Lumasiran: ILLUMINATE-A Study Overview

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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 54-month OLE.[1]
- The study met the primary endpoint of LS mean percent change from baseline in 24-hr UOx excretion corrected for BSA at 6 months (-65.4% in the lumasiran group 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] At the end of the study, the mean percent change from baseline was -56% in the placebo/lumasiran group at Month 54 and -54% in the lumasiran/lumasiran group at Month 60.[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 Month 60, 37 of the 39 patients (95%) experienced an AE. The most common lumasiran-related AEs were ISRs, which occurred in 14 patients (36%); all were transient and mild in severity. The serious AEs (N=6, 15%), severe AEs (N=4, 10%) and treatment discontinuations (N=1, 3%) reported during the study were considered not related to lumasiran by the investigator.[2]

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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 54-month OLE.[1] Of the 39 patients enrolled, 13 of the 13 in the placebo/lumasiran group and 24 of the 26 in the lumasiran/lumasiran group completed treatment in the 54-month OLE. Baseline is defined as the period prior to the first lumasiran dose; hence, the lumasiran/lumasiran group has 6 more months of on-lumasiran follow-up (up to 36 months of lumasiran

exposure) than the placebo/lumasiran group (up to 30 months of lumasiran exposure).[2] The inclusion and exclusion criteria for ILLUMINATE-A are presented below 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/24hr/1.73m^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 are shown below in **Table 2**.[1,5]

Table 2. Baseline Demographics and Disease Characteristics.[1,5,a]

Baseline Characteristic[b]	Placebo (N=13)	Lumasiran (N=26)	Overall (N=39)
Median age (range), years	11.0 (6-60)	16.5 (6-47)	14.0 (6-60)
Mean age at informed consent (range), y	17.0 (6-60)	18.7 (6-47)	18.1 (6-60)
Age category, n (%)			
6 to <18 years	8 (62)	14 (54)	22 (56)
18 to <65 years	5 (38)	12 (46)	17 (44)
Female sex, n (%)	5 (38)	8 (31)	13 (33)
Race, n (%)			
Asian	3 (23)	3 (12)	6 (15)
White	9 (69)	21 (81)	30 (77)
Other[c]	1 (8)	2 (8)	3 (8)
Geographic region, n (%)			
Europe	8 (62)	10 (38)	18 (46)
Middle East	3 (23)	5 (19)	8 (21)
North America	2 (15)	11 (42)	13 (33)
Pyridoxine (vitamin B6) use, n (%)	9 (69)	13 (50)	22 (56)
24-hr UOx excretion, mean (SD), mmol/24hr/1.73$m^{2,d}$	1.79 (0.68)	1.84 (0.60)	1.82 (0.62)
POx level, mean (SD), µmol/L[e]	19.3 (9.5)	14.8 (7.6)	16.3 (8.4)
Kidney function measures			
eGFR, mean (SD), mL/min/1.73 $m^{2,f}$	78.8 (30.0)	83.0 (25.5)	81.6 (26.8)
eGFR category, n (%)			
≥90 mL/min/1.73m^2	4 (31)	9 (35)	13 (33)
60 to <90 mL/min/1.73m^2	6 (46)	13 (50)	19 (49)
30 to <60 mL/min/1.73m^2	3 (23)	4 (15)	7 (18)
Patients reporting history of KSEs, n (%)[g]			
Lifetime	10 (77)	23 (88)	33 (85)
12 months prior to consent	4 (31)	11 (42)	15 (38)
Genotype, n (%)[h]			
PR/*	6 (46)	11 (42)	17 (44)
M/M or M/N	4 (31)	6 (23)	10 (26)

N/N	3 (23)	9 (35)	12 (31)

