Lumasiran for Advanced Primary Hyperoxaluria Type 1: Phase 3 ILLUMINATE-C Trial

M. Michael, J. W. Groothoff, H. Shasha-Lavsky, J. C. Lieske, Y. Frishberg, E. Simkova, A. L. Sellier-Leclerc, A. Devresse, F. Guebre-Egziabher, S. A. Bakkaloglu, et al.

Lumasiran for Advanced Primary Hyperoxaluria Type 1: Phase 3 ILLUMINATE-C Trial

Mini Michael, Jaap W. Groothoff, Hadas Shasha-Lavsky, John C. Lieske, Yaacov Frishberg, Eva Simkova, Anne-Laure Sellier-Leclerc, Arnaud Devresse, Fitsum Guebre-Egziabher, Sevcan A. Bakkaloglu, Chebl Mourani, Rola Saqan, Richard Singer, Richard Willey, Bahru Habtemariam, John M. Gansner, Ishir Bhan, Tracy McGregor, and Daniella Magen

Rationale & Objective: Lumasiran reduces urinary and plasma oxalate (POx) in patients with primary hyperoxaluria type 1 (PH1) and relatively preserved kidney function. ILLUMINATE-C evaluates the efficacy, safety, pharmacokinetics, and pharmacodynamics of lumasiran in patients with PH1 and advanced kidney disease.

Study Design: Phase 3, open-label, single-arm trial.

Setting & Participants: Multinational study; enrolled patients with PH1 of all ages, estimated glomerular filtration rate ≤45 mL/min/1.73 m^2 (if age ≥12 months) or increased serum creatinine level (if age <12 months), and POx ≥20 μmol/L at screening, including patients with or without systemic oxalosis.

Intervention: Lumasiran administered subcutaneously; 3 monthly doses followed by monthly or quarterly weight-based dosing.

Outcome: Primary end point: percent change in POx from baseline to month 6 (cohort A; not receiving hemodialysis at enrollment) and percent change in predialysis POx from baseline to month 6 (cohort B; receiving hemodialysis at enrollment). Pharmacodynamic secondary end points: percent change in POx area under the curve between dialysis sessions (cohort B only); absolute change in POx; percent and absolute change in spot urinary oxalate-creatinine ratio; and 24-hour urinary oxalate adjusted for body surface area.

Results: All patients (N = 21; 43% female; 76% White) completed the 6-month primary analysis period. Median age at consent was 8 (range, 0-59) years. For the primary end point, least-squares mean reductions in POx were 33.3% (95% CI, −15.2% to 81.8%) in cohort A (n = 6) and 42.4% (95% CI, 34.2%-50.7%) in cohort B (n = 15). Improvements were also observed in all pharmacodynamic secondary end points. Most adverse events were mild or moderate. No patient discontinued treatment or withdrew from the study. The most commonly reported lumasiran-related adverse events were injection-site reactions, all of which were mild and transient.

Limitations: Single-arm study without placebo control.

Conclusions: Lumasiran resulted in substantial reductions in POx with acceptable safety in patients with PH1 who have advanced kidney disease, supporting its efficacy and safety in this patient population.

Funding: Alnylam Pharmaceuticals.

Trial Registration: Registered at ClinicalTrials.gov with study number NCT04152200 and at EudraCT with study number 2019-001346-17.

Visual Abstract online

Complete author and article information provided before references.

Correspondence to M. Michael (mmichael@bcm.edu)

Am J Kidney Dis. XX(XX):1-11. Published online month xx, xxxx.

doi: 10.1053/j.ajkd.2022.05.012

Primary hyperoxaluria type 1 (PH1) is a rare, progressive, autosomal recessive genetic disease characterized by excessive hepatic oxalate production.[1,2] PH1 is caused by mutations in the *AGXT* gene, which encodes the liver peroxisomal enzyme alanine-glyoxylate aminotransferase.[1,2] When alanine-glyoxylate aminotransferase is deficient, glyoxylate is oxidized to oxalate, which is mainly excreted by the kidneys. Oxalate, in the form of its calcium salt, is insoluble and can readily crystallize in the renal parenchyma and urinary tract. In PH1, excess urinary oxalate (UOx) results in recurrent kidney stones, progressive kidney disease, and, ultimately, kidney failure (Fig S1).[1,3] As kidney function declines, elimination of oxalate via the kidneys is reduced, such that plasma levels of oxalate increase and exceed saturation. Calcium oxalate can then accumulate in bone, heart, retina, skin, vasculature, the nervous system, and other tissues, resulting in multiple-organ damage. This devastating phenomenon, systemic oxalosis, typically arises when the estimated glomerular filtration rate (eGFR) has decreased to <30 to 45 mL/min/1.73 m^2.[1,2]

Patients with PH1 often exhibit signs and symptoms such as urolithiasis and/or nephrocalcinosis at a young age.[3-5] Without treatment, PH1 often progresses inexorably, and death from kidney failure and/or complications of systemic oxalosis can occur.[1,5-7] Historically, approximately 40% of patients with PH1 have shown progression to kidney failure at the time of diagnosis.[4,5] Patients progressing to or presenting with kidney failure require invasive approaches such as dialysis and liver transplant or combined liver and kidney transplant.[1] Unlike other forms of chronic kidney disease in which dialysis is generally initiated when eGFR decreases to <15 mL/min/1.73 m^2, in patients with PH1, dialysis is indicated when plasma oxalate (POx) levels increase to the point at which supersaturation of calcium oxalate in the blood is thought to

PLAIN-LANGUAGE SUMMARY

Primary hyperoxaluria type 1 (PH1) is a rare genetic disease characterized by excessive hepatic oxalate production that frequently causes kidney failure. Lumasiran is an RNA interference therapeutic that is administered subcutaneously for the treatment of PH1. Lumasiran has been shown to reduce oxalate levels in the urine and plasma of patients with PH1 who have relatively preserved kidney function. In the ILLUMINATE-C study, the efficacy and safety of lumasiran were evaluated in patients with PH1 and advanced kidney disease, including a cohort of patients undergoing hemodialysis. During the 6-month primary analysis period, lumasiran resulted in substantial reductions in plasma oxalate with acceptable safety in patients with PH1 complicated by advanced kidney disease.

occur, leading to systemic oxalosis.[8] Dialysis regimens for PH1 are typically more frequent (as often as 6 times per week) than standard dialysis (3 times per week) and can impact patient quality of life.[1,8-10] Even intensive dialysis is often inadequate to effectively clear accumulating oxalate.[9] Although ~60% to 80% of POx can be removed following a hemodialysis session,[11] POx rebounds to 80% of the predialysis load within 24 hours because endogenous oxalate production from the liver persists and solubilized calcium oxalate from systemic stores (eg, bone turnover) enters the plasma. As a result, systemic oxalosis with end-organ damage may still develop in patients undergoing intensive dialysis.[8,12]

Lumasiran is a subcutaneously administered, liver-directed RNA interference therapeutic approved by the US Food and Drug Administration for the treatment of PH1 to reduce UOx levels in pediatric and adult patients[13] and by the European Commission for the treatment of PH1 in all age groups.[14] It targets and promotes degradation of the messenger RNA encoding glycolate oxidase, an enzyme upstream of alanine-glyoxylate aminotransferase. By blocking the production of glycolate oxidase, lumasiran reduces levels of glyoxylate, the substrate for oxalate synthesis, and consequently decreases hepatic oxalate production.[13-15]

Current evidence supports the use of UOx and POx measurements as surrogate end points for clinical trials in patients with primary hyperoxaluria.[16,17] POx level is a useful predictor of the risk of kidney failure and systemic oxalosis in patients with an eGFR <45 mL/min/1.73 m^2 and is considered a more appropriate end point to predict clinical benefit of treatment for patients with chronic kidney disease stages 3b-5.[16-18]

In the phase 3 ILLUMINATE-A (ClinicalTrials.gov identifier, NCT03681184; EudraCT identifier, 2018-001981-40) and ILLUMINATE-B (ClinicalTrials.gov identifier, NCT03905694; EudraCT identifier, 2018-004014-17) studies, lumasiran resulted in substantial reductions in UOx and POx levels, with an acceptable safety profile in patients with PH1 whose kidney function was relatively preserved.[19,20]

Here, we report results from the 6-month primary analysis period of ILLUMINATE-C, a phase 3 study designed to evaluate the efficacy, as measured by changes in POx levels, and safety of lumasiran in patients of all ages with PH1 with advanced kidney disease.

