Lumasiran: Kidney Related Outcomes

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SUMMARY

- Assessments of renal function and other kidney related outcomes measures were evaluated across the lumasiran clinical studies:
  - In the Phase 1/2 and Phase 2 OLE studies, mean eGFR values remained stable through Month 54 of the OLE period among patients treated with lumasiran.[1] The rates of kidney stone-related AEs decreased during the Phase 2 OLE compared with Part B of the Phase 1/2 study.[2]
  - In the ILLUMINATE-A study, mean eGFR values remained stable though Month 36 among lumasiran treated patients in the continuous lumasiran group and in the placebo crossover group. The KSE rate decreased among lumasiran treated patients in continuous lumasiran group and placebo crossover group.[3]
  - In the ILLUMINATE-B study, mean eGFR values remained stable through Month 30 in lumasiran treated patients. The KSE rate remained unchanged through the first 6 months and remained low through Month 30 of lumasiran treatment.[4]
  - The ILLUMINATE-C study included patients with eGFR ≤45 mL/min/1.73m^2 (cohort A), and patients on hemodialysis (cohort B). Mean eGFR values were 19.8 ± 9.6 (SD) mL/min/1.73 m^2 at baseline and 16.4 ± 9.8 mL/min/1.73 m^2 at month 6 for cohort A.[5] In the 6-month primary analysis, KSE rates decreased in both cohort A and cohort B.[6]
- Across the lumasiran clinical studies, the most common treatment-related AEs were mild ISRs. There were no treatment-emergent deaths or treatment-related severe AEs, serious AEs, or discontinuations.[1,3,4,7]

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PHASE 1/2 AND PHASE 2 OLE STUDIES

The Phase 1/2 study was a single-blind, placebo-controlled, single and multiple ascending dose study to evaluate the safety, tolerability, PK, and PD of lumasiran in healthy adult subjects (Part A) and in patients with PH1 (Part B). All 20 patients enrolled in the Phase 1/2 Part B study completed the study and enrolled in the Phase 2 OLE study. The data below includes only patients included in Part B of the study. The primary endpoint was incidence of AEs, including kidney stone-related AEs.[2,8]

Change in eGFR levels over time was evaluated as a secondary endpoint to assess renal function during the study. GFR was calculated based on the MDRD formula for patients ≥18 years of age at screening and the Schwartz Bedside Formula for patients <18 years of age at screening.[1]

Patient Demographics & Baseline Characteristics

Relevant baseline characteristics are detailed in **Table 1**.[1]

Table 1. Phase 2 OLE Relevant Baseline Characteristics.[1,a]

Characteristic	All Treated (n=20)
Age at screening, median (range), years	11.5 (6 – 43)
White race, n (%)	15 (75)
eGFR, median (range), mL/min/1.73 m^2	72.2 (42.5 – 130.7)

Abbreviations: eGFR = estimated glomerular filtration rate; OLE = open-label extension.
[a]Baseline data was derived from the Phase 1/2 parent study.

