ORIGINAL ARTICLE

Lumasiran, an RNAi Therapeutic for Primary Hyperoxaluria Type 1

Sander F. Garrelfs, M.D., Yaacov Frishberg, M.D., Sally A. Hulton, M.D., Michael J. Koren, M.D., William D. O'Riordan, M.D., Pierre Cochat, M.D., Ph.D., Georges Deschênes, M.D., Ph.D., Hadas Shasha-Lavsky, M.D., Jeffrey M. Saland, M.D., William G. van't Hoff, M.D., Daniel G. Fuster, M.D., Daniella Magen, M.D., Shabbir H. Moochhala, M.B., Ch.B., Ph.D., Gesa Schalk, M.D., Eva Simkova, M.D., Jaap W. Groothoff, M.D., Ph.D., David J. Sas, D.O., Kristin A. Meliambro, M.D., Jiandong Lu, Ph.D., Marianne T. Sweetser, M.D., Ph.D., Pushkal P. Garg, M.D., Akshay K. Vaishnaw, M.D., Ph.D., John M. Gansner, M.D., Ph.D., Tracy L. McGregor, M.D., and John C. Lieske, M.D., for the ILLUMINATE-A Collaborators*

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Garrelfs at Location AMC, Rm. H8-253, Department of Pediatric Nephrology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, Noord-Holland, the Netherlands, or at s.f.garrelfs@amsterdamumc.nl.

*A complete list of collaborators in the ILLUMINATE-A trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Garrelfs and Frishberg contributed equally to this article.

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ABSTRACT

BACKGROUND

Primary hyperoxaluria type 1 (PH1) is a rare genetic disease caused by hepatic overproduction of oxalate that leads to kidney stones, nephrocalcinosis, kidney failure, and systemic oxalosis. Lumasiran, an investigational RNA interference (RNAi) therapeutic agent, reduces hepatic oxalate production by targeting glycolate oxidase.

METHODS

In this double-blind, phase 3 trial, we randomly assigned (in a 2:1 ratio) patients with PH1 who were 6 years of age or older to receive subcutaneous lumasiran or placebo for 6 months (with doses given at baseline and at months 1, 2, 3, and 6). The primary end point was the percent change in 24-hour urinary oxalate excretion from baseline to month 6 (mean percent change across months 3 through 6). Secondary end points included the percent change in the plasma oxalate level from baseline to month 6 (mean percent change across months 3 through 6) and the percentage of patients with 24-hour urinary oxalate excretion no higher than 1.5 times the upper limit of the normal range at month 6.

RESULTS

A total of 39 patients underwent randomization; 26 were assigned to the lumasiran group and 13 to the placebo group. The least-squares mean difference in the change in 24-hour urinary oxalate excretion (lumasiran minus placebo) was −53.5 percentage points (P<0.001), with a reduction in the lumasiran group of 65.4% and an effect seen as early as month 1. The between-group differences for all hierarchically tested secondary end points were significant. The difference in the percent change in the plasma oxalate level (lumasiran minus placebo) was −39.5 percentage points (P<0.001). In the lumasiran group, 84% of patients had 24-hour urinary oxalate excretion no higher than 1.5 times the upper limit of the normal range at month 6, as compared with 0% in the placebo group (P<0.001). Mild, transient injection-site reactions were reported in 38% of lumasiran-treated patients.

CONCLUSIONS

Lumasiran reduced urinary oxalate excretion, the cause of progressive kidney failure in PH1. The majority of patients who received lumasiran had normal or near-normal levels after 6 months of treatment. (Funded by Alnylam Pharmaceuticals; ILLUMINATE-A ClinicalTrials.gov number, NCT03681184.)