Methods

Study Design and Patients

ILLUMINATE-C (ClinicalTrials.gov identifier, NCT04152200; EudraCT identifier, 2019-001346-17) is a multicenter, multinational, single-arm, phase 3 study of lumasiran in patients with PH1 and advanced kidney disease consisting of a 6-month primary analysis period followed by a long-term (54 months) extension period (Fig S2). Cohort A included patients who were not receiving hemodialysis at study enrollment. Cohort B included patients who were receiving hemodialysis at study enrollment; elective changes to the hemodialysis regimen (changes in dialysis frequency or duration, filter size or type, and blood flow) were not permitted during the screening and 6-month primary analysis except when medically necessary.

Eligibility Criteria

Patients of all ages with a genetically confirmed diagnosis of PH1 were eligible. Other requirements at screening included POx ≥20 μmol/L (upper limit of normal, 12.11 μmol/L) and eGFR ≤45 mL/min/1.73 m^2 if at least 12 months of age or increased serum creatinine level if younger than 12 months. Patients receiving pyridoxine therapy were required to have been receiving a stable regimen for at least 90 days before providing informed consent and to continue to receive this regimen through the month-6 visit. Dose adjustments for interval weight gain were permitted. Patients undergoing hemodialysis (cohort B) were required to have been receiving a stable hemodialysis regimen for at least 4 weeks before the screening POx assessment and to maintain this regimen through the month-6 visit. Patients who were receiving peritoneal dialysis alone or combined hemodialysis/peritoneal dialysis therapy were excluded from the study because of the nonstandardized nature of peritoneal dialysis and changes in the kinetic properties of the peritoneal membrane over time.[21] Dialysis regimen modifications were permitted when medically necessary according to investigator judgment in consultation with the patient's treating physician. The full eligibility criteria are provided in the protocol (Supplementary File 2).

Lumasiran was administered subcutaneously using weight-based dosing (Fig S3; Table S1). Although lumasiran is not expected to be dialyzable because of its large

molecular weight, in patients receiving dialysis, lumasiran was administered no later than 120 minutes after dialysis. The study was approved by institutional review boards or ethics committees at the participating study sites and is being conducted in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki. All patients or their legal guardians provided informed consent/assent per local and national requirements. An independent data monitoring committee oversaw the safety and overall conduct of this study. Data were collected by study investigators and analyzed by the study sponsor.

End Points

Primary end points were percent change in POx from baseline to month 6 (cohort A) and percent change in predialysis POx from baseline to month 6 (cohort B). POx measurements were collected monthly from baseline to month 6. The primary end point and pharmacodynamic secondary end points at month 6 were the average of measurements from month 3 through month 6. Pharmacodynamic secondary end points for the primary analysis period included percent change in POx area under the curve (AUC) between dialysis sessions (cohort B only), absolute change in POx, percent and absolute change in spot urinary oxalate-creatinine ratio, and 24-hour UOx adjusted for body surface area. Pharmacodynamic end points were collected monthly from baseline to month 6. Plasma pharmacokinetic (PK) parameters of lumasiran were also evaluated and collected at day 1 and month 6. Select exploratory end points included change in urinary and plasma glycolate, frequency of antidrug antibodies, and change in cardiac measures of systemic oxalosis. The full list of secondary and exploratory end points is provided in the protocol (Supplementary File 2). Safety assessments included monitoring of adverse events (AEs) and laboratory parameters. Change in medullary nephrocalcinosis grade, change in kidney stone event rates, and change in eGFR (cohort A) are secondary end points in the long-term extension period.

Total oxalate, glycolate, and PK assessments were evaluated at a central laboratory by validated liquid chromatography–tandem mass spectrometry assays, which were developed by Alnylam to meet regulatory requirements and have not yet been published. Nephrocalcinosis was assessed, and kidney stone events were defined as previously described.[20] eGFR was calculated from serum creatinine based on the Modification of Diet in Renal Disease (MDRD) Study equation for patients aged at least 18 years and the Schwartz bedside formula[22] for patients aged 1 to less than 18 years. Cardiac systemic oxalosis was assessed by echocardiograms during screening and at month 6; echocardiograms were centrally read. The numbers of patients with abnormal left ventricular ejection fraction (LVEF; <55%), global longitudinal strain (GLS; <15%), or early transmitral diastolic inflow divided by early diastolic mitral annular velocity (E/e'; >15) at baseline who showed an improvement of ≥5% in LVEF, ≥2% in GLS, and/or ≥2% in E/e', respectively, as well as the actual measurements and changes from baseline values for LVEF, GLS, or E/e' at each scheduled postbaseline visit, were summarized.

Antidrug Antibodies

Antidrug antibodies (immunoglobulins G, M) against lumasiran were evaluated in plasma at baseline and months 1, 3, and 6 using a validated enzyme-linked immunoassay.

Statistical Analyses

A planned sample size of 20 patients, including at least 6 patients in each cohort, at least 4 patients younger than 6 years at consent, and at least 2 patients at least 6 and younger than 18 years at consent, was determined based on feasibility considerations. The safety population included all patients who received lumasiran. The efficacy population (full analysis set) included all patients who received any amount of lumasiran and had at least 1 valid POx value at baseline and at the month-3 through month-6 assessments. The PK population included all patients who received any amount of lumasiran and had at least 1 evaluable postdose blood sample for PK parameters and evaluable PK data.

The primary analysis of percent change from baseline in POx (cohort A) and predialysis POx (cohort B) was performed using a restricted maximum likelihood–based mixed-effect model repeated-measures approach and included scheduled visits and baseline POx as fixed effects and patient as a random factor; autoregressive(1) was used to model the within-patient variability. The primary estimate is the least-squares mean of the percent change in POx from baseline to month 3 through month 6 averaged over these time points.

Subgroup analyses by age and by weight-based dosing groups were performed to further understand treatment effect. For patients in cohort B, a secondary end point of percent change from baseline in POx area under the curve from 0 to 24 hours ($AUC_{0\text{-}24h}$) was evaluated at month 6. Analyses of secondary end points of absolute change in POx, percent and absolute change in spot urinary oxalate-creatinine ratio, and 24-hour UOx were also performed using the mixed-effect model repeated-measures approach. Full details of the analyses are provided in the Statistical Analysis Plan (Supplementary File 3). Statistical analyses were performed using Statistical Analysis Software (SAS Institute) version 9.4 or later.