Abbreviations: BSA = body surface area; eGFR = estimated glomerular filtration rate; hr = hour; KSE = kidney stone event; M = missense; MDRD = Modification of Diet in Renal Disease; N = nonsense; PH1 = primary hyperoxaluria type 1; POx = plasma oxalate; PR = pyridoxine-responsive; SD = standard deviation; ULN = upper limit of normal; UOx = urinary oxalate.
[a]Patients remained on background therapies, including hyperhydration, crystallization inhibitors, and/or pyridoxine therapy through Month 12 before adjustments were made to the regiment based on clinical discretion.
[b]Values presented as mean (SD) unless otherwise indicated.
[c]Included 1 patient in the placebo group who reported more than one race and 2 patients in the lumasiran group who reported "other."
[d]For the lumasiran/lumasiran group, baseline is the median of all valid 24-hr urine assessments obtained before the first dose of lumasiran without any non-protocol-related sample issues. For the placebo/lumasiran group, baseline is the median of all valid 24-hr urine assessments at Month 6 without any non-protocol-related sample issues (or, if the patient did not have 2 valid 24-hr urine pharmacodynamic assessments at Month 6, then the baseline was calculated using the latest 3 valid 24-hr urine pharmacodynamic collections obtained before the first dose of lumasiran). The ULN range for 24-hr urinary oxalate is 0.514 mmol/24hr/1.73m2 of BSA. To convert values to mg/24 hr/1.73m2, multiply by 90.
[e]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.
[f]eGFR was calculated with the MDRD formula for patients ≥18 years of age at screening and the Schwartz Bedside Formula for patients 6 to <18 years of age at screening.
[g]A KSE 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.
[h]PR was defined as NM_000030.3(AGXT):c.508G>A (p.Gly170Arg) or NM_000030.3(AGXT):c.454T>A (p.Phe152Ile). The asterisk (*) denotes any genotype of PR, M, or N.

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 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/24hr/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 ≤1.5×ULN 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; hr = hour; POx = plasma oxalate; ULN = upper limit of 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/24hr/1.73m^{2}. The confidence interval is a Clopper-Pearson exact confidence interval.

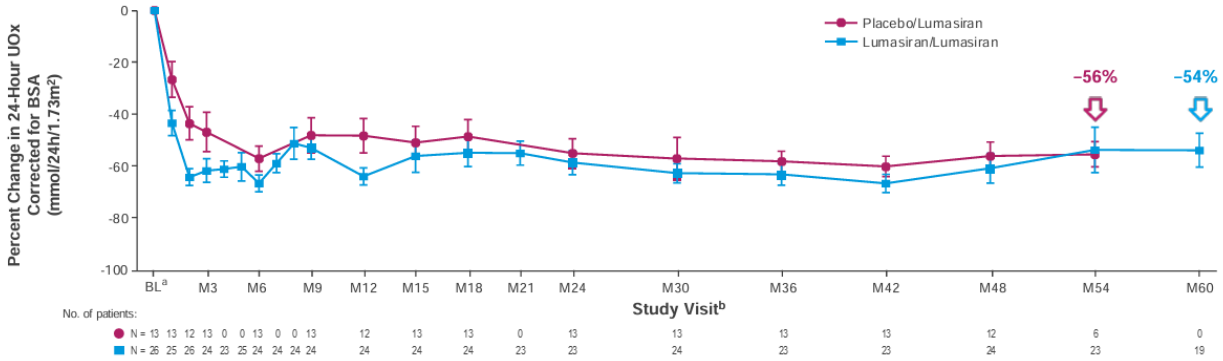
Urinary Oxalate

In the 6-month double-blind 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, 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. Patients in the lumasiran/lumasiran group had a sustained reduction in 24-hr UOx through Month 36, with a mean reduction from baseline of 63%. Patients in the 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.[4]

At the end of the study, the mean percent change from baseline in 24-hr UOx levels was -56% in the placebo/lumasiran group at Month 54 and -54% in the lumasiran/lumasiran group at Month 60 (**Figure 1**).[2]

Figure 1. Mean (SEM) Percent Change 24-Hour in UOx Levels Through Month 60.[2]



Abbreviations: BL = baseline; hr = hour; M = month; SEM = standard error of the mean; ULN = upper limit of normal; UOx = urinary oxalate.
[a]For the lumasiran/lumasiran group, baseline is the median of all valid 24-hr urine assessments obtained before the first dose of lumasiran without any non-protocol-related sample issues. For the placebo/lumasiran group, baseline is the median of all valid 24-hr urine assessments at Month 6 without any non-protocol-related sample issues (or, if the patient did not have 2 valid 24-hr urine pharmacodynamic assessments at Month 6, then the baseline was calculated using the latest 3 valid 24-hr urine pharmacodynamic collections obtained before the first dose of lumasiran).
From Saland et al.[2]

