (15)
White	21 (81)	9 (69)	30 (77)
Other[b]	2 (8)	1 (8)	3 (8)
Geographic region, n (%)			
Europe	10 (38)	8 (62)	18 (46)
Middle East	5 (19)	3 (23)	8 (21)
North America	11 (42)	2 (15)	13 (33)
Pyridoxine (vitamin B6) use, n (%)	13 (50)	9 (69)	22 (56)
24-hr UOx excretion, mmol/24 hr/1.73 $m^{2,c}$	1.84 (0.60)	1.79 (0.68)	1.82 (0.62)
POx level, µmol/L[d]	14.8 (7.6)	15.5 (7.3)	15.0 (7.4)
Kidney function measures			
Mean eGFR (SD), mL/min/1.73 $m^{2,e}$	83.0 (25.5)	78.9 (26.8)	81.6 (25.7)
eGFR category, n (%)			
≥90 mL/min/1.73m^2	9 (35)	4 (31)	13 (33)
60 to <90 mL/min/1.73m^2	13 (50)	6 (46)	19 (49)
30 to <60 mL/min/1.73m^2	4 (15)	3 (23)	7 (18)

Abbreviations: eGFR = estimated glomerular filtration rate; hr = hour; POx = plasma oxalate; SD = standard deviation; ULN = upper limit of the normal; UOx = urinary oxalate.

[a]Values presented as mean (SD) unless otherwise indicated

[b]Included 1 patient in the placebo group who reported more than one race and 2 patients in the lumasiran group who reported "other".

[c]The baseline value is the median of the values from all valid 24-hr urine samples obtained before the first dose of lumasiran or placebo. The ULN range for 24-hr urinary oxalate is 0.514 mmol/24 hr/1.73 m^2 of BSA. To convert values to mg/24 hr/1.73m^2, multiply by 90.

[d]The ULN range is 12.11 µmol/L. The POx analysis set included 23 patients in the lumasiran group and 10 patients in the placebo group.

[e]eGFR was calculated with the Modification of Diet in Renal Disease formula for patients 18 years of age and older and with the Schwartz Bedside Formula for patients 6 to less than 18 years of age.

EFFICACY RESULTS

A summary of the efficacy results at month 6 of the double-blind treatment period is presented below in **Table 3**.[1]

Table 3. Change from Baseline to month 6 in the Primary Endpoint and Hierarchically Tested Secondary Endpoints at Month 6.[1]

Endpoint	Lumasiran (N=26)	Placebo (N=13)	Difference, Lumasiran–Placebo	*P*-value
Primary endpoint				
Percent change in 24-hr UOx excretion (95% CI)[a,b]	-65.4 (-71.3 to -59.5)	-11.8 (-19.5 to -4.1)	-53.5 (-62.3 to -44.8)	<0.001
Secondary endpoints				
Absolute change in 24-hr UOx corrected for BSA (95% CI), mmol/24 hr/1.73 m^{2}[a,b]	-1.24 (-1.37 to -1.12)	-0.27 (-0.44 to -0.10)	-0.98 (-1.18 to -0.77)	<0.001
Percent change in 24-hr UOx:Cr ratio (95% CI)[b]	-62.5 (-70.7 to -54.4)	-10.8 (-21.6 to 0.0)	-51.8 (-64.3 to -39.3)	<0.001
Percent change in POx (95% CI)[b,c]	-39.8 (-45.8 to -33.8)	-0.3 (-9.1 to 8.5)	-39.5 (-50.1 to -28.9)	<0.001
Percentage of patients with 24-hr UOx excretion ≤1.5xULN at month 6 (95% CI)[a,d]	84 (64 to 95)	0 (0 to 25)	84 (55 to 94)	<0.001
Percentage of patients with 24-hr UOx excretion ≤ULN at month 6 (95% CI)[a,d]	52 (31 to 72)	0 (0 to 25)	52 (23 to 70)	0.001
Absolute change in POx (95% CI), µmol/L[b,d]	-7.5 (-9.0 to -5.9)	1.3 (-1.0 to 3.5)	-8.7 (-11.5 to -6.0)	<0.001

