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CLINICAL RESEARCH

Randomized Clinical Trial on the Long-Term Efficacy and Safety of Lumasiran in Patients With Primary Hyperoxaluria Type 1

Sally A. Hulton[1], Jaap W. Groothoff[2], Yaacov Frishberg[3], Michael J. Koren[4], J. Scott Overcash[5], Anne-Laure Sellier-Leclerc[6], Hadas Shasha-Lavsky[7], Jeffrey M. Saland[8], Wesley Hayes[9], Daniella Magen[10], Shabbir H. Moochhala[11], Martin Coenen[12], Eva Simkova[13], Sander F. Garrelfs[2], David J. Sas[14], Kristin A. Meliambro[8], Taylor Ngo[15], Marianne T. Sweetser[15], Bahru A. Habtemariam[15], John M. Gansner[15], Tracy L. McGregor[15] and John C. Lieske[16]

[1]Department of Nephrology, Birmingham Women's and Children's Hospital, Birmingham, UK; [2]Department of Pediatric Nephrology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; [3]Division of Pediatric Nephrology, Shaare Zedek Medical Center and Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel; [4]Jacksonville Center for Clinical Research, Jacksonville, Florida, USA; [5]Velocity Clinical Research, San Diego, California, USA; [6]Hôpital Femme Mère Enfant and Centre d'Investigation Clinique Institut National de la Santé et de la Recherche Médicale, Hospices Civils de Lyon, ERKnet, Bron, France; [7]Pediatric Nephrology Unit, Galilee Medical Center and Azrieli Faculty of Medicine, Bar-Ilan University, Nahariya, Israel; [8]Icahn School of Medicine at Mount Sinai, New York, New York, USA; [9]Department of Pediatric Nephrology, Great Ormond Street Hospital, London, UK; [10]Pediatric Nephrology Institute, Rambam Health Care Campus, Haifa, Israel; [11]UCL Department of Renal Medicine, Royal Free Hospital, London, UK; [12]Department of Clinical Chemistry and Clinical Pharmacology, University Hospital Bonn, Bonn, Germany; [13]Al Jalila Children's Hospital, Dubai, United Arabs Emirates; [14]Division of Pediatric Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, USA; [15]Alnylam Pharmaceuticals, Cambridge, Massachusetts, USA; and [16]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, USA

Introduction: Primary hyperoxaluria type 1 (PH1) is a rare genetic disease caused by hepatic overproduction of oxalate, leading to kidney stones, nephrocalcinosis, kidney failure, and systemic oxalosis. In the 6-month double-blind period (DBP) of ILLUMINATE-A, a phase 3, randomized, placebo-controlled trial in patients with PH1 ≥6 years old, treatment with lumasiran, an RNA interference therapeutic, led to substantial reductions in urinary oxalate (UOx) levels.

Methods: We report data to month 12 in the extension period (EP) of ILLUMINATE-A, including patients who continued lumasiran (lumasiran/lumasiran) or crossed over from placebo to lumasiran (placebo/lumasiran).

Results: In the lumasiran/lumasiran group ($n = 24$), the reduction in 24-hour UOx level was sustained to month 12 (mean reduction from baseline, 66.9% at month 6; 64.1% at month 12). The placebo/lumasiran group ($n = 13$) had a similar time course and magnitude of 24-hour UOx reduction (mean reduction, 57.3%) after 6 months of lumasiran. Kidney stone event rates seemed to be lower after 6 months of lumasiran in both groups compared with the 12 months before consent, and this reduction was maintained at month 12 in the lumasiran/lumasiran group. At study start, 71% of patients in the lumasiran/lumasiran group and 92% in the placebo/lumasiran group had nephrocalcinosis. Nephrocalcinosis grade improved after 6 months of lumasiran in the lumasiran/lumasiran and placebo/lumasiran groups (13% and 8% of patients, respectively). After an additional 6 months of lumasiran, 46% of patients had improvement in nephrocalcinosis grade within the lumasiran/lumasiran group. Estimated glomerular filtration rate (eGFR) remained stable during the course of lumasiran treatment. The most common adverse events (AEs) related to lumasiran were mild, transient injection-site reactions (ISRs).

Conclusion: Long-term lumasiran treatment enabled sustained lowering of UOx levels with acceptable safety and encouraging results on clinical outcomes.

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Correspondence: Sally-Anne Hulton, Department of Nephrology, Birmingham Women's and Children's Hospital NHS Foundation Trust, Steelhouse Lane, Birmingham B4 6NH, UK. E-mail: sally.hulton@bch.nhs.uk

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PH1 is a rare, progressive, genetic disease characterized by overproduction of hepatic oxalate owing to mutations in the *AGXT* gene, which encodes the enzyme alanine–glyoxylate aminotransferase.[1,2] Alanine–glyoxylate aminotransferase converts the oxalate precursor glyoxylate to glycine. With absent or reduced activity of alanine–glyoxylate aminotransferase, glyoxylate is oxidized to oxalate, a toxic metabolite largely excreted by the kidneys.[1]

PH1 is associated with high morbidity and mortality in all age groups owing to hepatic oxalate overproduction.[1,3,4] In the kidneys, excess oxalate combines with calcium to form insoluble calcium oxalate crystals. This can lead to recurrent kidney stones, which, along with their associated hospitalizations and interventional procedures, are a major cause of morbidity.[1,5] In addition, calcium oxalate crystals can aggregate within the tubular lumen and adhere to the apical membrane of the tubular cells; the tubular cells can then internalize the calcium oxalate crystals, resulting in inflammation, nephrocalcinosis, and progressive kidney damage.[1] As kidney function deteriorates, renal excretion of oxalate is reduced, resulting in increased plasma oxalate, which in turn leads to systemic oxalosis.[1] Devastating multiorgan damage from systemic oxalosis occurs when insoluble calcium oxalate crystals are deposited in extrarenal tissues, such as the blood vessels, bone, heart, eye, bone marrow, and skin.[1] Without treatment, death from complications of oxalosis and/or kidney failure can occur.[1,3]

Management options for PH1 have been limited.[1,6] Hyperhydration, consisting of daily fluid intake of 2 to 3 l/m^2 body surface area, and calcium oxalate crystallization inhibitors such as citrate may reduce the intrarenal precipitation of calcium oxalate crystals[1,7] but do not address the underlying cause of oxalate overproduction. Pyridoxine can reduce UOx excretion but is effective in a subset of patients with PH1.[6,8] Approximately half of patients with PH1 progress to kidney failure by early adulthood, and nearly all by age 60 years.[9,10] Once kidney function is severely impaired, intensive hemodialysis (4–6 times per week) with or without peritoneal dialysis is often used to clear oxalate from the blood, but it is time-consuming and generally inadequate to prevent systemic accumulation of oxalate.[1,8] To date, liver transplantation has been the only metabolic cure for PH1, but it is associated with significant morbidity and mortality. Dual liver–kidney transplantation is frequently performed to both address the metabolic defect in the liver and restore lost kidney function.[1] Because a substantial reduction in UOx and plasma oxalate is expected to confer clinical benefit in patients with PH1,[5] therapies that can reduce the production of hepatic oxalate are essential to address the underlying cause of PH1.