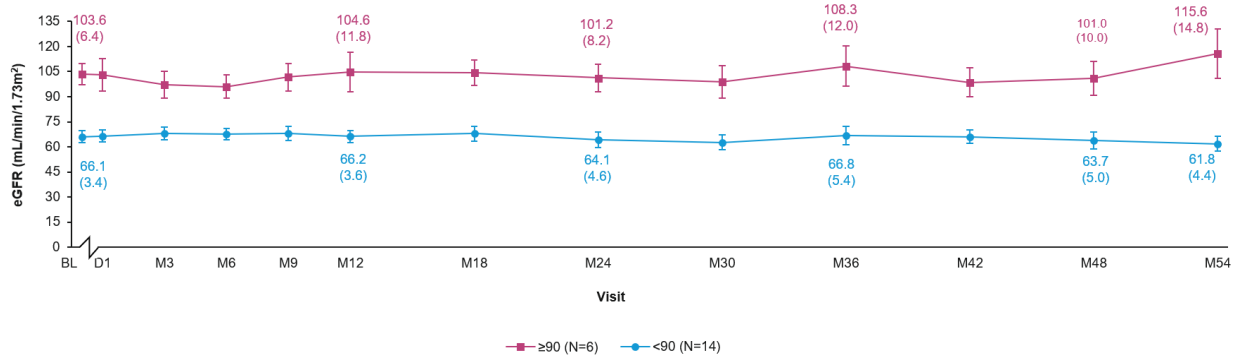
Kidney Function Measures

eGFR

In the Phase 2 OLE, the mean eGFR remained stable over time. The mean absolute change from baseline in eGFR ranged from -3.8 to 1.9 mL/min/1.73m^2 at Month 54. Over 48 months of follow-up, the mean (SEM) annual rate of change in eGFR value was −0.6 (0.7) mL/min/1.73m^2.[1]

The stability of the eGFR values was consistent over time in a subgroup analysis stratified by an eGFR of ≥90 versus <90 mL/min/1.73 m^2 at the Phase 1/2 parent study-derived baseline (**Figure 1**).[1]

Figure 1. Mean (SEM) eGFR Values Through Month 54 Stratified by Baseline eGFR.[1]



Abbreviations: BL = baseline; D = day; eGFR = estimated glomerular filtration rate; M = month; SEM; standard error of mean.
Footnotes: BL is the derived baseline value from the Phase 1/2 parent study.
From Frishberg et al.[1]

Safety

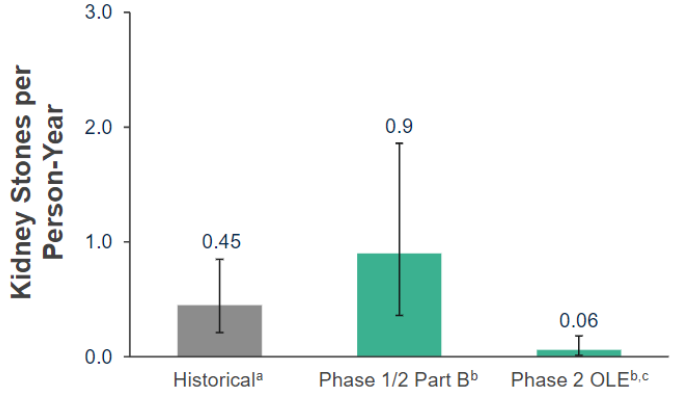
At Month 54 of the Phase 2 OLE, 20 patients (100%) reported AEs, of which 11 patients (55%) experienced treatment-related AEs. The most common treatment-related AEs were ISRs, which occurred in 8 patients (40%). All ISRs were mild in severity, and no ISRs were reported after Month 18 through the end of the study. SAEs were reported in 7 patients (35%) and severe AEs were reported in 2 patients (10%), none of which were related to lumasiran. There were no AEs that led to treatment discontinuation, withdrawal from the study, or death.[1]

Kidney Stone-Related AEs

In the 12 months prior to consent (historical), 6 patients (30%) reported ≥1 kidney stone. During Part B of the Phase 1/2 study, 4 patients (20%) reported kidney stone-related AEs during lumasiran treatment. After continuing to the Phase 2 OLE, 3 patients (15%) reported kidney stone-related AEs. The rate of kidney stone-related AEs decreased during the Phase 2 OLE compared with Part B of the Phase 1/2 study

(**Figure 2**).[2] At Month 54 of the Phase 2 OLE, the rate of kidney stone-related AEs was 0.17 per person year.[1]

Figure 2. Kidney Stones in the Phase 1/2 Part B and Phase 2 OLE Studies.[2]



Abbreviations: AE = adverse event; CI = confidence interval; OLE = open-label extension.
Footnotes: Error bars represent 95% CI. Duration of follow-up: historical, 20 person-years; Phase 1/2 Part B, 7.8 person-years; Phase 2 OLE, 48.0 person-years.
[a]Historical describes the number of symptomatic kidney stone episodes reported in the 12 months prior to consent for the 001 study.
[b]In the Phase 1/2 Part B and Phase 2 OLE studies, kidney stones were described as kidney stone-related AEs.
[c]Data presented from Phase 2 OLE with a data cut-off of March 1, 2021.
From Lieske et al.[2]