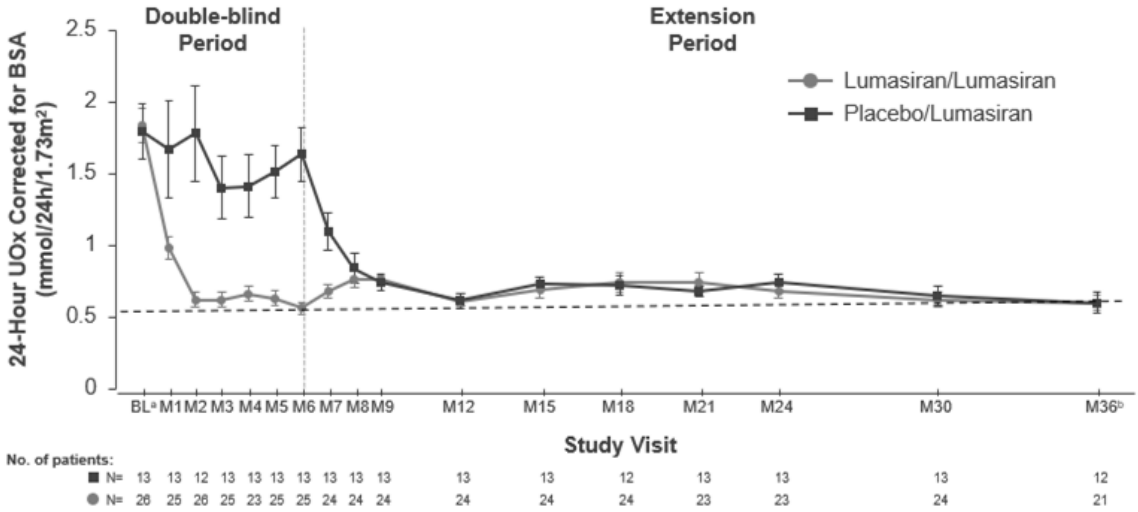
Abbreviations: BSA = body surface area; CI = confidence interval; POx = plasma oxalate; ULN = upper limit of the normal; UOx = urinary oxalate; UOx:Cr = urinary oxalate:creatinine.
[a]Measurements of urinary oxalate excretion were corrected for BSA.
[b]The change from baseline to month 6 was calculated as the mean change or mean percent change across month 3 through 6. The least squares mean, between group difference in the least squares mean, 95% confidence intervals, and P-value for comparisons of lumasiran and placebo were derived with a mixed model for repeated measures. A difference of less than 0 represents a favorable outcome for lumasiran.
[c]The plasma oxalate analysis set included 23 patients in the lumasiran group and 10 patients in the placebo group.
[d]Data were available for 25 patients in the lumasiran group and 13 patients in the placebo group. The ULN range is 0.514 mmol/24 hr/1.73 m^{2}. The confidence interval is a Clopper-Pearson exact confidence interval.

Urinary Oxalate

In the 6-month DB period, the LS mean percent change from baseline in 24-hr UOx in the lumasiran group was -65.4% (95% CI: -71.3 to -59.5) compared with -11.8% (95% CI: -19.5 to -4.1) in the placebo group (**Figure 1**), resulting in a between-group LS mean difference of -53.5% (95% CI: -62.3 to -44.8; P<0.001).[1]

In the extension period, patients had sustained reductions in 24-hr UOx, corrected for BSA (**Figure 1**). Patients that were initially randomized to lumasiran (lumasiran/lumasiran group) had a sustained reduction in 24-hr UOx through month 36, with a mean reduction from baseline of 63%. Patients that were initially randomized to placebo who crossed over to lumasiran (placebo/lumasiran group) demonstrated a similar time course and magnitude of 24-hr UOx reduction, with a mean reduction of 58% after 30 months of treatment.[2]