Lumasiran is an RNA interference therapeutic that was approved in November 2020 by the US Food and Drug Administration for the treatment of PH1 to lower UOx levels in pediatric and adult patients[11] and by the European Commission for the treatment of PH1 in all age groups.[12] Lumasiran is designed to reduce hepatic oxalate overproduction by targeting the mRNA of glycolate oxidase, encoded by *HAO1*. Reduced levels of glycolate oxidase decrease the amount of glyoxylate, the immediate precursor of oxalate, thereby reducing hepatic oxalate production while increasing concentrations of a readily excreted precursor, glycolate.[11–13] In the phase 3 ILLUMINATE-A trial, 39 patients aged ≥6 years with PH1 and an eGFR ≥30 ml/min per 1.73 m^2 were randomly assigned to lumasiran or placebo. At the end of the 6-month DBP, patients treated with lumasiran had a significant reduction in 24-hour UOx excretion compared with placebo (least-squares mean difference, −53.5%; $P < 0.001$), meeting the primary end point.[14] All hierarchically tested secondary end points were met, including additional measures of urinary and plasma oxalate. Lumasiran had an acceptable safety profile; the main safety finding was mild, transient ISRs, which did not result in treatment discontinuation.[14]

Here, we report data to month 12 in the EP of ILLUMINATE-A, including patients who, after the 6-month DBP, either continued lumasiran or crossed over from placebo to lumasiran.

METHODS

Study Design and Patients

ILLUMINATE-A (ClinicalTrials.gov number, NCT03681184; EudraCT number: 2018-001981-40) is a 60-month study evaluating the efficacy and safety of lumasiran in children and adults with PH1 at 16 sites in 8 countries (France, Germany, Israel, The Netherlands, Switzerland, United Arab Emirates, United Kingdom, and United States). The study protocol was developed by the sponsor, Alnylam Pharmaceuticals, and has been published.[14]

Briefly, eligible patients[14] were ≥6 years old with genetically confirmed PH1, eGFR ≥30 ml/min per 1.73 m^2, and 24-hour UOx excretion ≥0.70 mmol/24 h per 1.73 m^2. The study includes a 6-month, randomized, placebo-controlled DBP[14] followed by a 54-month EP (Supplementary Figure S1). During the 6-month DBP, patients were randomized (2:1) to receive lumasiran or placebo by s.c. injection.[14] Lumasiran (3.0 mg per kilogram of body weight) or placebo was administered once monthly for 3 doses, followed by

maintenance doses given once every 3 months beginning 1 month after the last loading dose. Investigators, patients, and sponsor were blinded to the end of the DBP. During the EP, investigators and patients were blinded until the last patient completed the assessments at the month 9 visit. All patients entering the EP initially received blinded monthly treatment: patients randomized to placebo received loading doses of lumasiran 3.0 mg/kg at months 6, 7, and 8, and patients randomized to lumasiran received a maintenance dose of lumasiran 3.0 mg/kg at month 6 and placebo at months 7 and 8. From month 9 and beyond, all patients received lumasiran 3.0 mg/kg every 3 months (maintenance dosing) (Supplementary Figure S1). All drug administration and study visits were scheduled based on 28-day months.

The study was approved by central and local institutional review boards or ethics committees and conducted in accordance with the Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki. All patients or their legal guardians provided written informed consent. Patients or their legal guardians were free to discontinue the study drug and/or stop participation in the study at any time and for any reason. The investigator or the sponsor could stop a patient's participation in the study at any time if this was considered to be in the patient's best interest. Detailed stopping rules are provided in the protocol.

Outcome Measures and Safety Assessments in the EP

Efficacy outcomes evaluated in the EP included the secondary end points of change from baseline (percent and absolute) in 24-hour UOx excretion, 24-hour UOx-to-creatinine ratios, and eGFR. Exploratory end points included change in urinary and plasma glycolate, change in the rate of kidney stone events, change in nephrocalcinosis evaluated by kidney ultrasound, change in UOx-to-creatinine ratios as evaluated in spot urine collections, and frequency of antidrug antibodies (ADAs). Change from baseline to month 12 (percentage and absolute) in total plasma oxalate, proportion of patients with 24-hour UOx $\leq 1.5 \times$ upper limit of normal in the EP, and change in nephrocalcinosis in age subgroups (<18 years and ≥ 18 years at consent) were evaluated in *post hoc* analyses. Safety assessments included monitoring of AEs, clinical laboratory assessments, vital signs, 12-lead electrocardiography, and physical examination. AEs were coded according to the Medical Dictionary for Regulatory Activities Version 21.1.

Urine and blood samples were collected for measurement of oxalate and glycolate with a validated liquid chromatography-tandem mass spectrometry assay. The kidney stone event rate was calculated as the total number of kidney stone events divided by the total patient exposure time (events per person-year). A kidney stone event was defined as an event that included at least 1 of the following: visit to a health care provider (e.g., outpatient clinic, urgent care, emergency department, procedure) because of a kidney stone; medication for renal colic; stone passage; or macroscopic hematuria owing to a kidney stone. Historical and prospectively documented kidney stone events were defined in the same way. Nephrocalcinosis was evaluated by kidney ultrasound scans centrally read by a radiologist at baseline, month 6, and month 12. Owing to the COVID-19 pandemic, the protocol was updated to extend the window for kidney ultrasound scans up to 7 months after each protocol-specified visit. The degree of medullary nephrocalcinosis in each kidney was graded on a validated, standardized, 4-point scale.[15] Changes in the grade of nephrocalcinosis were grouped into the following 4 categories of overall change, accounting for both kidneys: no change (both kidneys), improving (both kidneys improving or 1 kidney improving and 1 no change), worsening (both kidneys worsening or 1 kidney worsening and 1 no change), and indeterminate (1 kidney improving and 1 worsening). Two patients who were randomized to lumasiran did not have valid kidney ultrasounds at baseline and were excluded from the nephrocalcinosis analysis, and 1 patient who was initially randomized to placebo and crossed over to receive lumasiran did not have a kidney ultrasound before the first dose of lumasiran at month 6 and was excluded from the month 12 nephrocalcinosis analysis. ADAs (IgG, IgM) against lumasiran were evaluated in plasma at baseline and months 1, 3, 6, 7, 9, and 12. ADA assessments were conducted by Charles River Laboratories Montreal ULC (Senneville, Quebec, Canada) using a validated enzyme-linked immunoassay.