<u>Proportion of Patients with 24-Hour UOx Excretion ≤1.5×ULN</u>

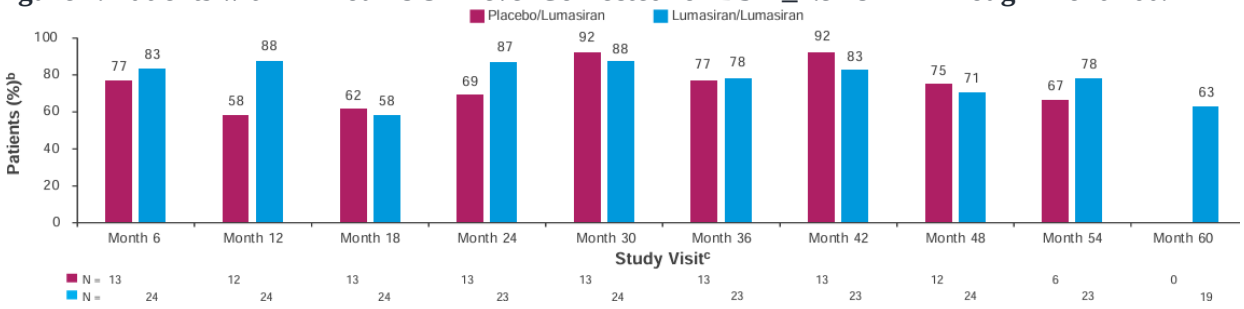
Beginning 2 months after lumasiran treatment initiation, ≥50% of patients in both the placebo/lumasiran and lumasiran/lumasiran group achieved 24-hr UOx excretion ≤1.5×ULN.[2]

In the 6-month double-blind period, 84% of lumasiran-treated patients achieved near normalization or normalization (≤ 1.5×ULN) of 24-hr UOx excretion when corrected for BSA, compared to 0% of placebo-treated patients (P<0.001).[1]

In the extension period, 76% of patients in the lumasiran/lumasiran group sustained near normalization or normalization of 24-hr UOx at Month 36. After 30 months of treatment, 92% patients in the placebo/lumasiran group achieved near normalization or normalization of 24-hr UOx.[4]

At the end of the study, the mean percent change from baseline in 24-hr UOx levels ≤1.5×ULN was 67% in the placebo/lumasiran group at Month 54 and 63% in the lumasiran/lumasiran group at Month 60 (**Figure 2**).[2]

Figure 2. Patients with 24-Hour UOx Level Corrected for BSA ≤1.5×ULN Through Month 60.[2,a]



Abbreviations: BSA = body surface area; hr = hour; ULN = upper limit of normal; UOx = urinary oxalate.
[a]ULN is 0.514 mmol/24hr/1.73m^2 = 45 mg/24hr/1.73m^2 (1 mmol/24hr/1.73m^2 = 90 mg/24hr/1.73m^2).
[b]Percentages are based upon the number of patients having 24-hr UOx corrected for BSA data at the visit.
[c]Visit is relative to the first dose of lumasiran (all-lumasiran-treated set).
From Saland et al.[2]

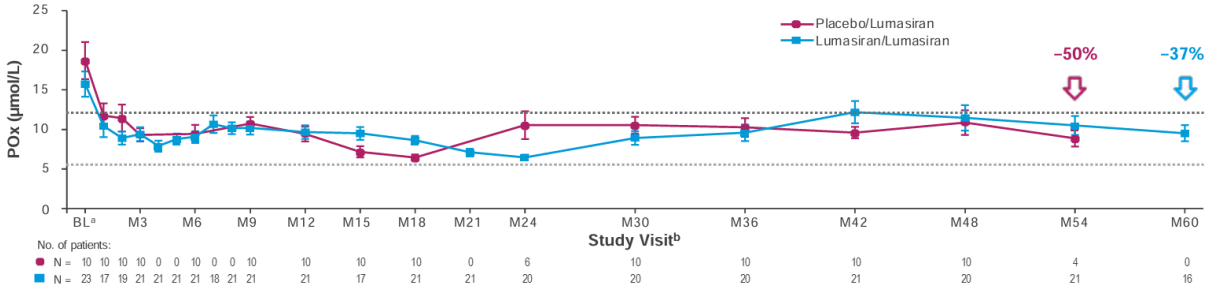
Plasma Oxalate

In the 6-month double-blind 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%.[4]