Primary hyperoxaluria type 1 (PH1) is a rare, progressive genetic disease with debilitating and life-threatening clinical manifestations due to increased hepatic oxalate production. The metabolic defect in PH1 results from a deficiency of the liver-specific peroxisomal enzyme alanine–glyoxylate aminotransferase (AGT), which converts the oxalate precursor glyoxylate to glycine.[1-3] With absent or deficient AGT activity, glyoxylate is oxidized to oxalate, leading to increased plasma oxalate levels. Hepatically produced oxalate is excreted largely by the kidneys and is the toxic mediator of end-organ damage in PH1. Patients with PH1 commonly present in childhood with kidney stones, nephrocalcinosis, end-stage kidney disease, or (if plasma oxalate levels rise sufficiently) systemic oxalosis with deposition of oxalate in tissues such as bone, retina, heart, and skin. The condition may remain undiagnosed or incorrectly diagnosed for years.[4,5] In one patient registry, 43% of patients who received a diagnosis of PH1 already had end-stage kidney disease at the time of diagnosis, and 14% of patients in the registry had died, with a median age at death of only 15.5 years.[5] Recent data have established that urinary oxalate levels in PH1 are a primary determinant of progression to end-stage kidney disease.[6,7] Therefore, the management of PH1 is directed toward reducing urinary oxalate levels whenever possible.

Current treatment options for PH1 are limited. Hyperhydration, high-dose pyridoxine (a coenzyme for AGT), and calcium oxalate crystallization inhibitors, such as citrate, may decrease the incidence of kidney stones and slow disease progression.[8-11] However, hyperhydration is burdensome, leading to poor adherence and the necessity for gastrostomy tube placement in some children.[12,13] Patients with advanced disease who can no longer eliminate excess oxalate because of impaired kidney function or kidney failure often receive intensive hemodialysis 6 days per week, sometimes with supplemental peritoneal dialysis. Liver transplantation can cure the metabolic defect in PH1 and has been shown to normalize oxalate levels, improve disease manifestations, and, if performed preemptively, prevent progression to end-stage kidney disease.[14-20] However, liver transplantation is associated with significant morbidity and mortality and with lifelong immunosuppressive therapy; dual liver–kidney transplantation is frequently performed to both address the metabolic defect in the liver and restore lost kidney function.[20-22]

Lumasiran is an investigational, subcutaneously administered, liver-directed RNA interference (RNAi) therapeutic agent. In patients with PH1, lumasiran reduces hepatic oxalate production and increases concentrations of a readily excreted precursor, glycolate,[23,24] by degrading the messenger RNA that encodes glycolate oxidase, an enzyme upstream of AGT (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Inhibition of glycolate oxidase is not expected to reduce hepatic oxalate production to the same extent in patients with either of the two non-PH1 genetic causes of primary hyperoxaluria, glyoxylate reductase–hydroxypyruvate reductase deficiency (PH2) or 4-hydroxy-2-oxoglutarate aldolase deficiency (PH3). In a phase 1–2 study, patients with PH1 treated with lumasiran had dose-dependent reductions in 24-hour urinary oxalate excretion (unpublished data).

Here, we report the results from the 6-month double-blind period of A Study to Evaluate Lumasiran in Children and Adults with Primary Hyperoxaluria Type 1 (ILLUMINATE-A), a phase 3 trial designed to evaluate the efficacy and safety of lumasiran as compared with placebo in patients with PH1 who are 6 years of age or older.

A Quick Take is available at NEJM.org

METHODS

TRIAL DESIGN AND OVERSIGHT

In this multinational, randomized, double-blind, placebo-controlled trial, we randomly assigned patients with PH1 in a 2:1 ratio to receive lumasiran or placebo subcutaneously for 6 months, after which all patients were to receive lumasiran in an extension period of up to 54 months. Lumasiran (3 mg per kilogram of body weight) or placebo was administered once monthly for three doses, followed by maintenance doses given once every 3 months beginning 1 month after the last loading dose (Fig. S2). Randomization was stratified according to mean urinary oxalate excretion (>1.70 or ≤1.70 mmol per 24 hours per 1.73 m^2), which was assessed with the use of the first two valid baseline 24-hour urine samples (see the Supplementary Appendix).

The protocol and the statistical analysis plan were developed by the sponsor, Alnylam Pharmaceuticals, and are available at NEJM.org. The trial was approved by the institutional review boards or ethics committees at the participating

trial sites and was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation and the provisions of the Declaration of Helsinki. All patients or their legal guardians provided written informed consent. An independent data and safety monitoring committee reviewed pertinent safety data. Data were collected by trial investigators and were analyzed by the sponsor. The authors interpreted the data, collaborated in manuscript preparation, and vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol. Adelphi Communications, under contract with Alnylam Pharmaceuticals, and a medical writer from Alnylam provided editorial assistance. The authors and their institutions were required to maintain data confidentiality during the trial.