Statistical Analyses

The current analysis was completed using data to May 1, 2020, when all active study patients had completed their month 12 visit. Efficacy and safety analyses were conducted in the all lumasiran-treated set, defined as all patients who received any amount of lumasiran and analyzed according to whether patients received lumasiran in the DBP before receiving lumasiran in the EP (lumasiran/lumasiran group) or initially received placebo in the DBP and crossed over to lumasiran in the EP (placebo/lumasiran group). Baseline in the all lumasiran-treated set was defined as the last non-missing value(s) before the first dose of lumasiran. For figures of percent change from baseline and actual values over time, study baseline is defined as the last

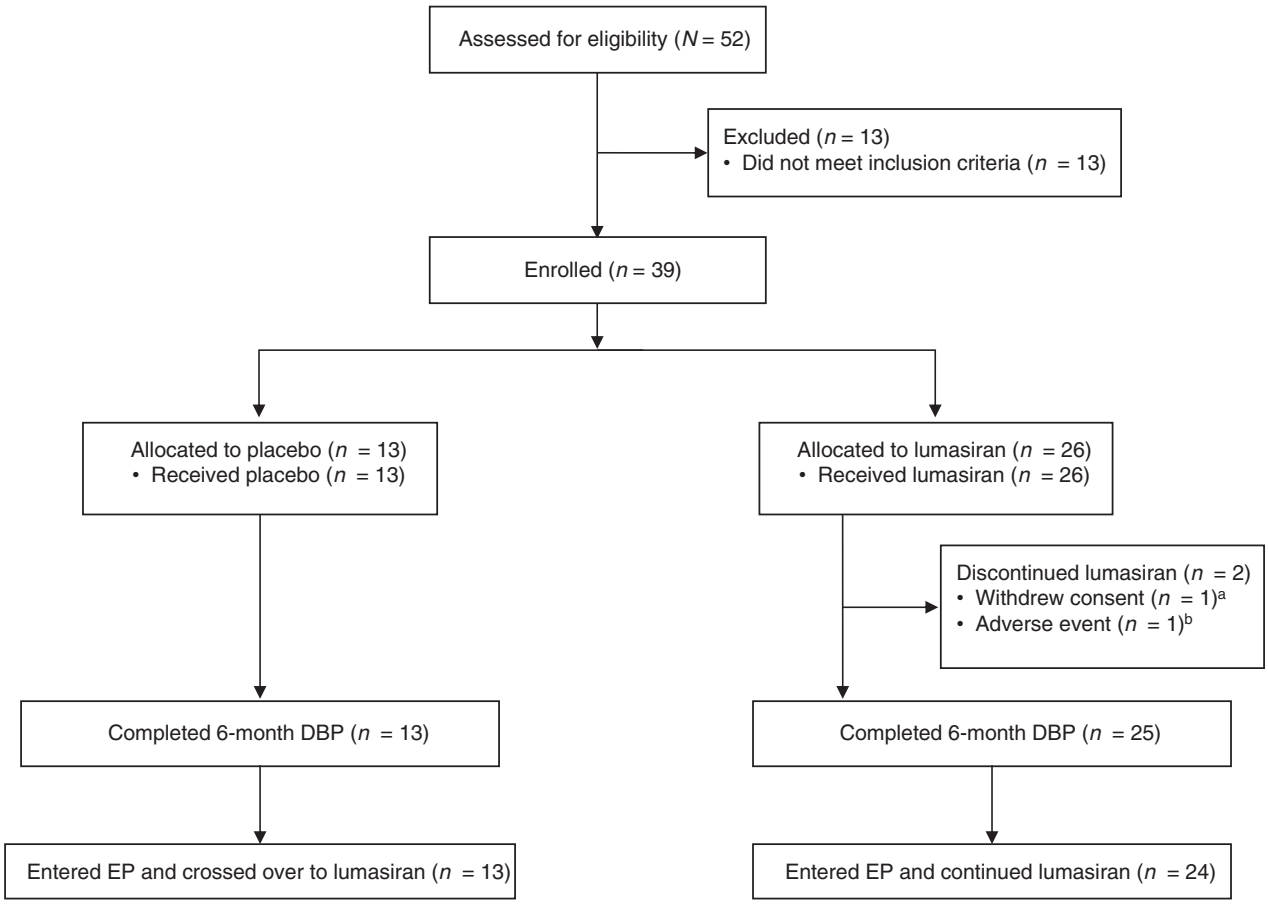


Figure 1. Patient disposition. [a]Participation stopped by parent/guardian owing to the patient's inability to comply with protocol-specific testing; patient did not complete 6-month DBP. [b]Discontinued treatment for adverse events (unrelated to treatment) of fatigue and disturbance in attention; completed 6-month DBP but did not enter EP. DBP, double-blind period; EP, extension period.

nonmissing value(s) before the study drug. The plasma oxalate analysis set, defined as all patients who received the study drug and had a baseline plasma oxalate level $\geq 1.5 \times$ the lower limit of quantitation, was used to evaluate change in plasma oxalate. The lower limit of quantitation of the plasma oxalate assay was 5.55 μmol/l. Values below the lower limit of quantitation were assigned a value of 5.55 μmol/l. Cumulative safety data from the first dose of lumasiran to May 1, 2020, are reported. Formal statistical hypothesis testing was performed on the primary and secondary efficacy end points evaluated during the DBP[14]; all end points in the present analysis were summarized using descriptive statistics.

RESULTS

Patients

Of 39 patients randomized between January 2019 and May 2019, a total of 24 of 26 patients initially randomized to receive lumasiran continued to receive lumasiran in the EP (lumasiran/lumasiran group) and 13 of 13 patients initially randomized to receive placebo crossed over to receive lumasiran (placebo/lumasiran group). There were 1 patient who withdrew from the study during the DBP and 1 patient who discontinued the treatment, completed the DBP, and did not enter the EP (Figure 1). In the current analysis, the mean (range) cumulative lumasiran exposure was 9.9 (2.8–15.1) calendar months. In addition, 3 patients (2 in the lumasiran/lumasiran group and 1 in the placebo/lumasiran group) had 1 missing dose of lumasiran. Baseline demographic and disease characteristics were generally balanced between continuous lumasiran and placebo crossover groups (Table 1).

Efficacy

Urinary and Plasma Oxalate

Long-term treatment with lumasiran led to sustained reduction in 24-hour UOx levels (Figure 2a and b). In the lumasiran/lumasiran group, mean (SEM) percent reduction from baseline in 24-hour UOx level was 66.9% (3.1) at month 6 and 64.1% (3.3) at month 12. The placebo/lumasiran group had a mean (SEM) percent reduction of 57.3% (4.9) at month 12 after 6 months of lumasiran treatment. The placebo/lumasiran group had a time course and magnitude of 24-hour UOx reduction similar to that of the patients in

Table 1. Baseline demographic and clinical characteristics[a]