ILLUMINATE-A STUDY

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. 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-hour 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 were to receive lumasiran in an optional 54-month OLE.[9]

The change from baseline in eGFR to Month 6 was evaluated as a secondary endpoint. eGFR was calculated with the MDRD formula for patients ≥18 years of age and with the Schwartz Bedside Formula for patients 6 to <18 years of age. The rate of KSEs and change from baseline in nephrocalcinosis grade were evaluated as exploratory endpoints.[9]

Patient Demographics & Baseline Characteristics

Relevant baseline characteristics are detailed in **Table 2**.[3]

Table 2. ILLUMINATE-A Relevant Baseline Characteristics.[3,a]

Characteristic	Placebo/Lumasiran	Lumasiran/Lumasiran
Age at informed consent, mean (range), y	17.0 (6 – 60)	18.7 (6 – 47)
Male, n (%)	8 (62)	18 (69)
Race, n (%)		
Asian	3 (23)	3 (12)
White	9 (69)	21 (81)
Other or >1 race	1 (8)	2 (8)
eGFR, mean (SD), mL/min/1.73m^2	78.8 (30.0)	83.0 (25.6)
Patients reporting history of KSEs[b], n (%)		
Lifetime	10 (77)	23 (88)

Characteristic	Placebo/Lumasiran	Lumasiran/Lumasiran
12 months prior to consent	4 (31)	11 (42)

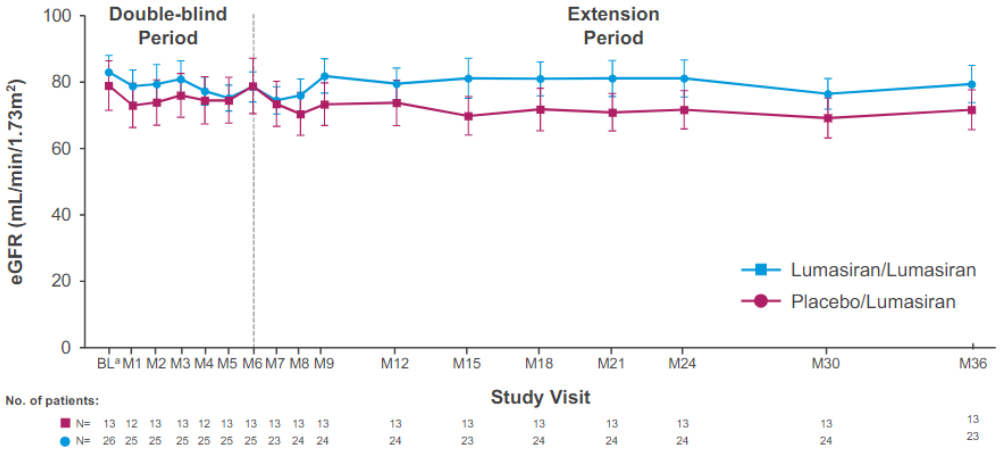
Abbreviations: eGFR = estimated glomerular filtration rate; KSE = kidney stone event; SD = standard deviation.
[a]Baseline is defined as the last nonmissing value prior to the first dose of lumasiran.
[b]A KSE is defined as an event that includes at least one of the following: visit to healthcare provider because of a kidney stone, medication for renal colic, stone passage, or macroscopic hematuria due to a kidney stone.