Results

Patient Disposition

From March through December 2020, 21 patients across 13 sites in 10 countries were enrolled in the study (Fig S4). There were 6 patients in cohort A and 15 patients in cohort B. All patients completed the 6-month primary analysis period. Baseline characteristics were generally balanced between cohorts and are presented in Table 1. All

Table 1. Baseline Demographic and Clinical Characteristics of the Patients

Characteristic	Cohort A (n = 6)	Cohort B (n = 15)	All Treated (N = 21)
Age at consent, y	9.0 (0-40)	6.0 (1-59)	8.0 (0-59)
Time from diagnosis to first dose, mo	72.2 (4-350)	16.6 (6-440)	21.6 (4-440)
Female sex	3 (50%)	6 (40%)	9 (43%)
Race			
White	4 (67%)	12 (80%)	16 (76%)
Asian	1 (17%)	3 (20%)	4 (19%)
Other	1 (17%)	0	1 (5%)
Geographic region			
Europe	0	8 (53%)	8 (38%)
North America	1 (17%)	2 (13%)	3 (14%)
Israel	1 (17%)	2 (13%)	3 (14%)
United Arab Emirates	0	3 (20%)	3 (14%)
Other[a]	4 (67%)	0	4 (19%)
Genotype[b]			
PR/*	0	5 (33%)	5 (24%)
M/M or M/N	5 (83%)	7 (47%)	12 (57%)
N/N	1 (17%)	3 (20%)	4 (19%)
Pyridoxine use	4 (67%)	7 (47%)	11 (52%)
Plasma oxalate[c], μmol/L	57.9 (22.7-134.0)	103.7 (56.3-167.0)	100.9 (22.7-167.0)
Spot urinary oxalate-creatinine ratio[d]			
Patients with measurement	6	2	8
Value, mmol/mmol	0.332 (0.075-1.380)	0.535 (0.451-0.618)	0.391 (0.075-1.380)
24-h urinary oxalate excretion[e]			
Patients with measurement	5	1	6
Value, mmol/d/1.73 m^2	2.01 (0.56-2.47)	1.28 (1.28-1.28)	1.64 (0.56-2.47)
eGFR[f]		NA	
Patients with measurement	5	–	5
Value, mL/min/1.73 m^2	16.5 (8.6-34.1)	–	16.5 (8.6-34.1)
Dialysis sessions per week	NA	6 (3-7)	NA

Values for continuous variables given as median (range). Abbreviations: eGFR, estimated glomerular filtration rate; NA, not applicable.
[a]Australia, Jordan, Lebanon, and Turkey.
[b]M=missense; N=nonsense; PR=pyridoxine-responsive; *=any genotype of PR, M, or N. Pyridoxine-responsive was defined as NM_000030.3(AGXT):c.508G>A (p.Gly170Arg) or NM_000030.3(AGXT):c.454T>A (p.Phe152Ile). Missense and nonsense were defined based on Mandrile et al.[4]
[c]Upper limit of normal = 12.11 μmol/L (1.09 mg/mL) as determined based on data from 75 healthy adults.
[d]1 mmol/mmol = 0.796 mg/mg.
[e]Upper limit of normal = 0.514 mmol/d/1.73 m^2 for body surface area–adjusted 24-hour urinary oxalate.
[f]eGFR was calculated only in patients aged ≥12 mo; calculated according to the Modification of Diet in Renal Disease Study equation for those aged ≥18 y and the Schwartz bedside formula[22] for those aged 1 to <18 y.

21 patients met the criteria for and were included in the safety analysis set, full analysis set, and PK analysis set.

Efficacy: Primary End Point

POx reduction was observed in both cohorts as early as month 1. The primary estimate of the least-squares mean percent reductions in POx from baseline to month 6 were 33.3% (95% CI, −15.2% to 81.8%) for cohort A and 42.4% (95% CI, 34.2%-50.7%) for cohort B (Fig 1; Table 2). A consistent treatment effect was observed across all prespecified subgroups in cohort B (Fig S5). In cohort A, the number of patients in each subgroup was too small to assess any trends.

Efficacy: Pharmacodynamic Secondary End Points

In cohort B, the least-squares mean percent reduction from baseline in POx $AUC_{0\text{-}24h}$ at month 6 was 41.4% (95% CI, 31.8%-51.0%; Fig 2; Table 2). The least-squares means of the absolute reduction in POx from baseline to month 6 were 35.3 (95% CI, 14.2-56.3) μmol/L in cohort A and 48.3 (95% CI, 40.8-55.9) μmol/L in cohort B (Fig 1; Table 2). All measures of UOx showed concordant findings, an observation consistent with reduced UOx in cohort A (Figs S6 and S7; Table 2).

The PK profiles for lumasiran were similar across cohorts A and B, and lumasiran was rapidly eliminated from the systemic circulation, consistent with previous reports[23] (Table S2).

Exploratory End Points

Across cohorts A and B, plasma glycolate levels initially increased and then plateaued, consistent with a reduction in hepatic glycolate oxidase activity mediated by lumasiran (Fig S8). An approximate doubling of plasma glycolate levels relative to baseline was observed. There were no treatment-emergent antidrug antibodies observed.