Baseline characteristic	Placebo/lumasiran (n = 13)	Lumasiran/lumasiran (n = 26)	All lumasiran treated (N = 39)
Median age at consent (range), yr	11.0 (6–60)	16.5 (6–47)	14.0 (6–60)
Age category at consent, n (%)			
6 to <18 yr	8 (62)	14 (54)	22 (56)
18 to <65 yr	5 (38)	12 (46)	17 (44)
Female, n (%)	5 (38)	8 (31)	13 (33)
Race, n (%)			
Asian	3 (23)	3 (12)	6 (15)
White	9 (69)	21 (81)	30 (77)
Other	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 use, n (%)	9 (69)	13 (50)	22 (56)
Mean (SD) 24-h UOx excretion, mmol/24 h per 1.73 m^2[b]	1.63 (0.67)	1.84 (0.60)	1.77 (0.62)
Mean (SD) plasma oxalate, µmol/l[c]	19.3 (9.5)	14.8 (7.6)	16.3 (8.4)
Kidney function			
Mean (SD) eGFR, ml/min per 1.73 m^2	78.8 (30.0)	83.0 (25.5)	81.6 (26.8)
≥90 ml/min per 1.73 m^2, n (%)	5 (38)	9 (35)	14 (36)
60 to <90 ml/min per 1.73 m^2, n (%)	3 (23)	13 (50)	16 (41)
30 to <60 ml/min per 1.73 m^2, n (%)	5 (38)	4 (15)	9 (23)

eGFR, estimated glomerular filtration rate; ULN, upper limit of normal; UOx, urinary oxalate.
[a]Baseline characteristics before the first dose of lumasiran are reported.
[b]ULN is 0.514 mmol/24 h per 1.73 m^2 (1 mmol/24 h per 1.73 m^2 = 90 mg/24 h per 1.73 m^2).
[c]ULN = 12.11 µmol/l.

the lumasiran/lumasiran group after the first 6 months of lumasiran (Figure 2a and b).

The proportion of patients achieving near-normalization (≤1.5 × upper limit of normal) or normalization (less than or equal to upper limit of normal) of 24-hour UOx excretion was also maintained with long-term lumasiran treatment. As found in Figure 3, 84.0% of patients in the lumasiran/lumasiran group achieved near-normalization or normalization of 24-hour UOx at month 6, and 87.5% did so at month 12. In the placebo/lumasiran group, 76.9% of patients achieved near-normalization or normalization of 24-hour UOx at month 12 after receiving 6 months of lumasiran treatment, a proportion comparable with that in the lumasiran/lumasiran group at month 6.

The reductions in 24-hour UOx-to-creatinine ratios from baseline were sustained in the lumasiran/lumasiran group, with a mean (SEM) of 66.2% (2.8) after 6 months of treatment and 62.9% (3.1) after 12 months of treatment. In the placebo/lumasiran group, 24-hour UOx-to-creatinine ratios were reduced by a mean (SEM) of 54.3% (4.7) after 6 months of lumasiran treatment (Supplementary Figure S2A). UOx-to-creatinine ratios in spot urine collections had similar results (Supplementary Figure S2B).

Patients initially randomized to lumasiran (lumasiran/lumasiran group) maintained their reduction from baseline in plasma oxalate at month 6 and month 12 (mean [SEM] reduction of 36.9% [4.9] and 35.0% [6.1], respectively) (Figure 4). Those initially randomized to placebo who crossed over to lumasiran (placebo/lumasiran group) had a similar time course and magnitude of plasma oxalate reduction (mean [SEM] reduction after 6 months of lumasiran treatment of 48.9% [5.1]). eGFR was similar in the lumasiran/lumasiran and placebo/lumasiran groups and remained stable during the course of lumasiran treatment (Figure 5).

Plasma and Urinary Glycolate

Plasma glycolate level (Figure 6) initially increased and then plateaued and remained stable with up to 12 months of lumasiran treatment in the lumasiran/lumasiran group. A similar trajectory was observed in the placebo/lumasiran group after initiation of lumasiran treatment. Changes in 24-hour urinary glycolate-to-creatinine ratios were consistent with those observed in plasma glycolate (Supplementary Figure S3).

Kidney Stone Events

Reported historical kidney stone event rates in the lumasiran/lumasiran group were higher than in the placebo/lumasiran group. Kidney stone event rates recalled in the 12 months before consent seemed to mirror those during the relatively short screening period (up to 2 months): 3.19 (95% CI, 2.57–3.96) versus 2.70 (95% CI, 1.41–5.19) per person-year, respectively, in the lumasiran/lumasiran group; 0.54 (95% CI, 0.26–1.13) versus 0.00 (95% CI, 0.00–2.15) per