Kidney Related Outcomes

eGFR

In ILLUMINATE-A study, the mean eGFR remained stable though Month 36 among lumasiran treated patients in the continuous lumasiran group and the placebo crossover group (**Figure 3**).[3]

Figure 3. Mean eGFR Through Month 36.[3]

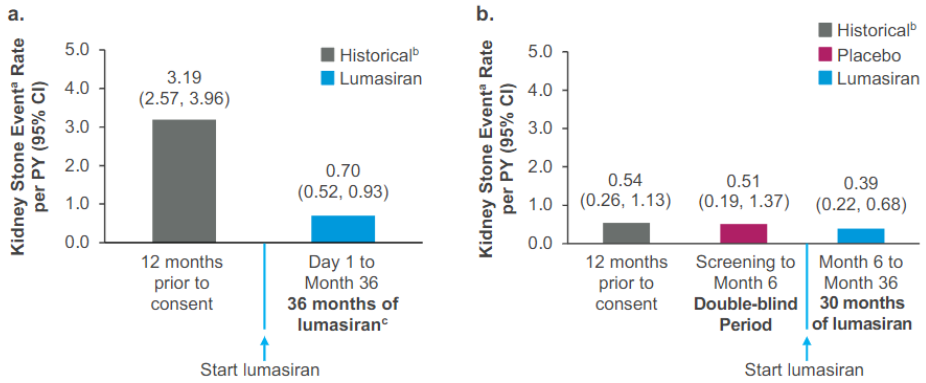


Abbreviations: BL = baseline; DB = double-blind; eGFR = estimated glomerular filtration rate; M = month; SEM = standard error of the mean.
[a]Baseline is the last assessment prior to the first dose of study drug (lumasiran or placebo) in the 6-month DB period.
From Saland et al.[3]

Kidney Stone Events

In the continuous lumasiran group, KSE 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 crossover cohort, KSE 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 4**).[3]

Figure 4. Kidney Stone Events During Lumasiran Treatment.[3]



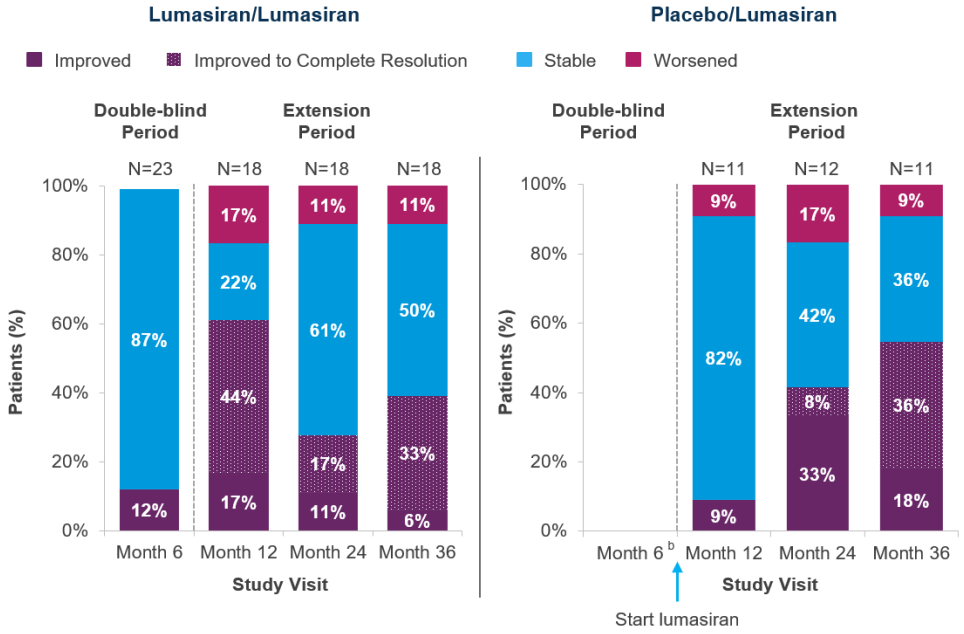
Abbreviations: CI = confidence interval; KSE = kidney stone event; PY = person-year.
[a]A KSE is defined as an event that includes at least one of the following: visit to healthcare provider because of a kidney stone, medication for renal colic, stone passage, or macroscopic hematuria due to a kidney stone.
[b]Patient-reported history of kidney stone events
[c]KSE rate (95% CI) was 1.09 (0.63, 1.88) per PY during the double-blind period (from day 1 to month 6).
From Saland et al.[3]