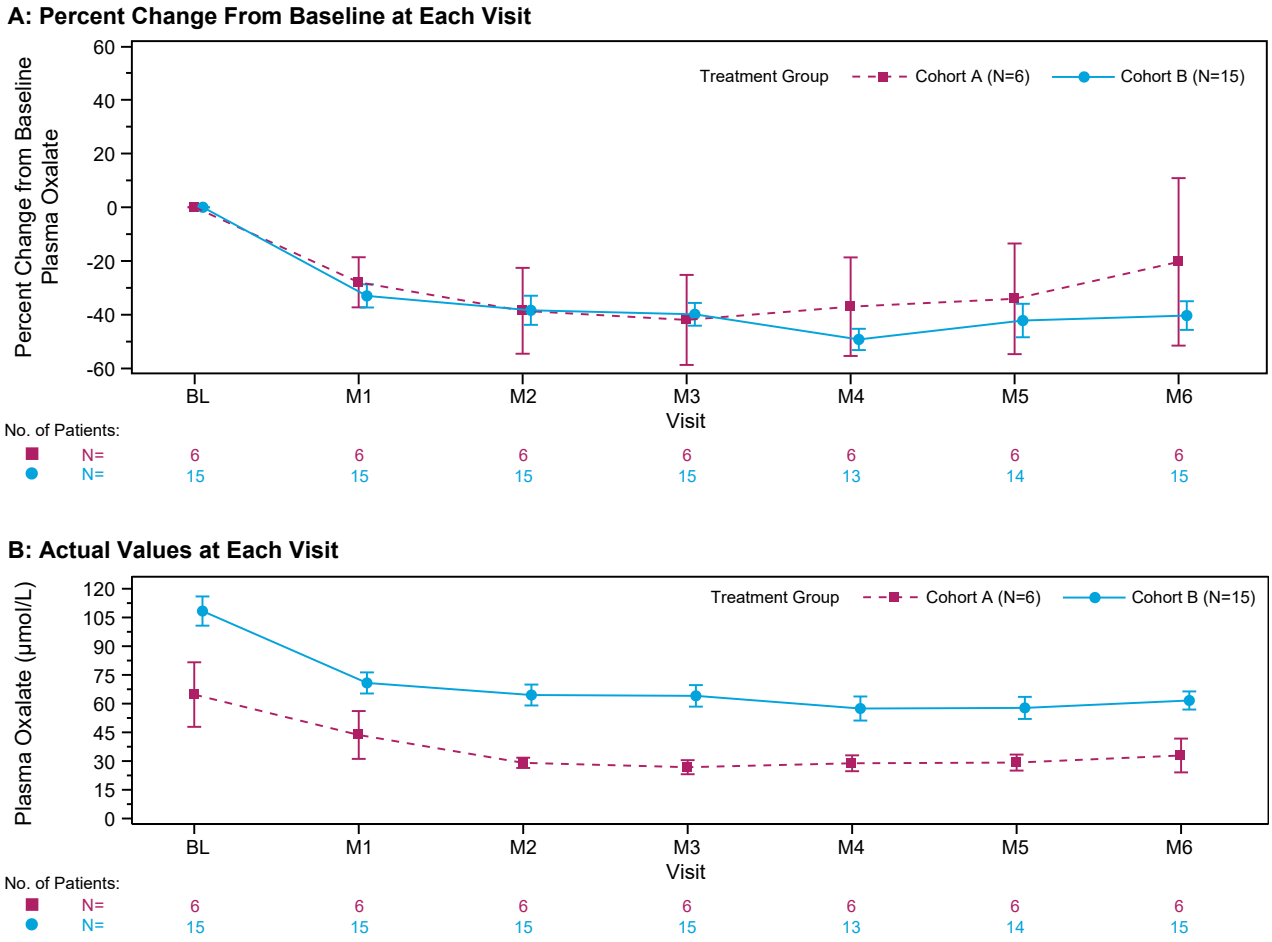

Figure 1. Plasma oxalate: mean (standard error of the mean) percent change from baseline at each visit (A) and actual values at each visit (B). Baseline value was the mean of the last 4 plasma oxalate level values collected before the first dose of lumasiran (pre-dialysis in cohort B). The upper limit of normal is 12.11 µmol/L for plasma oxalate, as determined based on data from 75 healthy adults. Abbreviations: BL, baseline; M, month.

Changes in cardiac measures of systemic oxalosis are detailed in Table S3. In cohort A, 1 patient had abnormal LVEF at baseline and exhibited improvement at month 6. In cohort B, 4 patients had abnormal LVEF at baseline; 2 of 4 patients showed improvements at month 6, whereas the other 2 did not. In cohort A, 1 patient had abnormal GLS at baseline and showed improvement at month 6. In cohort B, 3 patients had abnormal GLS at baseline, and all 3 showed improvement at month 6. There were no E/e′ abnormalities at baseline (Table S3).

Other Outcomes

Among 6 patients in cohort A with kidney ultrasound results at baseline and month 6, medullary nephrocalcinosis was present at baseline in 5 patients. Of those 5 patients, medullary nephrocalcinosis grade remained stable in 2 patients, worsened in none, and improved in 3 (2 unilateral improvements and 1 bilateral improvement) at month 6. Of 11 patients in cohort B with kidney ultrasound results at baseline and month 6, medullary nephrocalcinosis was present at baseline in 2 patients. Nephrocalcinosis improved in both patients (1 unilateral improvement and 1 bilateral improvement). Among the patients without nephrocalcinosis at baseline (cohort A: 1 patient; cohort B: 9 patients), the cohort A patient had bilateral worsening, and levels in all 9 cohort B patients remained stable at month 6 (Table S4).

For cohort A, the rates of kidney stone events per person-year were 3.20 (95% CI, 1.96-5.22) in the 12-month period before informed consent and 1.48 (95% CI, 0.55-3.92) in the primary analysis period. For cohort B, the rates of kidney stone events per person-year were 0.07 (95% CI, 0.01-0.71) in the 12-month period before informed consent and 0.00 (95% CI, 0.00-0.53) in the primary analysis period (Table S4). For cohort A, mean eGFRs 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 (Fig S9).

In cohort B, the dialysis regimen was modified in 2 (13%) patients during the primary analysis period (weight adjustments in 1 patient and transient modifications in

Table 2. Primary and Pharmacodynamic Secondary End Points

End Point	Cohort A (n = 6)	Cohort B (n = 15)
Primary end point		
Percent change in plasma oxalate from baseline to month 6[a]	−33.3 ± 17.6 (−81.8, 15.2)	−42.4 ± 4.0 (−50.7, −34.2)
Secondary end points		
Percent change in plasma oxalate $AUC_{0\text{-}24h}$ between dialysis sessions from baseline to month 6[b]	NA	−41.4 ± 4.4 (−51.0, −31.8)
Absolute change in plasma oxalate[c] from baseline to month 6, μmol/L[a]	−35.3 ± 7.4 (−56.3, −14.2)	−48.3 ± 3.6 (−55.9, −40.8)
Percent change in spot urinary oxalate-creatinine ratio from baseline to month 6[a]	−39.5 ± 9.4 (−64.1, −14.9)	NA
Absolute change in spot urinary oxalate-creatinine ratio[d] from baseline to month 6, mmol/mmol[a]	−0.188 ± 0.016 (−0.229, −0.147)	NA
Percent change in BSA-adjusted 24-hour urinary oxalate from baseline to month 6[a]	−10.6 ± 6.8 (−32.0, 10.9)[e]	NA
Absolute change in BSA-adjusted 24-hour urinary oxalate from baseline to month 6, mmol/d/1.73 m^2[a]	−0.53 ± 0.11 (−0.89, −0.18)[e]	NA

Values given as least-squares mean ± SEM (95% CI). Abbreviations: $AUC_{0\text{-}24h}$, area under the curve from 0 to 24 hours; BSA, body surface area; NA, not applicable; POx, plasma oxalate; SEM, standard error of the mean.
[a]Change from baseline to month 6 was calculated as the change across months 3 through 6. The least-squares mean with corresponding SEM and 95% CI were derived using the restricted maximum likelihood–based mixed model for repeated measures model. The model included scheduled visits and baseline POx as fixed effects and patient as a random factor. Autoregressive(1) was used to model the within-patient variability.
[b]Least-squares mean percent change from baseline in POx $AUC_{0\text{-}24h}$ at month 6 and its associated 95% CI were estimated using the restricted maximum likelihood–based mixed model for repeated measures approach including data evaluated at months 3 and 6. The model included scheduled visits and baseline POx as fixed effects and patient as a random factor. Autoregressive(1) was used to model the within-patient variability.
[c]Upper limit of normal = 12.11 μmol/L (1.09 mg/mL), as determined based on data from 75 healthy adults.
[d]1 mmol/mmol = 0.796 mg/mg.
[e]n = 5.

response to a COVID-19 diagnosis in the other). The modifications were permitted as medically necessary, so the patients were not excluded. All patients using pyridoxine at baseline continued pyridoxine therapy during the primary analysis period.

Safety

Of 21 patients, 17 (81%) had at least 1 AE reported during the 6 months of the primary analysis period (Table 3). The majority of AEs were mild or moderate in severity. Serious AEs reported were primarily associated with dialysis procedural complications and were consistent with the underlying advanced kidney disease in this patient population. There were no lumasiran-related serious or severe AEs and no deaths of patients who received lumasiran. There were no treatment discontinuations or study withdrawals. The most frequently reported AEs were pyrexia (29%) and injection-site reactions (24%; Table 3).

The most common AE related to lumasiran was injection-site reaction (24% of patients [5 of 21]). All injection-site reactions were mild and transient, and the most common signs and symptoms included erythema, discoloration, and hematoma at the injection site. There were no clinically relevant trends related to lumasiran in laboratory measures (including hematology, blood chemistry, and liver function tests), vital signs, physical examinations, or electrocardiograms.

Discussion

In patients with PH1 and advanced kidney disease, including those receiving dialysis, POx is directly related to the pathophysiology of oxalosis.[16] Conservative management and dialysis are generally unable to maintain neutral POx balance and halt disease progression, particularly in patients who do not experience a full response to pyridoxine. As described in a recent natural history study of 17 patients with PH1, predialysis POx levels remained greater than the target despite intensive dialysis, and an increasing evidence of oxalosis, including cardiac dysfunction, developed over time.[12] A reduction in hepatic oxalate production, as measured by POx, is expected to reduce the need for dialysis, ameliorate or prevent the development of systemic oxalosis through induction of a negative oxalate balance, and potentially reduce the need for liver transplant in patients with PH1. Therapies that can effectively reduce hepatic oxalate production have the potential to halt or even reverse disease progression and be effective in patients of all ages and at all stages of the disease, including those receiving dialysis, which may lead to improvements in their quality of life. Additional data will be gathered during the extension period of this study.