TRIAL PARTICIPANTS

Key eligibility criteria included an age of 6 years or older, diagnosis of PH1 confirmed by genetic analysis, an estimated glomerular filtration rate (eGFR) of at least 30 ml per minute per 1.73 m^2 of body-surface area, 24-hour urinary oxalate excretion of at least 0.70 mmol per 24 hours per 1.73 m^2, and no clinical evidence of extrarenal systemic oxalosis as determined by the investigator. A complete list of inclusion and exclusion criteria is provided in the protocol.

For patients taking pyridoxine (vitamin B_6), the regimen was required to have been stable for at least 90 days before randomization. All patients were to continue the PH1 standard-of-care regimen that had been in place at the time of enrollment in the trial, including hyperhydration, crystallization inhibitors, pyridoxine therapy, or a combination of these treatments, through month 12 of the trial.

ASSESSMENTS AND END POINTS

The primary end point was the percent change from baseline to month 6 in 24-hour urinary oxalate excretion corrected for body-surface area, estimated as the mean percent change from baseline across months 3 through 6. Correction for body-surface area effectively normalizes age-related variation in oxalate excretion.[25] Values were averaged across the visits from month 3 through month 6, when steady state was expected to have been reached, in order to yield more stable estimates of the effect of treatment.

The secondary end points, listed in hierarchical order for statistical testing, were the absolute change in 24-hour urinary oxalate excretion from baseline to month 6 (mean change across months 3 through 6), the percent change in the 24-hour urinary oxalate:creatinine ratio from baseline to month 6 (mean percent change across months 3 through 6), the percent change in the plasma oxalate level from baseline to month 6 (mean percent change across months 3 through 6), the percentage of patients with 24-hour urinary oxalate excretion no higher than 1.5 times the upper limit of the normal range at month 6, the percentage of patients with 24-hour urinary oxalate excretion no higher than the upper limit of the normal range at month 6, and the absolute change in the plasma oxalate level from baseline to month 6 (mean change across months 3 through 6). The change in eGFR from baseline to month 6 was also assessed as a secondary end point but was not included in the prespecified hierarchical testing because significant differences were not anticipated at this early time point. Exploratory end points included assessments of the change in spot urinary oxalate:creatinine ratio, urinary and plasma glycolate levels, the rate of kidney-stone events, nephrocalcinosis grade, and the frequency of antidrug antibodies. (The full list of exploratory end points is provided in the protocol.)

Urinary and plasma oxalate and glycolate levels were measured with validated liquid chromatography–tandem mass spectrometry assays performed in a central laboratory by technicians who were unaware of the treatment assignments. Medullary nephrocalcinosis was graded per kidney on a semiquantitative scale of 0 to 3 with the use of kidney ultrasonography, with 0 indicating the absence of nephrocalcinosis and a higher grade indicating greater severity.[26] Kidney ultrasound images were graded by a single radiologist who was unaware of the treatment assignment and time point. We have not measured intraobserver reliability during the double-blind period because of the relatively small numbers of ultrasounds. Changes in the grade of nephrocalcinosis were grouped into four categories of overall change, accounting for both kidneys: no change, improving, worsening, and indeterminate (one kidney improving and one worsening). Kidney-stone events, as assessed by the investigator, were defined as at least one of the following events: visit to a health care provider, receipt of medication for renal colic, stone

passage, or macroscopic hematuria due to a kidney stone. Safety assessments included monitoring of adverse events and laboratory assessments as specified in the protocol.

STATISTICAL ANALYSIS

A sample of 24 patients was estimated to provide at least 90% power to detect a difference (lumasiran vs. placebo) of −37 percentage points in the change in 24-hour urinary oxalate excretion at a two-sided 5% significance level, under the assumption of a mean percent reduction of 17% in the placebo group and a standard deviation of 25% in both groups. To account for potential dropouts, we planned to enroll 30 patients.

Efficacy analyses were performed in the full analysis set (all patients who underwent randomization and received at least one dose of lumasiran or placebo, analyzed according to their randomly assigned treatment group). The analyses of the end points used to evaluate changes in the plasma oxalate level involved the plasma oxalate analysis set, which included all patients who received lumasiran or placebo and had a baseline plasma oxalate level at least 1.5 times the lower limit of quantitation. The lower limit of quantitation of the plasma oxalate assay was 5.55 μmol per liter. Values below the lower limit of quantitation were assigned a value of 5.55 μmol per liter in the summary statistics.