Nephrocalcinosis

The degree of medullary nephrocalcinosis in each kidney was graded using a validated 4-point scale; stable (ie, no change in either kidney), improving (ie, both kidneys improving or 1 kidney improving and 1 with no change), worsening (ie, both kidneys worsening or 1 kidney worsening and 1 with no change), or indeterminate (ie, 1 kidney improving and 1 worsening).[3]

After 36 months of lumasiran treatment, 6 of the 13 (46%) patients in the lumasiran/lumasiran group with medullary nephrocalcinosis at baseline had no detectable nephrocalcinosis. After 30 months of lumasiran treatment, 4 of the 10 (40%) patients in the placebo crossover group with medullary nephrocalcinosis at baseline had no detectable nephrocalcinosis (**Figure 5**).[3]

Figure 5. Change in From Baseline at Month 36 in Medullary Nephrocalcinosis.[3]



Lumasiran/lumasiran group includes 2 patients whose status was "indeterminate".
From Saland et al.[3]

Safety

At Month 36, 36 patients (92%) experienced an AE. The most common treatment-related AE was ISRs, which occurred in 19 patients (49%). Other AEs which occurred during lumasiran treatment included abdominal pain (21%) and headache (18%). SAEs were reported in 4 (10%) patients, and severe AEs were reported in 2 patients (5%), neither were considered related to lumasiran treatment. There was 1 patient that discontinued study treatment due to an AE, which was not considered related to lumasiran treatment. There were no deaths in the study.[3]

ILLUMINATE-B STUDY

ILLUMINATE-B (N=18) was a phase 3, open-label, single-arm study with a 6-month primary analysis period followed by an ongoing 54-month extension period 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.[10]

The change from baseline in eGFR was evaluated as a secondary endpoint to assess renal function during the study. eGFR was calculated based on the Schwartz Bedside formula in patients ≥12 months old. The rate of KSEs and change from baseline in nephrocalcinosis grade were evaluated as exploratory endpoints.[10]

Patient Demographics & Baseline Characteristics

Relevant baseline characteristics are detailed in **Table 3**.[10]

Table 3. ILLUMINATE-B Baseline Kidney Function Measures.[10]

Characteristic	< 10 kg (n=3)	10 to <20 kg (n=12)	≥ 20 kg (n = 3)	All Treated (n=18)
Age at consent, median (range), months	10.1 (3 – 14)	50.1 (23 – 72)	62.2 (54 – 72)	50.1 (3 – 72)
Time from diagnosis to first dose date, median, months	11.6	28.6	46.4	23.5
eGFR[a] mL/min/1.73 m^2, median (range)				
Overall, median (range)	135 (135 – 135)	111 (76 – 174)	90 (65 – 135)	111 (65 – 174)
Patients reporting history of KSEs[b], n (%)	0	2 (17)	1 (33)	3 (17)
Presence of nephrocalcinosis at baseline, n (%)	3 (100)	10 (83)	1 (33)	14 (78)

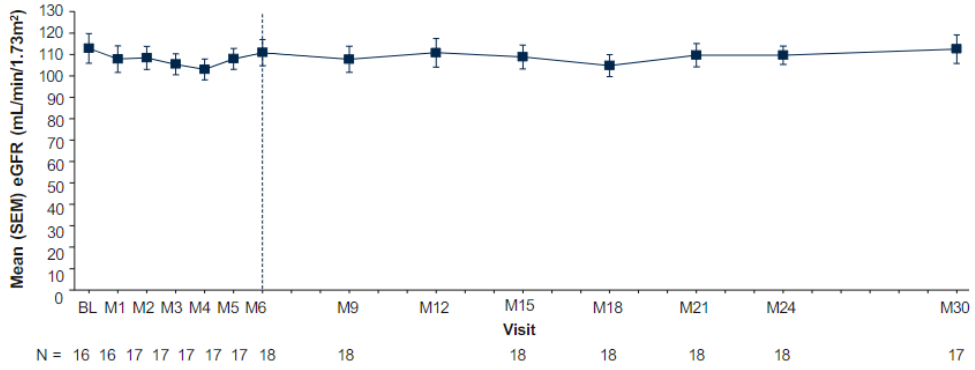
Abbreviations: eGFR = estimated glomerular filtration rate; KSE = kidney stone event.
[a]Two patients are missing baseline eGFR values because their age at baseline was <12 months old.
[b]KSEs at baseline were self-reported by patients in the 12 months prior to study initiation