ILLUMINATE-C evaluated the efficacy and safety of lumasiran in patients with PH1 who have advanced kidney disease. Lumasiran was generally well tolerated and resulted in a substantial reduction in POx in patients with

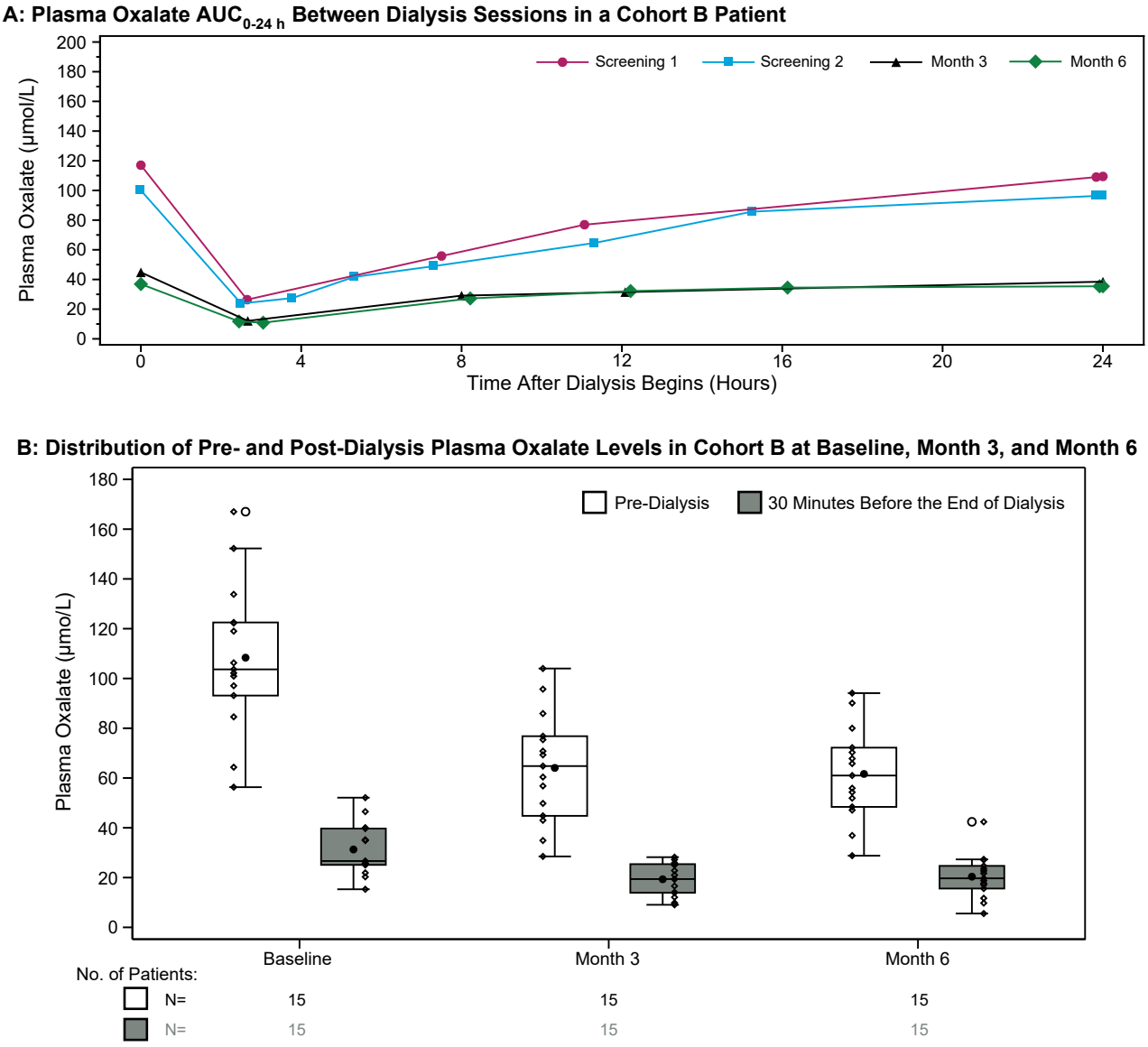

Figure 2. Pre- and postdialysis plasma oxalate levels in cohort B. During screening, 2 separate profile assessments were performed at least 7 days apart. (A) Plasma oxalate area under the curve from 0 to 24 hours ($AUC_{0\text{-}24h}$) between dialysis sessions in a cohort B patient. (B) Distribution of pre- and postdialysis plasma oxalate levels in cohort B at baseline, month 3, and month 6. Filled symbols represent the means; open circles represent outliers.

decreased kidney function, including those receiving dialysis, during the 6-month primary analysis period. It is possible that the substantial reduction in POx observed in ILLUMINATE-C may underestimate the effect of lumasiran on hepatic oxalate production because all patients had advanced kidney disease at enrollment. In patients with PH1 who receive a combined liver/kidney transplant, even though POx decreases after normalization of hepatic oxalate production by liver transplant compared with pretransplant levels, POx levels may remain increased, even with continuing and intensive hemodialysis, presumably as a result of the high body oxalate burden that may be removed over time.[24,25] In a case of sequential liver/kidney transplant, POx has been shown to decrease from approximately 60 times normal before liver transplant to approximately 28 times normal following liver transplant, with a further reduction to approximately 7 times normal following kidney transplant, suggesting that strategies to reduce hepatic oxalate production may not fully reduce POx levels until kidney function is restored.[26] Indeed, even in patients with kidney failure unrelated to PH1, POx level is often increased 10 times or more versus normal.[24,27-29]

In previous studies, treatment with lumasiran was shown to achieve substantial and sustained reductions in UOx with an acceptable safety profile in patients with relatively preserved kidney function.[19,20] Treatment with lumasiran also led to rapid and sustained reductions in UOx in cohort A in ILLUMINATE-C. As expected, anuria in

Table 3. Safety

	Cohort A (n = 6)		Cohort B (n = 15)		All Treated (N = 21)	
	No. of Patients	No. of Events (ER)[a]	No. of Patients	No. of Events (ER)[a]	No. of Patients	No. of Events (ER)[a]
AEs	5 (83%)	20 (735.6)	12 (80%)	54 (777.1)	17 (81%)	74 (765.5)
AEs occurring in ≥2 patients						
Pyrexia	1 (17%)	1 (36.8)	5 (33%)	7 (100.7)	6 (29%)	8 (82.8)
Injection-site reaction	1 (17%)	1 (36.8)	4 (27%)	4 (57.6)	5 (24%)	5 (51.7)
Device-related infection	0	NA	2 (13%)	4 (57.6)	2 (10%)	4 (41.4)
Diarrhea	0	NA	2 (13%)	4 (57.6)	2 (10%)	4 (41.4)
Vomiting	1 (17%)	1 (36.8)	1 (7%)	1 (14.4)	2 (10%)	2 (20.7)
AEs leading to study treatment discontinuation	0	NA	0	NA	0	NA
AEs leading to study withdrawal	0	NA	0	NA	0	NA
Death	0	NA	0	NA	0	NA
Serious AEs	1 (17%)	2 (73.6)	5 (33%)	13 (187.1)	6 (29%)	15 (155.2)
Abdominal pain	0	NA	1 (7%)	1 (14.4)	1 (5%)	1 (10.3)
AVF operation	0	NA	1 (7%)	1 (14.4)	1 (5%)	1 (10.3)
AVF thrombosis	0	NA	1 (7%)	1 (14.4)	1 (5%)	1 (10.3)
Catheter-site swelling	0	NA	1 (7%)	1 (14.4)	1 (5%)	1 (10.3)
Device-related infection	0	NA	2 (13%)	2 (28.8)	2 (10%)	2 (20.7)
Device-related thrombosis	0	NA	1 (7%)	1 (14.4)	1 (5%)	1 (10.3)
Dialysis device insertion	0	NA	1 (7%)	1 (14.4)	1 (5%)	1 (10.3)
Hemorrhage	0	NA	1 (7%)	1 (14.4)	1 (5%)	1 (10.3)
Hypokalemia	1 (17%)	1 (36.8)	0	NA	1 (5%)	1 (10.3)
Pyrexia	0	NA	1 (7%)	1 (14.4)	1 (5%)	1 (10.3)
Seizure	0	NA	1 (7%)	1 (14.4)	1 (5%)	1 (10.3)
Skin scar contracture	0	NA	1 (7%)	1 (14.4)	1 (5%)	1 (10.3)
Spontaneous hematoma	0	NA	1 (7%)	1 (14.4)	1 (5%)	1 (10.3)
Vomiting	1 (17%)	1 (36.8)	0	NA	1 (5%)	1 (10.3)
Severe AEs	0	NA	3 (20%)	6 (86.3)	3 (14%)	6 (62.1)