Figure 1. Mean 24-Hr UOx Through Month 36.[2]



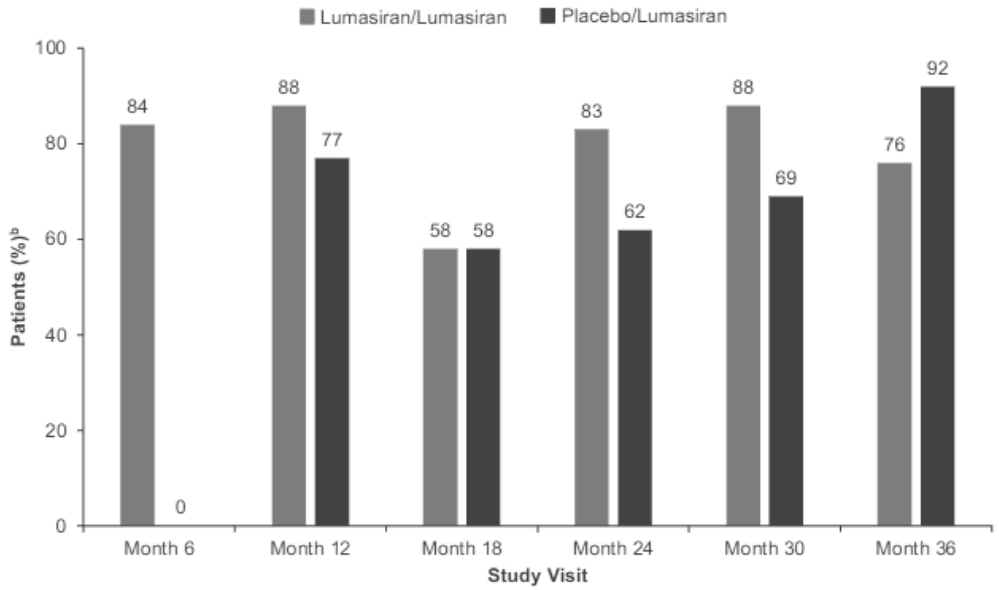
Adapted from Salant et al.[2]
Abbreviations: BL = baseline; M = month; SEM = standard error of the mean; ULN = upper limit of the normal; UOx = urinary oxalate.
Footnotes: Dotted line represents the ULN of 0.514 mmol/24 hr/1.73 m^2 (1 mmol/24 hr/1.73 m^2 = 90 mg/24 hr/1.73 m2) for 24-hr UOx excretion.
[a]Baseline is the median of all valid 24-hr urine assessments collected prior to the first dose date/time of study drug (lumasiran or placebo) without any nonprotocol-related sample issues.

Proportion of Patients with 24-UOx Excretion ≤1.5xULN

In the 6-month DB period, 84% of lumasiran-treated patients achieved near normalization or normalization (≤ 1.5xULN) of 24-hr UOx excretion when corrected for BSA, compared to 0% of placebo-treated patients.[1]

In the extension period, 76% of lumasiran/lumasiran-treated patients sustained near normalization or normalization of 24-hr UOx at month 36. After 30 months of treatment, 92% of the placebo/lumasiran crossover patients achieved near normalization or normalization of 24-hr UOx (**Figure 2**).[2]

Figure 2. Patients with 24-hr UOx Level ≤1.5xULN Corrected for BSA Through Month 36.[2,a]