At the end of the study, the mean percent change from baseline in POx levels was -50% in the placebo/lumasiran group at Month 54 and -37% in the lumasiran/lumasiran group at Month 60 (**Figure 3**).[2]

Figure 3. Mean (SEM) POx Levels Through Month 60.[2]



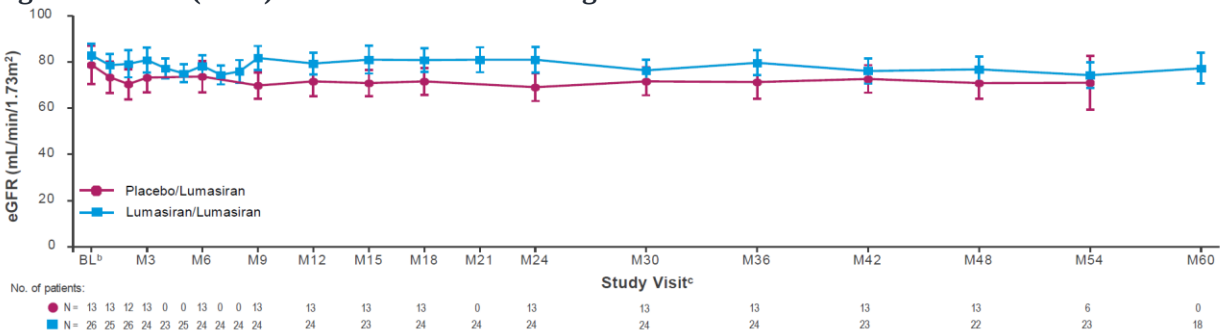
Abbreviations: BL = baseline; LLOQ = lower limit of quantitation; M = month; POx = plasma oxalate; SEM = standard error of mean; ULN = upper limit of normal.
Footnotes: Top gray dotted line represents the ULN of 12.11 µmol/L for POx. Bottom gray dotted line represents the LLOQ of the POx assay at 5.55 µmol/L; values below the LLOQ were assigned a value of 5.55 µmol/L.
[a]For the lumasiran/lumasiran group, baseline is defined as the mean of all measurements prior to the first dose of lumasiran. For the placebo/lumasiran group, baseline is the mean of the last 2 non-missing measurements prior to the first dose of lumasiran.
[b]Visit is relative to the first dose of lumasiran.
From Saland et al.[2]

Kidney Function Measures

eGFR

The mean eGFR remained stable through the end of the study among lumasiran treated patients (**Figure 4**). The mean (SEM) change from baseline was -12.86 (3.89) mL/min/1.73m^2 in the placebo/lumasiran group and -2.89 (2.75) mL/min/1.73m^2 in the lumasiran/lumasiran group. In the all-lumasiran-treated set, the mean annual rate of eGFR change per year at Month 48 was -1.19 mL/min/1.73m^2.[2]

Figure 4. Mean (SEM) eGFR Over Time During Lumasiran Treatment.[2]



Abbreviations: BL = baseline; eGFR = estimated glomerular filtration rate; M = month; MDRD = Modification of Diet in Renal Disease; SEM = standard error of the mean.
[a]eGFR was calculated with the MDRD formula for patients ≥18 years of age at screening and the Schwartz Bedside Formula for patients 6 to <18 years of age at screening.
[b]BL is the last assessment collected prior to the first dose date/time of lumasiran.
[c]Visit is relative to the first dose of lumasiran.
From Saland et al.[2]