Abbreviations: AE, adverse event; AVF, arteriovenous fistula; ER, exposure-adjusted event rate per 100 patient-years; NA, not applicable.
[a]Total number of AEs in a given preferred term. If a patient had multiple events in a given category, the patient was counted multiple times.

cohort B was nearly universal, precluding meaningful analysis of UOx. The postbaseline increase in plasma glycolate observed in ILLUMINATE-C was consistent with the mechanism of action of lumasiran and with previous findings in patients with relatively preserved kidney function,[19,20] suggesting comparable liver uptake of lumasiran and target suppression with the recommended weight-based dosing regimen in patients with advanced PH1. Case reports have described increased plasma and urinary glycolate concentrations, without apparent adverse clinical consequences, in patients with glycolate oxidase deficiency.[30-33]

Plasma PK data showed a rapid decrease in lumasiran concentrations, with lumasiran levels reaching the lower limit of quantification within 24 hours in most patients. This observation is consistent with findings in patients with relatively preserved kidney function[23] and suggests that kidney function does not influence liver uptake of lumasiran.

Lumasiran demonstrated an acceptable safety profile in the 6-month primary analysis period of ILLUMINATE-C. Consistent with what was previously reported in patients with preserved kidney function,[19,20] the most common AEs related to lumasiran treatment were injection-site reactions, all of which were mild and transient.

There is hope in the medical community that novel therapies that target hepatic oxalate production will obviate the need for a liver transplant.[34-36] Kidney-only transplant has been performed with good outcomes in a limited number of patients after adequate response to pyridoxine.[37] More recently, in a young patient diagnosed with PH1 following a kidney transplant, graft kidney function stabilized following lumasiran and aggressive kidney replacement therapy, allowing for discontinuation of dialysis.[38] The challenge the community now faces is to understand what might be a suitable POx level at which kidney-only transplant could be considered for patients with PH1, acknowledging that such a decision would not rely on a POx level alone. POx levels may fluctuate during follow-up, unrelated to changes in serum creatinine or eGFR[39]; in addition, there is poor agreement in POx values between laboratories.[40] It may be important to consider the normal range of POx in patients without PH1 who are undergoing dialysis at a given laboratory to help guide these decisions.

In conclusion, in the ILLUMINATE-C phase 3 study, patients of all ages with advanced PH1 had substantial reductions in POx after receiving 6 months of lumasiran treatment, with encouraging early results on measures of systemic oxalosis and a generally acceptable safety profile; the most commonly reported lumasiran-related AEs were injection-site reactions. These results, along with previous reports from ILLUMINATE-A and ILLUMINATE-B,[19,20] provide evidence supporting the effectiveness and safety of lumasiran across the full spectrum of disease severity in PH1.

Supplementary Material

Supplementary File 1 (PDF)

Figure S1: PH1 pathogenesis and therapeutic hypothesis for lumasiran.

Figure S2: Study design.

Figure S3: Lumasiran dosing and administration schedule.

Figure S4: Patient disposition.

Figure S5: Percent change in POx in prespecified subgroups.

Figure S6: Percent change from baseline in spot urinary oxalate-creatinine ratio at each visit in cohort A.

Figure S7: Percent change from baseline in 24-hour urinary oxalate excretion at each visit in cohort A.

Figure S8: Plasma glycolate levels.

Figure S9: Spaghetti plots of eGFR by patient in cohort A.

Table S1: Dosing regimen.

Table S2: Plasma PK parameters.

Table S3: Change from baseline in cardiac measures of systemic oxalosis, as assessed by echocardiography.

Table S4: Change from baseline in nephrocalcinosis grade and kidney stone events.

Supplementary File 2 (PDF)

Study protocol.

Supplementary File 3 (PDF)

Statistical analysis plan.

Article Information

Authors' Full Names and Academic Degrees: Mini Michael, MD, Jaap W. Groothoff, MD, PhD, Hadas Shasha-Lavsky, MD, John C. Lieske, MD, Yaacov Frishberg, MD, Eva Simkova, MD, Anne-Laure Sellier-Leclerc, MD, Arnaud Devresse, MD, PhD, Fitsum Guebre-Egziabher, MD, PhD, Sevcan A. Bakkaloglu, MD, Chebl Mourani, MD, Rola Saqan, MD, Richard Singer, MBChB, Richard Willey, MS, Bahru Habtemariam, PharmD, John M. Gansner, MD, PhD, Ishir Bhan, MD, MPH, Tracy McGregor, MD, and Daniella Magen, MD.

Authors' Affiliations: Division of Pediatric Nephrology, Department of Pediatrics, Texas Children's Hospital/Baylor College of Medicine, Houston, TX (MM); Department of Pediatric Nephrology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands (JWG); Pediatric Nephrology Unit, Galilee Medical Center, Azrieli Faculty of Medicine, Bar Ilan University, Nahariya, Israel (HS-L); Division of Pediatric Nephrology, Shaare Zedek Medical Center, Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel (YF); Pediatric Nephrology Institute, Rambam Health Care Campus, Haifa (DM), Israel; Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN (JCL); Nephrology - Medical Affairs, Al Jalila Children's Hospital, Dubai, United Arab Emirates (ES); Hôpital Femme Mère Enfant en Centre d'Investigation Clinique, Institut National de la Santé et de la Recherche Médicale (INSERM), Hospices Civils de Lyon, ERKnet, Bron, France (A-LS-L); Nephrology and Renal Function Unit, Edouard Herriot Hospital, Hospices Civils de Lyon, INSERM 1060, Lyon (FG-E), France; Division of Nephrology, Cliniques Universitaires Saint-Luc, Brussels, Belgium (AD); Department of Pediatric Nephrology, Faculty of Medicine, Gazi University, Ankara, Turkey (SAB); Department of Pediatrics, Hôtel-Dieu de France Hospital, Beirut, Lebanon (CM); Pharmaceutical Research Center, Jordan University of Science and Technology, Irbid, Jordan (RSaqan); Renal Service, Canberra Health Services, Garran, ACT, Australia (RSinger); and Alnylam Pharmaceuticals, Cambridge, MA (RW, BH, JMG, IB, TM).