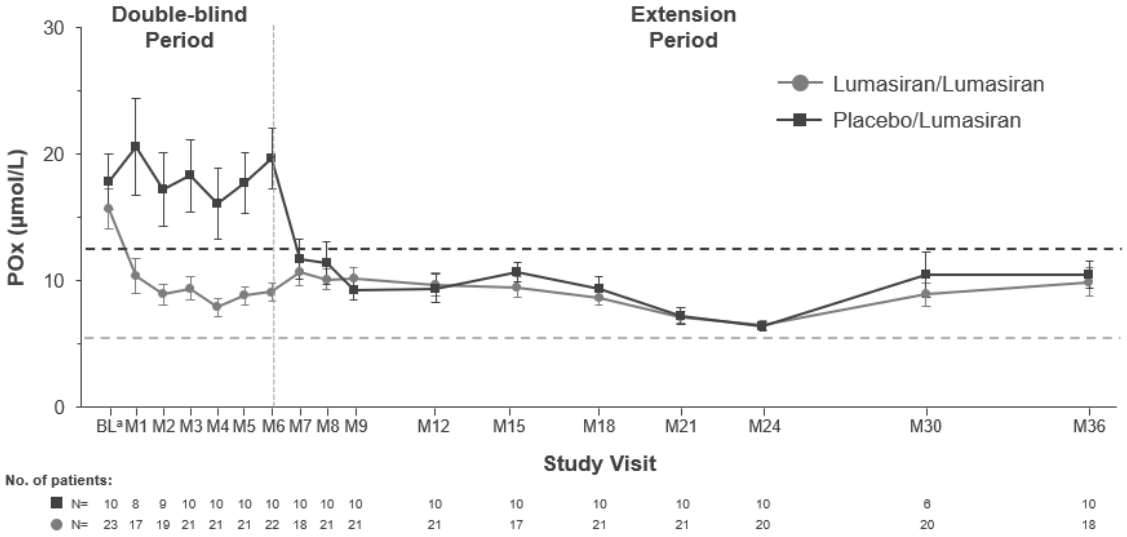
Adapted from Saland et al.[2]
Abbreviations: BSA = body surface area; ULN = upper limit of the normal; UOx = urinary oxalate.
[a]ULN is 0.514 mmol/24 hr/1.73m^2 = 45 mg/24 hr/1.73m^2 (1 mmol/24 hr/1.73m^2 = 90 mg/24 hr/1.73m^2).
[b]Percentages are based upon the number of patients having 24-hr UOx corrected for BSA data at the visit.

Plasma Oxalate

In the 6-month DB period, the decline in POx levels was significantly greater in the lumasiran treated group when compared with the placebo group. Among the 33 patients with a baseline POx level of at least 1.5× LLOQ, the LS mean difference in the percent change in POx levels from baseline to month 6 was -39.5% (95% CI, -50.1 to -28.9; P<0.001).[1]

In the extension period, patients in the lumasiran/lumasiran group maintained a reduction in POx through month 36 (mean percent reduction of 36% at month 36 compared to baseline). Patients in the placebo/lumasiran group demonstrated a similar time course and magnitude of POx reduction. After 30 months of treatment, POx mean percent reduction for placebo/lumasiran patients was 35% (**Figure 3**).[2]

Figure 3. Mean (SEM) POx Levels Through Month 36.[2]



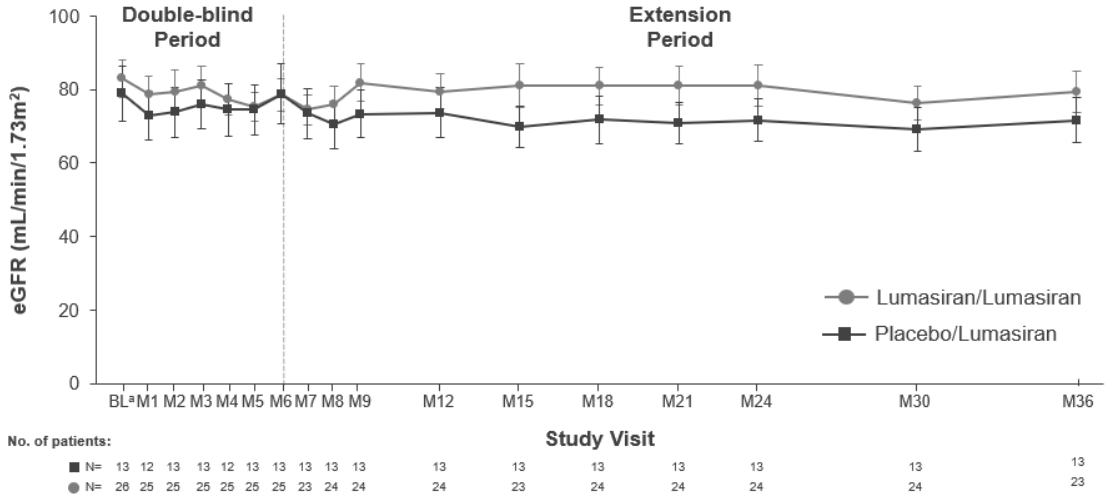
Adapted from Saland et al.[2]
Abbreviations: BL = baseline; DB = double-blind; LLOQ = lower limit of quantitation; M = month; POx = plasma oxalate; SEM = standard error of mean.
Dark gray dotted line represents the ULN of 12.11 µmol/L for POx. Light gray dotted line represents the LLOQ of the POx assay at 5.55 µmol/L; values below the LLOQ were assigned a value of 5.55 µmol/L.
[a]Baseline is the mean of all measurements prior to the first dose date/time of study drug (lumasiran or placebo) in the 6-month DB period.