Kidney Stone Events

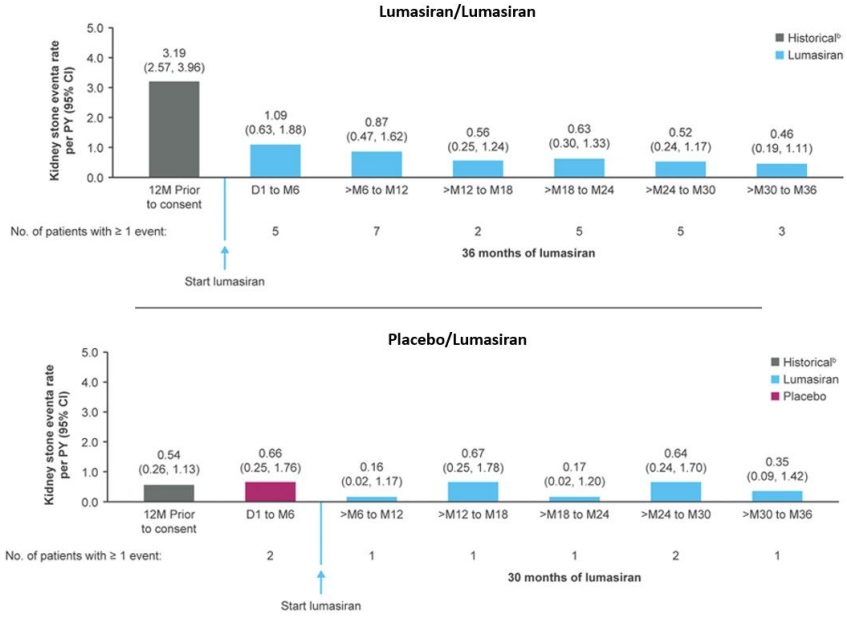
During the patient-reported 12-month historical recall period, KSE rates (95% CI) were 3.19 (2.57, 3.96) per PY in the lumasiran/lumasiran group and 0.54 (0.26, 1.13) per PY in the placebo/lumasiran group.[4]

In the all-lumasiran-treated set (i.e., all patients who received any amount of lumasiran), KSE rates (95% CI) decreased from 2.31 (1.88, 2.84) per PY during the patient-reported 12-month historical recall period to 0.60 (0.46, 0.77) per PY with 36 months of lumasiran treatment. KSE rates for the lumasiran/lumasiran group and placebo/lumasiran group are shown in intervals through Month 36 in **Figure 5**.[4]

KSE rates were 0.47 per PY with 60 months of lumasiran treatment in the lumasiran/lumasiran group and 0.54 per PY with 54 months of lumasiran treatment in the placebo/lumasiran group.[2]

During the final 6 months of lumasiran treatment, KSE rates were 0.09 per PY in the lumasiran/lumasiran group and 0.68 per PY in the placebo/lumasiran group. No KSEs occurred during lumasiran treatment in 13 of the 26 patients (50%) in the lumasiran/lumasiran group and in 8 of the 13 patients (62%) in the placebo/lumasiran group.[2]

Figure 5. Kidney Stone Events Through Month 36 of Lumasiran Treatment by Treatment Group.[4]



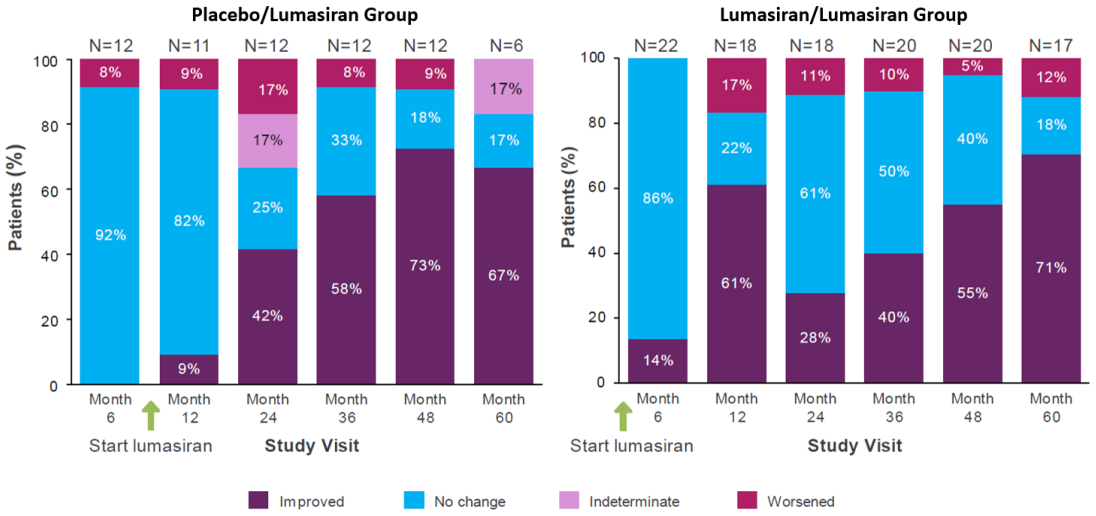
Abbreviations: CI = confidence interval; D = day; KSE = kidney stone event; M = month; PY = person-year.
[a]A KSE is defined as an event that includes at least one of the following: visit to healthcare provider because of a kidney stone, medication for renal colic, stone passage, or macroscopic hematuria due to a kidney stone.
[b]Patient-reported history of KSEs.
From Saland et al.[4]