Address for Correspondence: Mini Michael, MD, Division of Pediatric Nephrology, Department of Pediatrics, Texas Children's Hospital/Baylor College of Medicine, Houston, TX 77030. Email: mmichael@bcm.edu

Authors' Contributions: Study design: YF, JWG, BH, JCL, TM, MM, HSL, JMG, DM; study investigator: SAB, AD, YF, JWG, FGE, JCL, DM, MM, CM, RSaqan, ALSL, HSL, ES, RSinger; enrolled patients: SAB, AD, JWG, FGE, JCL, DM, MM, CM, RSaqan, ALSL, HSL, ES, RSinger; collection and assembly of data: SAB, AD, JWG, FGE, JCL, DM, MM, CM, RSaqan, ALSL, HSL, ES, RSinger, RW; data analysis: RW; data interpretation: all authors. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for their own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

Support: This study was funded by Alnylam Pharmaceuticals. Medical writing and editorial assistance were provided by Peloton Advantage, LLC, an OPEN Health company, and Ana Camejo, PhD, an employee of Alnylam Pharmaceuticals, in accordance with Good Publication Practice (GPP3) guidelines, and funded by Alnylam Pharmaceuticals. The Sponsor was involved in the study design; collection, analysis, and interpretation of data and data checking of information provided in the manuscript. However, ultimate responsibility for opinions, conclusions, and data interpretation lies with the authors.

Financial Disclosure: Dr Michael is principal investigator (PI) for Alnylam Pharmaceuticals. Dr Groothoff received consultancy fees from Alnylam Pharmaceuticals and study grants from Alnylam Pharmaceuticals, Dicerna Pharmaceuticals, and uniQure Pharmaceuticals. Dr Shasha-Lavsky is PI for Alnylam Pharmaceuticals and received travel and accommodation expenses from Alnylam Pharmaceuticals to attend international investigators' meetings. Dr Lieske received grants from Alnylam Pharmaceuticals, Dicerna Pharmaceuticals, Retrophin, OxThera, and Siemens, as well as other from NovoBiome and Orfan-BridgeBio and grants and other from Allena and Synlogic. Dr Frishberg received consultancy fees from Alnylam Pharmaceuticals and is a member of the safety review committee. Dr Simkova is a PI for Alnylam Pharmaceuticals and received travel and accommodation expenses from Alnylam Pharmaceuticals to attend international investigators' meeting. Dr Sellier-Leclerc received consultancy fees from Alnylam Pharmaceuticals and Dicerna Pharmaceuticals and is a PI for research funded by OxThera. Dr Devresse is a PI for Alnylam Pharmaceuticals and received consultancy fees from Alnylam Pharmaceuticals. Dr Guebre-Egziabher is a PI for Alnylam Pharmaceuticals and Amgen. Dr Saqan is a PI for Alnylam Pharmaceuticals and a secondary

investigator for Novartis and serves on the institutional review board. Drs Willey, Gansner, and Bhan are employees of Alnylam Pharmaceuticals and are shareholders or hold stock options from Alnylam Pharmaceuticals. Drs Habtemariam and McGregor were previously employed by and are shareholders of Alnylam Pharmaceuticals. Dr Magen receives research funding, consultancy fees, and nonfinancial support from Alnylam Pharmaceuticals. The remaining authors declare that they have no relevant financial interests.

Acknowledgments: The authors thank the patients, the patients' families, investigators, study staff, and collaborators for their participation in the lumasiran clinical studies.

Data sharing: Deidentified individual participant data that support these results will be made available in a secure-access environment 12 months after study completion and when the product and indication have been approved for no less than 12 months in the US and the EU. Access will be provided contingent upon the approval of a research proposal and the execution of a data sharing agreement. Requests for access to data can be submitted via the website www.vivli.org.

Peer Review: Received January 12, 2022. Evaluated by 2 external peer reviewers, with direct editorial input from a Statistics/Methods Editor, an Associate Editor, and the Editor-in-Chief. Accepted in revised form May 25, 2022.

References

1. Cochat P, Rumsby G. Primary hyperoxaluria. *N Engl J Med*. 2013;369(7):649-658. doi:10.1056/NEJMra1301564
2. Danpure CJ. Primary hyperoxaluria. The Online Metabolic and Molecular Bases of Inherited Disease 2019. Accessed January 11, 2022. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225543281
3. Lieske JC, Monico CG, Holmes WS, et al. International registry for primary hyperoxaluria. *Am J Nephrol*. 2005;25(3):290-296. doi:10.1159/000086360
4. Mandrile G, van Woerden CS, Berchialla P, et al. Data from a large European study indicate that the outcome of primary hyperoxaluria type 1 correlates with the AGXT mutation type. *Kidney Int*. 2014;86(6):1197-1204. doi:10.1038/ki.2014.222
5. van der Hoeven SM, van Woerden CS, Groothoff JW. Primary hyperoxaluria type 1, a too often missed diagnosis and potentially treatable cause of end-stage renal disease in adults: results of the Dutch cohort. *Nephrol Dial Transplant*. 2012;27(10):3855-3862. doi:10.1093/ndt/gfs320
6. Hopp K, Cogal AG, Bergstralh EJ, et al. Phenotype-genotype correlations and estimated carrier frequencies of primary hyperoxaluria. *J Am Soc Nephrol*. 2015;26(10):2559-2570. doi:10.1681/asn.2014070698
7. Harambat J, Fargue S, Acquaviva C, et al. Genotype-phenotype correlation in primary hyperoxaluria type 1: the p.Gly170Arg AGXT mutation is associated with a better outcome. *Kidney Int*. 2010;77(5):443-449. doi:10.1038/ki.2009.435
8. Cochat P, Hulton SA, Acquaviva C, et al. Primary hyperoxaluria type 1: indications for screening and guidance for diagnosis and treatment. *Nephrol Dial Transplant*. 2012;27(5):1729-1736. doi:10.1093/ndt/gfs078
9. Lawrence JE, Wattenberg DJ. Primary hyperoxaluria: the patient and caregiver perspective. *Clin J Am Soc Nephrol*. 2020;15(7):909-911. doi:10.2215/cjn.13831119
10. National Organization for Rare Disorders. Rare Disease Database. Primary hyperoxaluria. 2020. Accessed May 11, 2021. https://rarediseases.org/rare-diseases/primary-hyperoxaluria/
11. Tang X, Voskoboev NV, Wannarka SL, Olson JB, Milliner DS, Lieske JC. Oxalate quantification in hemodialysate to assess dialysis adequacy for primary hyperoxaluria. *Am J Nephrol*. 2014;39(5):376-382. doi:10.1159/000360624
12. Sas DJ, Enders FT, Gunderson TM, et al. Natural history of clinical, laboratory, and echocardiographic parameters of a primary hyperoxaluria cohort on long term hemodialysis. *Front Med (Lausanne)*. 2021;8:592357. doi:10.3389/fmed.2021.592357
13. *Oxlumo* [package insert]. Cambridge, MA: Alnylam Pharmaceuticals; 2020.
14. *Oxlumo* [summary of product characteristics]. Amsterdam, The Netherlands: Alnylam Netherlands; 2020.
15. Liebow A, Li X, Racie T, et al. An investigational RNAi therapeutic targeting glycolate oxidase reduces oxalate production in models of primary hyperoxaluria. *J Am Soc Nephrol*. 2017;28(2):494-503. doi:10.1681/asn.2016030338
16. Milliner DS, McGregor TL, Thompson A, et al. End points for clinical trials in primary hyperoxaluria. *Clin J Am Soc Nephrol*. 2020;15(7):1056-1065. doi:10.2215/cjn.13821119
17. Shah RJ, Vaughan LE, Enders FT, Milliner DS, Lieske JC. Plasma oxalate as a predictor of kidney function decline in a primary hyperoxaluria cohort. *Int J Mol Sci*. 2020;21(10). doi:10.3390/ijms21103608
18. Milliner DS, Cochat P, Hulton SA, et al. Plasma oxalate and eGFR are correlated in primary hyperoxaluria patients with maintained kidney function-data from three placebo-controlled studies. *Pediatr Nephrol*. 2021;36(7):1785-1793. doi:10.1007/s00467-020-04894-9
19. 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
20. Sas DJ, Magen D, Hayes W, et al. Phase 3 trial of lumasiran for primary hyperoxaluria type 1: a new RNAi therapeutic in infants and young children. *Genet Med*. 2022;24(3):654-662. doi:10.1016/j.gim.2021.10.024
21. van Biesen W, Heimburger O, Krediet R, et al. Evaluation of peritoneal membrane characteristics: clinical advice for prescription management by the ERBP working group. *Nephrol Dial Transplant*. 2010;25(7):2052-2062. doi:10.1093/ndt/gfq100
22. Schwartz GJ, Muñoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol*. 2009;20(3):629-637. doi:10.1681/asn.2008030287
23. Frishberg Y, Deschênes G, Groothoff JW, et al. Phase 1/2 study of lumasiran for treatment of primary hyperoxaluria type 1: a placebo-controlled randomized clinical trial. *Clin J Am Soc Nephrol*. 2021;16(7):1025-1036. doi:10.2215/cjn.14730920
24. Hoppe B, Kemper MJ, Bökenkamp A, Portale AA, Cohn RA, Langman CB. Plasma calcium oxalate supersaturation in children with primary hyperoxaluria and end-stage renal failure. *Kidney Int*. 1999;56(1):268-274. doi:10.1046/j.1523-1755.1999.00546.x
25. Bergstralh EJ, Monico CG, Lieske JC, et al. Transplantation outcomes in primary hyperoxaluria. *Am J Transplant*. 2010;10(11):2493-2501. doi:10.1111/j.1600-6143.2010.03271.x
26. Rosenblatt GS, Jenkins RD, Barry JM. Treatment of primary hyperoxaluria type 1 with sequential liver and kidney transplants