Kidney Function Measures

eGFR

Through month 36, eGFR remained stable with lumasiran treatment in both cohorts (**Figure 4**).[2]

Figure 4. Mean (SEM) eGFR Through Month 36.[2]

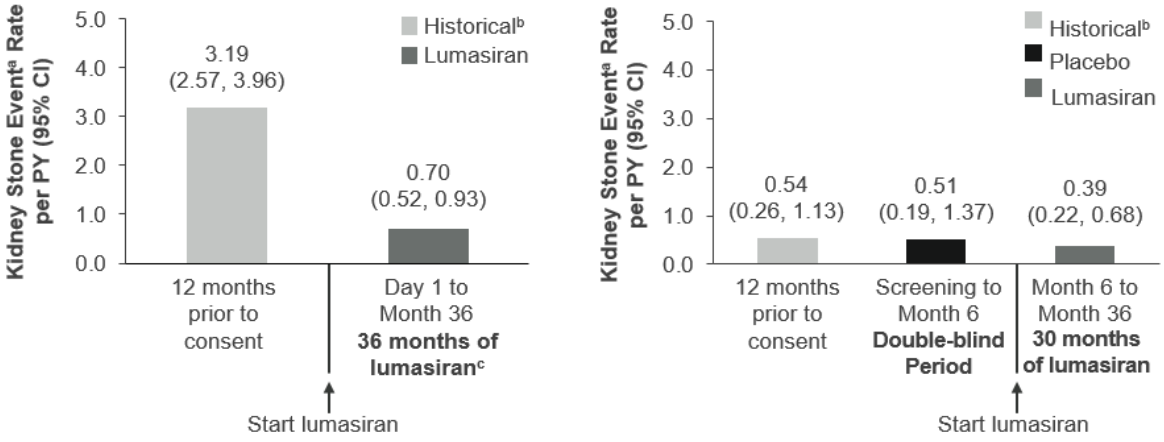


Adapted from Saland et al.[2]
Abbreviations: BL = baseline; DB = double-blind; eGFR = estimated glomerular filtration rate; M = month; SEM = standard error of the mean.
[a]Baseline is the last assessment prior to the first dose of study drug (lumasiran or placebo) in the 6-month DB period.

Kidney Stone Events

In the lumasiran/lumasiran group, kidney stone event rates decreased from 3.19/person-year during the patient-reported historical recall period to 0.70/person-year with 36 months of lumasiran treatment. In the placebo/lumasiran cohort, kidney stone event rates decreased from 0.54/person-year during the patient reported historical recall period to 0.39/person-year with 30 months of lumasiran treatment (**Figure 5**).[2]

Figure 5. Kidney Stone Event Rates.[2]



Adapted from Saland et al.[2]
Abbreviations: CI = confidence interval; DB = double-blind; PY = person-year.
[a]A kidney stone event is defined as an event that includes at least one of the following: visit to healthcare provider because of a kidney stone, medication for renal colic, stone passage, or macroscopic hematuria due to a kidney stone.
[b]Patient-reported history of kidney stone events.
[c]Kidney stone event rate (95% CI) was 1.09 (0.63, 1.88) per PY during the DB period (from day 1 to month 6).