Nephrocalcinosis

The degree of medullary nephrocalcinosis in each kidney was graded using a validated 4-point scale: stable (i.e., no change in either kidney), improving (i.e., both kidneys improving, or 1 kidney improving and 1 with no change), worsening (i.e., both kidneys worsening, or 1 kidney worsening and 1 with no change), or indeterminate (i.e., 1 kidney improving and 1 worsening).[2]

Medullary nephrocalcinosis generally remained stable or improved at Month 60, as shown in **Figure 6**. Among the 20 patients who had medullary nephrocalcinosis at baseline, medullary nephrocalcinosis grade improved in 16 patients (80%) at Month 60.[2]

Figure 6. Change From Baseline in Medullary Nephrocalcinosis During Lumasiran Treatment.[2]



From Saland et al.[2]

SAFETY RESULTS

The safety profile of treatment with lumasiran through Month 60 is summarized in **Table 4**. At Month 60, 37 of the 39 patients (95%) experienced an AE. The most common lumasiran-related AEs were ISRs, which occurred in 14 patients (36%); all were transient, mild in severity, and resolved without sequelae.[2]

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 60.[2,4]

Event, n (%)	Placebo (N=13)	Lumasiran (N=26)	Overall (N=39)
Any AE	12 (92)	25 (96)	37 (95)
AE related to study drug	6 (46)	13 (50)	19 (49)
Serious AE[a]	1 (8)	5 (19)	6 (15)
Severe AE[b]	0	4 (15)	4 (10)
AE leading to discontinuation of study treatment[c]	0	1 (4)	1 (3)
AEs occurring in ≥15% of patients[d]			
ISR[e]	5 (38)	9 (35)	14 (36)
Abdominal pain	1 (8)	8 (31)	9 (23)
COVID-19 infection	4 (31)	4 (15)	8 (21)
Headache	2 (15)	5 (19)	7 (18)
Nasopharyngitis	2 (15)	4 (15)	6 (15)
Death	0	0	0

Abbreviations: AE = adverse event; ISR = injection site reaction; MedDRA = Medical Dictionary for Regulatory Activities.
[a]Six patients (15%) experienced a serious AE (abdominal pain [N=2], dysuria [N=1], follicular lymphoma [N=1], postprocedural complication [N=1], postprocedural infection [N=1], renal impairment [N=1], urinary tract infection [N=1], and urosepsis [N=1]).
[b]Four patients (10%) experienced a severe AE (acute pyelonephritis [N=1], follicular lymphoma [N=1], postprocedural complication [N=1], postprocedural infection [N=1], urinary tract infection [N=1], and urosepsis [N=1]).
[c]One patient (3%) discontinued lumasiran treatment due to fatigue and disturbance in attention, which began during the double-blind period.
[d]AEs occurred during lumasiran treatment. All terms are MedDRA preferred terms except for ISRs.[4]
[e]Defined as AEs that were mapped to the high-level term "Injection Site Reactions" or events reported by the sites as ISRs.[4]

ABBREVIATIONS

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

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