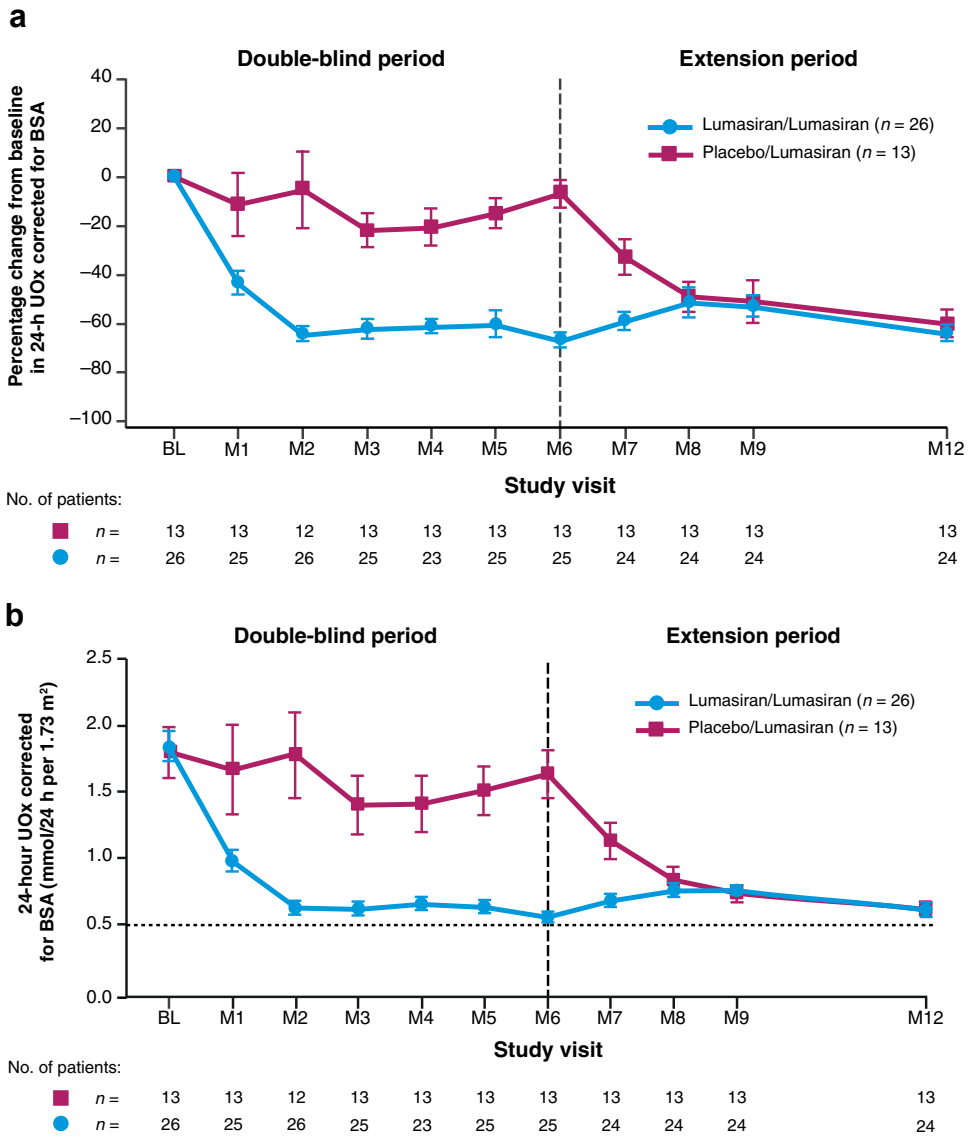


Figure 2. Change in 24-hour urinary oxalate. (a) Percentage change. Data are mean ± SEM. Percentage change at each visit was calculated using the study baseline. (b) 24-Hour urinary oxalate excretion. Data are mean ± SEM of observed values. Dotted line represents the upper limit of normal of 0.514 mmol/24 h per 1.73 m^2 (1 mmol/24 h per 1.73 m^2 = 90 mg/24 h per 1.73 m^2) for 24-hour UOx excretion. BL, baseline; BSA, body surface area; M, month; UOx, urinary oxalate.

person-year, respectively, in the placebo/lumasiran group.

In the lumasiran/lumasiran group, the kidney stone event rate seemed to be lower during the 6-month DBP relative to that during the 12 months before consent, and this reduction persisted to month 12 after an additional 6 months of lumasiran treatment (Figure 7a and b). In the placebo/lumasiran group, the kidney stone event rate during the 6 months of placebo treatment was similar to the rate reported for the 12 months before consent. After patients crossed over from placebo to lumasiran, the kidney stone event rate seemed to decrease compared with both the historical recall period and the placebo treatment period (Figure 7a and b).

Nephrocalcinosis

At study start, 71% of patients (17 of 24) in the lumasiran/lumasiran group and 92% (12 of 13) in the placebo/lumasiran group had nephrocalcinosis based on kidney ultrasounds. In the lumasiran/lumasiran group, nephrocalcinosis improved in 13% of patients (3 of 24) and remained stable in 83% (20 of 24) at month 6 (Figure 8). Continued treatment with an additional 6 months of lumasiran resulted in more patients exhibiting improvement: at month 12, 46% of patients (11 of 24) had improved nephrocalcinosis (8 bilateral, 3 unilateral) and 13% (3 of 24) had worsening (1 bilateral, 2 unilateral) as compared with baseline (Figure 8). In the placebo/lumasiran group, nephrocalcinosis improved in 8% (1 of 12; unilateral),

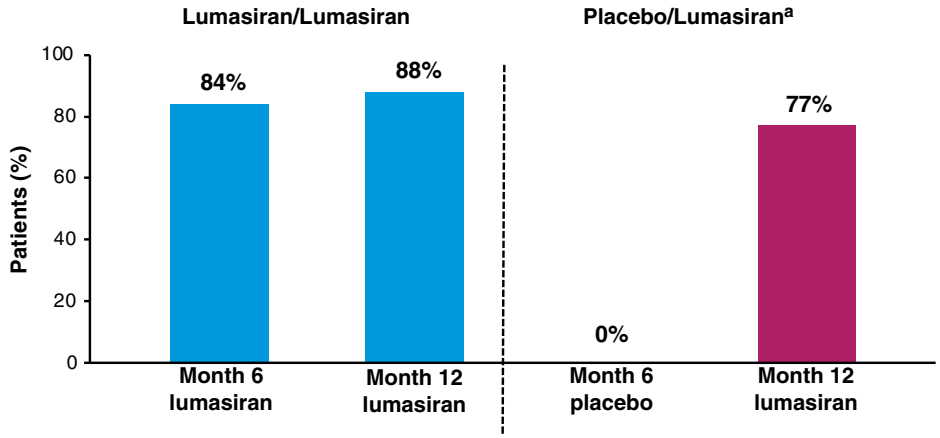


Figure 3. Proportion of patients with 24-hour urinary oxalate level ≤1.5 × ULN. [a]Patients initially randomized to placebo. ULN is 0.514 mmol/24 h per 1.73 m^2 (1 mmol/24 h per 1.73 m^2 = 90 mg/24 h per 1.73 m^2). ULN, upper limit of normal.

remained stable in 75% (9 of 12), and worsened in 8% (1 of 12; unilateral) at month 12 compared with month 6 before the start of lumasiran treatment in these patients (Figure 8).

Of all patients with valid ultrasound results and nephrocalcinosis at baseline, 15% (4 of 27) and 79% (11 of 14) had improvement after 6 and 12 months of treatment, respectively. Of all patients with valid ultrasound results and no nephrocalcinosis at baseline, 100% (7 of 7) had no change after 6 months of treatment, 25% (1 of 4) developed nephrocalcinosis, and 75% (3 of 4) had no change after 12 months of treatment.

Overall, nephrocalcinosis improved or remained stable in most of the patients treated with lumasiran, in both patients aged <18 years and those aged ≥18 years at consent (Supplementary Figure S4).

Frequency of ADAs

No patient tested positive for ADAs in the EP. There was 1 patient who tested positive for ADAs (with a low titer [1:50]) at month 6, with no observable effect on efficacy or safety. Results of subsequent samples were negative.

Safety

Safety outcomes as of the data cutoff are found in Table 2. AEs were reported in 33 (85%) patients; most of the AEs were mild in severity. There was 1 patient who had a serious AE of urosepsis (severe) during the EP that was considered not related to the study drug. There were no treatment interruptions or discontinuations related to lumasiran, and no deaths were reported. The most frequently reported AEs (≥10% incidence) were ISRs, abdominal pain, headache, rhinitis, and upper respiratory tract infection (Table 2). The most common AEs related to lumasiran were mild, transient ISRs, with erythema, pain, pruritus, and swelling at the injection site as the most common symptoms. No clinically relevant changes in laboratory measures (including liver function tests), vital signs,