SAFETY RESULTS

The safety profile of treatment with lumasiran for up to 36 months is summarized in **Table 4** and is consistent with the DB period. The majority of AEs were mild in severity. The most common treatment-related AEs were ISRs, all of which were mild in severity.[2]

Four patients (10%) experienced a serious AE (abdominal pain [N=2], dysuria [N=1], nephrectomy [N=1], post-procedural complication [N=1], and urosepsis [N=1]). Two patients (5%) experienced a severe AE (postprocedural complication [N=1] and urosepsis [N=1]). One patient (3%) discontinued lumasiran treatment due to fatigue and disturbance in attention. The serious AEs, severe AEs, and treatment discontinuations reported during the study were considered not related to lumasiran by the investigator.[2]

Table 4. Safety Profile of Lumasiran Through Month 36.[2,a]

Event, n (%)	Placebo/ Lumasiran (N=13)	Lumasiran/ Lumasiran (N=26)	All Lumasiran (N=39)
Any AE	12 (92)	24 (92)	36 (92)
Serious AE	1 (8)	3 (12)	4 (10)
Severe AE	0	2 (8)	2 (5)
AE leading to discontinuation of study treatment	0	1 (4)	1 (3)
AEs occurring in ≥15% of patients[b]			
ISR[c]	6 (46)	13 (50)	19 (49)
Abdominal pain	1 (8)	7 (27)	8 (21)
Headache	2 (15)	5 (19)	7 (18)
COVID-19 infection	3 (23)	3 (12)	6 (15)
Death	0	0	0

Abbreviations: AE = adverse event; DB = double-blind; ISR = injection site reaction.
[a]Placebo/lumasiran includes patients who received placebo during the 6-month DB period and switched to lumasiran during the extension period (up to 30 months of lumasiran exposure). Lumasiran/lumasiran includes patients who received lumasiran during the 6-month DB period (up to 36 months of lumasiran exposure). All lumasiran includes all patients who received any lumasiran during the study.
[b]AEs occurred during lumasiran treatment. All terms are MedDRA preferred terms except for ISRs.
[c]Defined as AEs that were mapped to the high-level term "Injection Site Reactions" or events reported by the sites as ISRs.

ABBREVIATIONS

AE = adverse event; BL = baseline; BSA = body surface area; CI = confidence interval; DB = double-blind; eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hr = hour; ISR = injection site reaction; LLOQ = lower limit of quantitation; LS = least squares; M = month; MedDRA = Medical Dictionary for Regulatory Activities; OLE = open-label extension; PH1 = primary hyperoxaluria type 1; POx = plasma oxalate; PY = person-year; SD = standard deviation; SEM = standard error of the mean; ULN = upper limit of the normal; UOx = urinary oxalate; UOx:Cr = urinary oxalate:creatinine.

Updated 26 June 2024

REFERENCES

1. Garrelfs SF, Frishberg Y, Hulton SA, et al. Lumasiran, an RNAi Therapeutic for Primary Hyperoxaluria Type 1. *N Engl J Med*. 2021;384(13):1216-1226. doi:10.1056/NEJMoa2021712
2. Saland JM, Lieske JC, Groothoff JW, et al. Efficacy and safety of lumasiran in patients with primary hyperoxaluria type 1: 36-month analysis of the ILLUMINATE-A trial. Presented at: National Kidney Foundation (NKF) Spring Clinical Meeting; April 11-15, 2023; Austin, TX, USA.
3. Protocol for: Garrelfs SF, Frishberg Y, Hulton SA, et al. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. *N Engl J Med*. 2021;384(13):1216-1226. doi:10.1056/NEJMoa2021712