Kidney Related Outcomes

eGFR

In ILLUMINATE-B study, the mean eGFR remained stable through Month 30 of the extension period. (**Figure 5**).[4]

Figure 5. Mean (SEM) eGFR Values Through Month 30.[4]

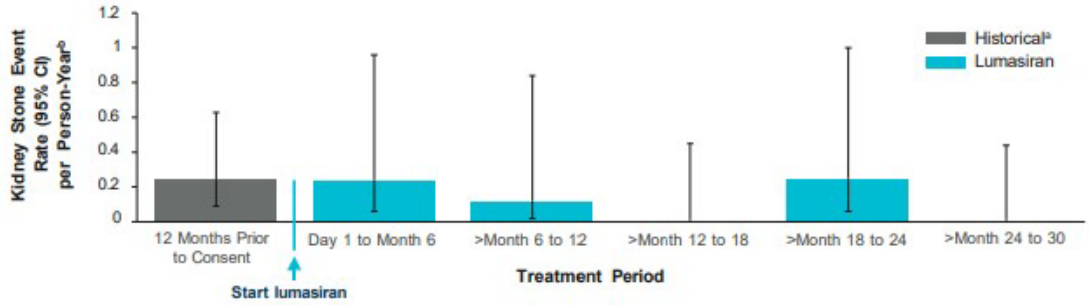


Abbreviations: BL = baseline; eGFR = estimated glomerular filtration rate; M = month; SEM = standard error of the mean.
Baseline value was the last non-missing value collected prior to the first dose of lumasiran.
From Michael et al.[4]

Kidney Stone Events

In the 12 months prior to informed consent, patient reported historical KSE rates were 0.24/person-year. KSE rates were unchanged between the 12-month historical recall and the first 6 months of treatment.[10] KSE rate remained low through Month 30 of lumasiran treatment (**Figure 6**).[4]

Figure 6. Kidney Stone Events During Lumasiran Treatment.[4]