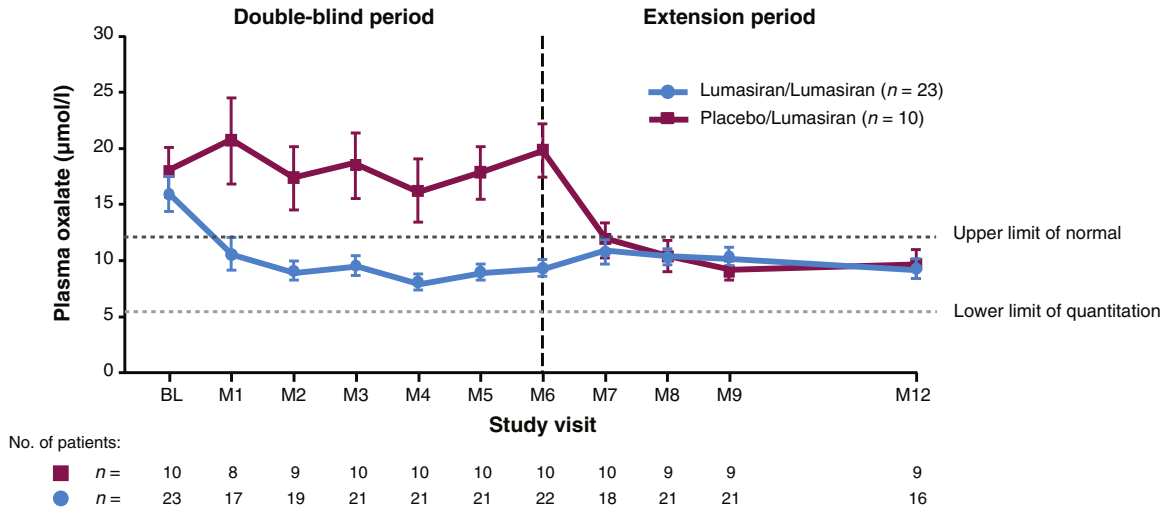


Figure 4. Plasma oxalate. Data are mean ± SEM of observed values. Dark gray dotted line represents the upper limit of normal of 12.11 µmol/l for plasma oxalate. Light gray dotted line represents the lower limit of quantitation of the plasma oxalate assay at 5.55 µmol/l; values below the lower limit of quantitation were assigned a value of 5.55 µmol/l. BL, baseline; M, month.

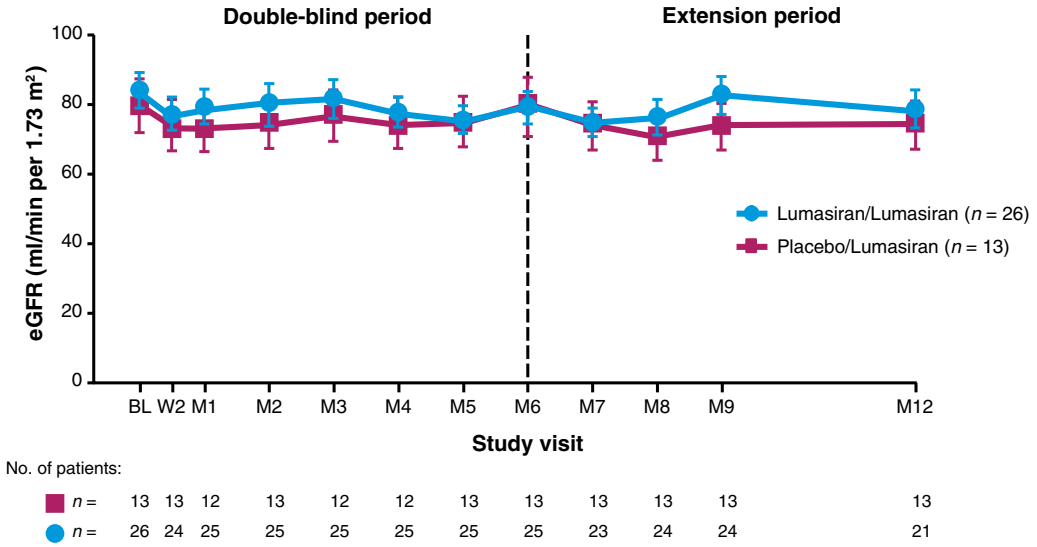


Figure 5. eGFR[a]. Data are mean ± SEM of observed values. [a]eGFR was calculated based on the Modification of Diet in Renal Disease formula for patients ≥18 years of age and the Schwartz Bedside Formula for patients <18 years of age at screening. BL, baseline; eGFR, estimated glomerular filtration rate; M, month; W, week.

and electrocardiograms related to lumasiran were observed. Overall, the safety profile of lumasiran was acceptable.

DISCUSSION

Excess oxalate, the toxic metabolite in PH1, can lead to recurrent kidney stones, nephrocalcinosis, progressive chronic kidney disease, and multiorgan damage from systemic oxalosis.[1,7] Substantial reduction in hepatic oxalate production is expected to preserve kidney function and confer long-term clinical benefit in patients with PH1.[5]

Treatment with lumasiran previously revealed a significant reduction in UOx excretion compared with placebo in the 6-month DBP of ILLUMINATE-A.[14] The current findings reveal the long-term efficacy and safety of lumasiran to month 12 in the EP of ILLUMINATE-A. Patients in the lumasiran/lumasiran group had a sustained reduction from baseline in UOx and plasma oxalate to month 12. Patients in the placebo/lumasiran group achieved a reduction in UOx and plasma oxalate after 6 months of lumasiran treatment that replicated the effect of lumasiran observed in the 6-month DBP,[14] confirming the results were robust and reproducible. After administration of lumasiran, plasma glycolate levels initially increased and then plateaued in both groups, consistent with a reduction in hepatic glycolate oxidase activity. There are no known metabolic consequences of the elevated concentrations of glycolate in the blood or urine.[16] In case reports of patients with glycolate oxidase deficiency, elevated plasma and urinary glycolate concentrations have been reported without apparent adverse clinical consequences.[17–20]

Clinical outcomes after lumasiran treatment are encouraging. Kidney function, as measured by eGFR, remained stable during lumasiran treatment. Kidney

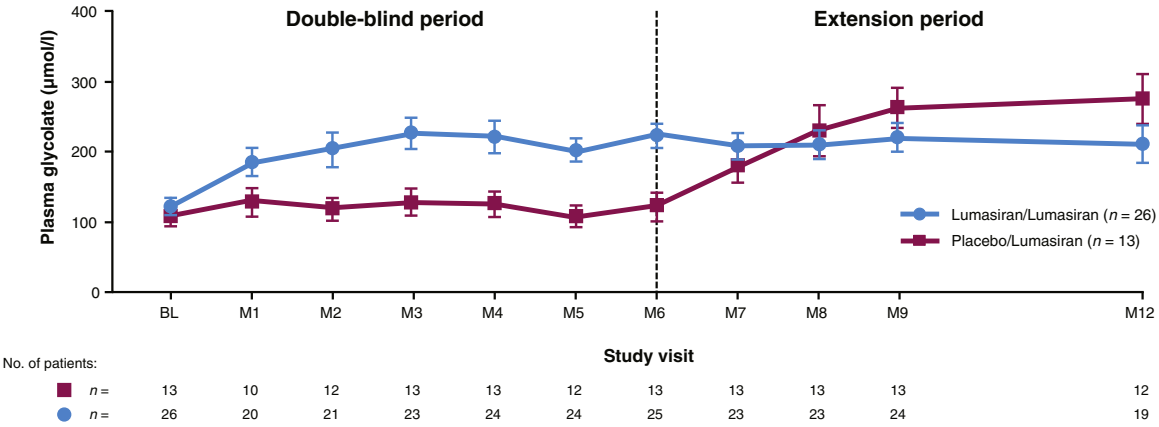
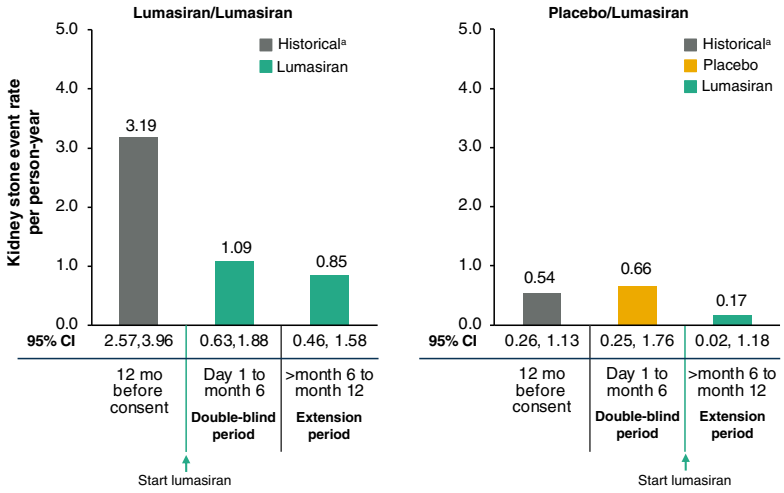