from the same living donor. *Urology*. 2006;68(2):427.e427-428. doi:10.1016/j.urology.2006.02.035

27. Worcester EM, Nakagawa Y, Bushinsky DA, Coe FL. Evidence that serum calcium oxalate supersaturation is a consequence of oxalate retention in patients with chronic renal failure. *J Clin Invest*. 1986;77(6):1888-1896. doi:10.1172/jci112516
28. McConnell KN, Rolton HA, Modi KS, Macdougall AI. Plasma oxalate in patients with chronic renal failure receiving continuous ambulatory peritoneal dialysis or hemodialysis. *Am J Kidney Dis*. 1991;18(4):441-445. doi:10.1016/s0272-6386(12)80111-9
29. Borland WW, Payton CD, Simpson K, Macdougall AI. Serum oxalate in chronic renal failure. *Nephron*. 1987;45(2):119-121. doi:10.1159/000184091
30. Clifford-Mobley O, Rumsby G, Kanodia S, Didi M, Holt R, Senniappan S. Glycolate oxidase deficiency in a patient with congenital hyperinsulinism and unexplained hyperoxaluria. *Pediatr Nephrol*. 2017;32(11):2159-2163. doi:10.1007/s00467-017-3741-1
31. Craigen WJ. Persistent glycolic aciduria in a healthy child with normal alanine-glyoxylate aminotransferase activity. *J Inherit Metab Dis*. 1996;19(6):793-794. doi:10.1007/bf01799176
32. Frishberg Y, Zeharia A, Lyakhovetsky R, Bargal R, Belostotsky R. Mutations in HAO1 encoding glycolate oxidase cause isolated glycolic aciduria. *J Med Genet*. 2014;51(8):526-529. doi:10.1136/jmedgenet-2014-102529
33. McGregor TL, Hunt KA, Yee E, et al. Characterising a healthy adult with a rare HAO1 knockout to support a therapeutic strategy for primary hyperoxaluria. *eLife*. 2020;9:e54363. doi:10.7554/eLife.54363
34. Chadban SJ, Ahn C, Axelrod DA, et al. KDIGO clinical practice guideline on the evaluation and management of candidates for kidney transplantation. *Transplantation*. 2020;104(4)(suppl 1):S11-S103. doi:10.1097/tp.0000000000003136
35. Devresse A, Cochat P, Godefroid N, Kanaan N. Transplantation for primary hyperoxaluria type 1: designing new strategies in the era of promising therapeutic perspectives. *Kidney Int Rep*. 2020;5(12):2136-2145. doi:10.1016/j.ekir.2020.09.022
36. Devresse A, Godefroid N, Anthonissen B, et al. Liver transplantation in primary hyperoxaluria type 1: we have to find an alternative. *Transplantation*. 2021;105(4):e46-e47. doi:10.1097/tp.0000000000003597
37. Lorenz EC, Lieske JC, Seide BM, et al. Sustained pyridoxine response in primary hyperoxaluria type 1 recipients of kidney alone transplant. *Am J Transplant*. 2014;14(6):1433-1438. doi:10.1111/ajt.12706
38. Stone HK, VandenHeuvel K, Bondoc A, Flores FX, Hooper DK, Varnell CD Jr. Primary hyperoxaluria diagnosed after kidney transplant: a review of the literature and case report of aggressive renal replacement therapy and lumasiran to prevent allograft loss. *Am J Transplant*. 2021;21(12):4061-4067. doi:10.1111/ajt.16762
39. Hillebrand P, Hoppe B. Plasma oxalate levels in primary hyperoxaluria type I show significant intra-individual variation and do not correlate with kidney function. *Pediatr Nephrol*. 2020;35(7):1227-1233. doi:10.1007/s00467-020-04531-5
40. Stokes F, Acquaviva-Bourdain C, Hoppe B, et al. Plasma oxalate: comparison of methodologies. *Urolithiasis*. 2020;48(6):473-480. doi:10.1007/s00240-020-01197-4

Lumasiran for Advanced Primary Hyperoxaluria Type 1: Phase 3 ILLUMINATE-C Trial

Study Design

Phase 3, open-label, single-arm trial

N = 21

- Genetically confirmed PH1
- Plasma oxalate (POx) ≥20 μmol/L
- eGFR ≤45 mL/min/1.73 m^2 if age ≥12 months; elevated SCr if <12 months

Cohort A (N = 6)
No hemodialysis at enrollment

Cohort B (N = 15)
Hemodialysis at enrollment

Lumasiran given subcutaneously 1×/mo for 3 mo, then monthly/quarterly weight-based dosing

Results

6 months

	Cohort A	Cohort B
Primary Endpoint		
Mean percent reduction from baseline in POx	**33.3%** (95% CI: −15.2%, 81.8%)	**42.4%** (95% CI: 34.2%, 50.7%)
Secondary Endpoints		
Mean percent reduction in interdialytic POx $AUC_{0\text{-}24h}$	NA	**41.4%** (SEM: 4.4%)
Mean of the absolute reduction in POx	**35.3 μmol/L** (SEM: 7.4)	**48.3 μmol/L** (SEM: 3.6)
Percent reduction in urinary oxalate-creatinine ratio	**39.5%** (SEM: 9.4%)	NA

The most commonly reported lumasiran-related adverse events were injection-site reactions (24% [5/21] of patients).

CONCLUSION: Lumasiran resulted in reductions in POx with generally acceptable safety in patients with PH1 of all ages who have advanced kidney disease.

Mini Michael, Jaap W. Groothoff, Hadas Shasha-Lavsky, et al

@AJKDonline | DOI: 10.1053/j.ajkd.2022.05.012