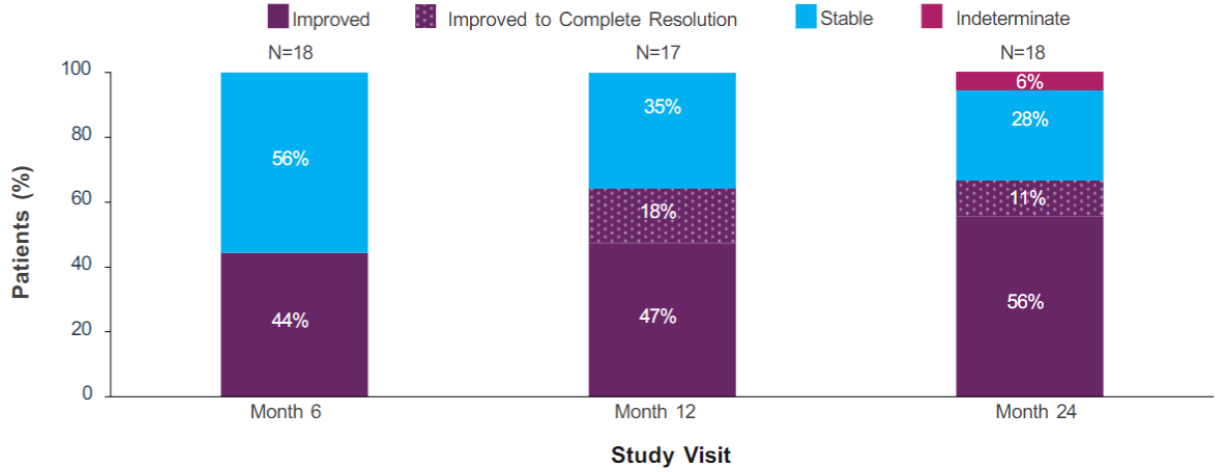


Abbreviations: CI = confidence interval; KSE = kidney stone event.
[a]Historical group: patient-reported history of KSEs; annualized rate was not calculated for patients < 6 months old.
[b]Rate is calculated as total number of KSEs divided by total person-years during the respective period. The 95% CI 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
KSE was defined as an event involving one or more of the following: healthcare provider visit for kidney stone, medication for renal colic, stone passage, and macroscopic hematuria caused by kidney stone.
From Michael et al.[4]

Nephrocalcinosis

At Month 24, an improvement in nephrocalcinosis grade was seen in 12 patients (67%), 1 patient (6%) was indeterminate (one side improved and the other side worsened), and 5 patients (28%) remained stable. Of the 5 patients who were stable, 4 patients had no nephrocalcinosis at baseline and remained stable with no nephrocalcinosis at Month 24. (**Figure 7**).[4]

Figure 7. Change from Baseline at Month 24 in Medullary Nephrocalcinosis.[4]



Worsened = grade higher than baseline; stable = grade same as baseline; improved = grade lower than baseline; indeterminate = one side improved and the other side worsened. There were no patients with worsening nephrocalcinosis grade. Change in nephrocalcinosis grade was indeterminate in 1 patient. Renal ultrasound was not performed at Month 30.
From Michael et al.[4]

Safety

At Month 30, 18 (100%) patients reported at least 1 AE which was mild to moderate in severity. The most common treatment-related AEs were mild and transient ISRs, which occurred in 3 patients (17%); symptoms included erythema, discoloration, and pain at injection site. There were no clinically relevant

changes in laboratory measures, vital signs, or electrocardiograms related to lumasiran. There were no AEs that led to treatment discontinuation, interruption, or withdrawal from the study.[4]

ILLUMINATE-C STUDY

ILLUMINATE-C (NCT04152200) was a phase 3, open-label study with a 6-month primary analysis period followed by an ongoing 54-month extension period to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of lumasiran in patients with advanced PH1 with eGFR ≤45 mL/min/1.73m^2 (or elevated serum creatinine if <12 months old) and plasma oxalate ≥ 20 µmol/L. Patients enrolled in the study include those not receiving hemodialysis (cohort A) and those receiving hemodialysis (cohort B). 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.[5]

The change from baseline in eGFR was evaluated in cohort A as a secondary endpoint to assess renal function during the study. eGFR was calculated with the MDRD formula for patients ≥18 years of age and with the Schwartz Bedside Formula for patients 1 to <18 years of age. The rate of KSEs and change from baseline in nephrocalcinosis grade were also evaluated as secondary endpoints in the extension period.[5]

Patient Demographics & Baseline Characteristics

Relevant baseline characteristics are detailed in **Table 4**.[5]

Table 4. ILLUMINATE-C Baseline Kidney Function Measures.[5]

Characteristic	Cohort A N=6	Cohort B N=15	All Treated N=21
Age at consent, median (range), years	9.0 (0 – 40)	6.0 (1 – 59)	8.0 (0 – 5.9)
Time from diagnosis to first dose, mo	72.2 (4 – 350)	16.6 (6 – 440)	21.6 (4 – 440)
eGFR[a], median (range), mL/min/1.73 m^2	N=5[a] 16.5 (8.6-34.1)	NA	N=5[a] 16.5 (8.6-34.1)
Number of dialysis therapy sessions per week, median (range)	NA	6 (3-7)	NA

Abbreviations: eGFR = estimated glomerular filtration rate; NA = not applicable.
[a]eGFR value available for 5 patients in cohort A.