Figure 6. Plasma glycolate. Data are mean ± SEM of observed values. BL, baseline; M, month.

a



b

Lumasiran/Lumasiran

Patient no.	12 months before consent	SCR	Double-blind period: day 1 to month 6	Extension period: >month 6 to month 12
1[a]				
2[a]	II			
3				
4	I			I
5	IIII			
6	III	I		I
7				
8	~~IIII~~ II	I	I	
9	IIII			
10				
11				
12				
13				I
14				
15				
16	I			I
17	II			
18	~~IIII~~ II	IIII	~~IIII~~	I
19				
20				
21				
22	~~IIII IIII IIII IIII IIII IIII IIII IIII IIII IIII~~	I	III	
23				
24		II	I	III
25	II		III	II
26				

Start lumasiran

Placebo/Lumasiran

Patient no.	12 months before consent	SCR	Double-blind period: day 1 to month 6	Extension period: >month 6 to month 12
27	II			I
28				
29	I			
30				
31				
32	II			
33				
34				
35	II		III	
36			I	
37				
38				
39				

Start lumasiran

Figure 7. Kidney stone events. (a) Kidney stone event rates. A kidney stone event (either historical event or event that occurred during the trial) is defined as an event that includes at least 1 of the following: visit to health care provider because of a kidney stone, medication for renal colic, stone passage, or macroscopic hematuria owing to a kidney stone. [a]Patient-reported history of kidney stone events. (b) Kidney stone events by patient. Each row represents 1 patient. Each tick mark indicates 1 kidney stone event. The timing for the historical events (prior 12 months) was not documented; kidney stone events portrayed in the figure are not drawn based on when each event occurred. [a]Patients 1 and 2 discontinued treatment or withdrew from the study during the 6-month double-blind period and did not receive lumasiran in the extension period. SCR, screening.

stone event rates in the lumasiran/lumasiran group seemed to be lower during the first 6 months of lumasiran treatment when compared with historical recall data in the 12 months before patient consent, and this decrease was maintained during an additional 6 months of treatment. Owing to the short follow-up time, we cannot rule out that the kidney stone events occurring after the start of lumasiran treatment might have originated from pre-existing kidney stones *in situ*. The reported historical kidney stone event rate in the lumasiran/lumasiran group was higher compared with the placebo/lumasiran group. Because treatment

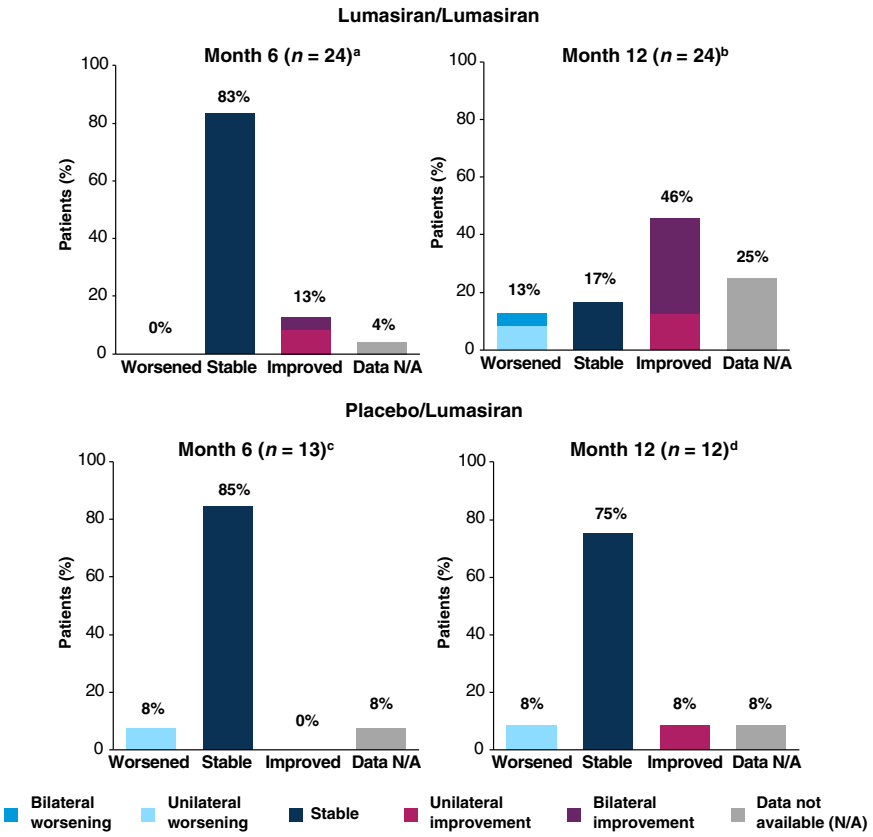


Figure 8. Nephrocalcinosis change from baseline. [a]After the first 6 months of treatment for patients originally randomized to lumasiran. Data N/A for 1 patient who did not have kidney ultrasound after 6 months of lumasiran treatment. [b]After 12 months of treatment for patients originally randomized to lumasiran. Data N/A for 4 patients who did not have kidney ultrasound after 12 months of lumasiran treatment, for 1 patient who discontinued treatment, and for 1 patient who withdrew from the study. [c]After 6 months of placebo treatment for patients originally randomized to placebo. Data N/A for 1 patient who had kidney ultrasound at month 6, but the images were not adequate for grading nephrocalcinosis. [d]After 6 months of lumasiran treatment for patients originally randomized to placebo who crossed over to lumasiran at month 6. Data N/A for 1 patient who did not have kidney ultrasound after 6 months of lumasiran treatment. N/A, not available.

randomization was not stratified by historical kidney stone events, some degree of imbalance may occur in a study with a small number of patients. Historical kidney stone events are limited by the retrospective nature of recall data, but the historical rates in this study were corroborated by those observed during the screening period in both the placebo/lumasiran and lumasiran/lumasiran groups. In addition, in the placebo/lumasiran group, historical kidney stone event rates were similar to event rates from baseline to month 6 during placebo administration. As a whole, this suggests that there was no differential recall bias between the groups and that historical recall data are a reasonable comparator for kidney stone event rates captured during the study.