Kidney Related Outcomes

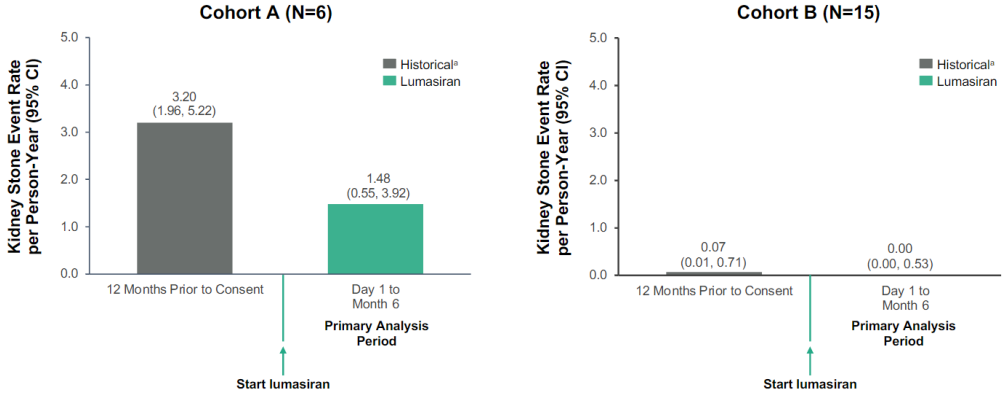
eGFR

The change in eGFR was evaluated for cohort A only. 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 m2 at Month 6.[5]

Kidney Stone Events

In the 12 months prior to informed consent, the rate of KSEs was 3.20/person-year (95% CI, 1.96, 5.22) and was 1.48/person-year (95% CI, 0.55, 3.92) in the 6-month primary analysis period for patients enrolled in cohort A. In the 12 months prior to informed consent, the rate of KSEs was 0.07/person-year (95% CI, 0.01, 0.71) and was 0.00/person-year (95% CI, 0.00, 0.53) in the 6-month primary analysis period for patients enrolled in cohort B (**Figure 8**).[6]

Figure 8. Kidney Stone Events During Lumasiran Treatment.[6]



Abbreviations: CI = confidence interval; KSE = kidney stone event.
[a]Historical group: patient-reported history of KSEs; annualized rate was not calculated for patients <6 months old.
From Groothoff et al.[6]

Nephrocalcinosis

In cohort A, medullary nephrocalcinosis was present at baseline in 5 of the 6 patients with kidney ultrasound results. At Month 6, of those 5 patients, the grade of medullary nephrocalcinosis remained stable in 2 patients, worsened in none, and improved in 3 (2 unilateral improvements and 1 bilateral improvement).[5]

In cohort B, medullary nephrocalcinosis was present at baseline in 2 of the 11 patients with kidney ultrasound results. At Month 6, an improvement in nephrocalcinosis was observed in both patients (1 unilateral improvement and 1 bilateral improvement).[5]

Of the 10 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 the grade of nephrocalcinosis remained stable in the 9 patients in cohort B.[5]

Safety

At Month 24, 21 patients (100%) experienced at least 1 AE. The most frequently reported AEs were pyrexia (38%), diarrhea (29%), and ISRs (24%). Treatment-related AEs were reported in 7 patients (33%). The most common treatment-related AEs were mild ISRs, which occurred in 5 patients (24%). There were no lumasiran-related severe or serious AEs, discontinuations, or study withdrawals. There were no deaths in the study.[7]

ABBREVIATIONS

AE = adverse event; BL = baseline; CI = confidence interval; eGFR = estimated glomerular filtration rate; ISR = injection-site reactions; KSE = kidney stone event; LC-MS/MS = liquid chromatography-tandem mass spectrometry; LLOQ = lower limit of quantitation; MDRD = Modification of Diet in Renal Disease; M = month; NA = not applicable; PH1 = primary hyperoxaluria type 1; PD = pharmacodynamic; PK = pharmacokinetic; POx = plasma oxalate; PY = person-year; SAE = serious adverse event; 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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