Development of nephrocalcinosis, an early, progressive disease manifestation,[1,3,4] is associated with an increased risk of kidney failure in patients with PH1.[21] Spontaneous improvement in nephrocalcinosis is not expected in older patients with PH1 on a stable management regimen; however, cases of stabilization or improvement in nephrocalcinosis have been reported with normalization of UOx levels in infants and young children 3 to 8 years after liver transplantation.[22–24] In the ILLUMINATE-A study, most patients treated with lumasiran had improved or stable nephrocalcinosis grade, and the percentage of patients experiencing unilateral and bilateral improvement increased over time. Changes in the severity of nephrocalcinosis were evaluated by noninvasive ultrasounds, evaluated by a central radiologist using a validated semiquantitative scale, at prespecified, frequent time points. Because the grading scale used was previously validated only in children[15] and is not most often used in clinical practice, we conducted a *post hoc* subgroup analysis to evaluate nephrocalcinosis by age and found that our method revealed changes in nephrocalcinosis in both children and adults.

Both change in the rate of kidney stone events and change in nephrocalcinosis evaluated by kidney ultrasound were exploratory end points in this study. Longer follow-up is needed to further evaluate the effect of lumasiran on kidney stones and nephrocalcinosis.

Table 2. Safety overview in patients with PH1 during lumasiran treatment

Event, *n* (%)	Placebo/ lumasiran (*n* = 13)	Lumasiran/ lumasiran (*n* = 26)	All lumasiran (*N* = 39)
Any AE	9 (69)	24 (92)	33 (85)
Serious AE[a]	0	1 (4)	1 (3)
Severe AE[a]	0	1 (4)	1 (3)
AE leading to discontinuation of study treatment[b]	0	1 (4)	1 (3)
AEs occurring in ≥10% of patients			
Injection-site reactions[c]	5 (39)	11 (42)	16 (41)
Abdominal pain	1 (8)	6 (23)	7 (18)
Headache	0	4 (15)	4 (10)
Rhinitis	2 (15)	2 (8)	4 (10)
Upper respiratory tract infection	1 (8)	3 (12)	4 (10)
Death	0	0	0

AE, adverse event; PH1, primary hyperoxaluria type 1.
[a]Urosepsis, considered not related to study drug by the investigator.
[b]Fatigue and disturbance in attention, considered not related to lumasiran by the investigator.
[c]Includes AEs of injection-site reaction, injection-site pain, injection-site erythema, and injection-site discomfort.
Safety data from first dose of lumasiran to data cutoff date of May 1, 2020.

Lumasiran was found to have an acceptable safety profile. The most common AEs related to lumasiran treatment were ISRs, all of which were mild and transient. The cumulative safety profile of lumasiran was consistent with that observed in the DBP.[14]

One limitation of this study is that patients aged <6 years were excluded; however, this age group is being studied in the ongoing ILLUMINATE-B trial (NCT03905694). The magnitude of oxalate reduction reported here for children aged ≥6 years and adults in ILLUMINATE-A is consistent with that reported in infants and children aged <6 years in ILLUMINATE-B (spot UOx-to-creatinine ratio least-squares mean reduction from baseline to month 6 of 72.0% in lumasiran-treated patients).[25] In addition, patients with an eGFR <30 ml/min per 1.73 m^2 were excluded from this study; however, this patient population is being studied in the ongoing ILLUMINATE-C trial (NCT04152200). The placebo-controlled period of ILLUMINATE-A was limited to 6 months. All patients will continue to receive open-label lumasiran in the EP and be monitored for efficacy and safety over time.

In conclusion, this phase 3 trial revealed that 12 months of lumasiran treatment had sustained efficacy with an acceptable safety profile in patients with PH1. In addition, the patients who crossed over from placebo to lumasiran treatment recapitulated the efficacy profile observed in the original treatment cohort, revealing the robust therapeutic benefit of lumasiran. Lumasiran enabled sustained lowering of UOx levels to normal or near normal and had encouraging results on clinical outcomes. Efficacy and safety data of lumasiran will continue to be collected in the EP.

DISCLOSURE

SAH reports receiving travel expenses to participate in clinical research meetings, consultancy fee from serving on the advisory board, and consultancy fees paid to Birmingham Children's Hospital Renal Research Fund from Alnylam Pharmaceuticals, and other from Dicerna Pharmaceuticals and Chiesi Pharmaceuticals. JWG reports receiving consultancy fees from Alnylam Pharmaceuticals and study grants from Alnylam Pharmaceuticals, Dicerna Pharmaceuticals, and uniQure Pharmaceuticals. YF reports receiving consultancy fees from Alnylam Pharmaceuticals and membership in the safety review committee. MJK is an employee of Jacksonville Center for Clinical Research, which provides research and consulting services to pharmaceutical companies, government, and other industries. JSO reports receiving institutional research funding from Alnylam Pharmaceuticals. ALSL reports receiving consultancy fees from Alnylam Pharmaceuticals and Dicerna Pharmaceuticals and serving as a principal investigator for a research funded by OxThera. HSL is a principal investigator for Alnylam Pharmaceuticals and reports receiving travel and accommodation expenses from Alnylam Pharmaceuticals to attend international investigators' meetings. JMS reports receiving grants, personal fees, and nonfinancial support from Alnylam Pharmaceuticals. WH reports receiving travel and accommodation expenses from Alnylam Pharmaceuticals to attend an international investigators' meeting. DM reports receiving research funding, consultancy fees, and nonfinancial support from Alnylam Pharmaceuticals. SHM reports receiving consultancy fees from Allena Pharmaceuticals, Alnylam Pharmaceuticals, and Dicerna Pharmaceuticals and is a principal investigator for a research funded by OxThera. MC is a principal investigator for Alnylam Pharmaceuticals. ES is a principal investigator for Alnylam Pharmaceuticals and reports receiving travel and accommodation expenses from Alnylam Pharmaceuticals to attend international investigators' meeting. SFG reports receiving nonfinancial support and grants from Alnylam Pharmaceuticals and grants from Dicerna Pharmaceuticals. DJS reports receiving grants and other from Alnylam Pharmaceuticals and personal fees from Advicenne. TN, MTS, and JMG are employees of Alnylam Pharmaceuticals and hold shares in Alnylam Pharmaceuticals. TLM and BAH are former employees of Alnylam Pharmaceuticals and hold shares in Alnylam Pharmaceuticals. JCL reports receiving grants from Alnylam Pharmaceuticals, Dicerna Pharmaceuticals, Retrophin, OxThera, and Siemens; other from Novobiome

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DATA SHARING STATEMENT

Because of the sensitive nature of the data collected for this study, the data set will not be made available to other researchers.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

CONSORT Statement

Figure S1. ILLUMINATE-A study design.

Figure S2. Percent change from baseline in (A) 24-hour UOx:creatinine ratios and (B) spot UOx:creatinine ratios.

Figure S3. 24-Hour urinary glycolate:creatinine ratios.

Figure S4. Nephrocalcinosis change from baseline in (A) patients aged $<$18 years and (B) patients aged $\geq$18 years.

ILLUMINATE-A Collaborators.

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