The primary analysis of the percent change in urinary oxalate excretion was based on a mixed-effects model for repeated measures, with two sensitivity analyses conducted to evaluate the treatment effect. A gatekeeping testing strategy for the primary and secondary end points (with the exception of eGFR) was implemented to control the overall type I error rate. We performed nine prespecified subgroup analyses of the primary end point of percent change in 24-hour urinary oxalate excretion. Full details of the analyses are provided in the statistical analysis plan. Statistical analyses were performed with SAS software, version 9.4 or later (SAS Institute).

RESULTS

TRIAL POPULATION

From January 2019 through May 2019, a total of 39 patients from 16 sites in eight countries were randomly assigned in a 2:1 ratio to receive lumasiran (26 patients) or placebo (13 patients) (Fig. S3). Among the 39 patients who underwent randomization, 38 completed the double-blind period and 1 (in the lumasiran group) withdrew from the trial because of an inability to adhere to trial procedures. Baseline demographic and disease characteristics were generally balanced between the two groups (Table 1 and Table S1). Overall, the median age at trial entry was 14 years (range, 6 to 60) and the mean baseline 24-hour urinary oxalate excretion was 1.82 mmol per 24 hours per 1.73 m^2. Pyridoxine use was reported by 56% of the patients in the trial. At baseline, 49% of patients had an eGFR of 60 to less than 90 ml per minute per 1.73 m^2 and 18% had an eGFR of 30 to less than 60 ml per minute per 1.73 m^2. At trial entry, 85% of patients had a history of kidney-stone events; during the 12 months before consent was obtained, kidney-stone events occurred in 11 patients (42%) in the lumasiran group and 4 patients (31%) in the placebo group. At trial entry, 54% of patients reported a history of nephrocalcinosis.

EFFICACY

Primary End Point

Patients treated with lumasiran had a rapid and sustained decrease in 24-hour urinary oxalate excretion, with declines seen at month 1 and steady state reached by the end of the loading-dose phase (Fig. 1A and 1B). The least-squares mean difference (lumasiran minus placebo) in the percent change in 24-hour urinary oxalate excretion from baseline to month 6 was −53.5 percentage points (95% confidence interval [CI], −62.3 to −44.8; P<0.001) (Table 2). The least-squares mean percent change from baseline was −65.4% in the lumasiran group and −11.8% in the placebo group. The robustness of the primary end-point result was confirmed through sensitivity analyses (Table S2). A consistent treatment effect was observed across all prespecified subgroups, including those based on baseline 24-hour urinary oxalate excretion, baseline pyridoxine use, and baseline eGFR (Fig. 1C). The mean maximum reduction in 24-hour urinary oxalate excretion after lumasiran administration was 76.0% (range, 35.8 to 93.6).

Secondary End Points

Treatment with lumasiran led to significant improvements in all the secondary end points that were tested hierarchically (Table 2). The least-squares mean difference (lumasiran minus placebo) in the absolute change in 24-hour urinary

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Lumasiran (N=26)	Placebo (N=13)	Overall (N=39)
Median age (range) — yr	16.5 (6–47)	11.0 (6–60)	14.0 (6–60)
Age category — no. (%)			
6 to <18 yr	14 (54)	8 (62)	22 (56)
18 to <65 yr	12 (46)	5 (38)	17 (44)
Female sex — no. (%)	8 (31)	5 (38)	13 (33)
Race — no. (%)†			
Asian	3 (12)	3 (23)	6 (15)
White	21 (81)	9 (69)	30 (77)
Other	2 (8)	1 (8)	3 (8)
Geographic region — no. (%)			
Europe	10 (38)	8 (62)	18 (46)
Middle East	5 (19)	3 (23)	8 (21)
North America	11 (42)	2 (15)	13 (33)
Pyridoxine use — no. (%)	13 (50)	9 (69)	22 (56)
24-Hour urinary oxalate excretion — mmol/24 hr/1.73 m^2‡	1.84±0.60	1.79±0.68	1.82±0.62
Plasma oxalate level — μmol/liter§	14.8±7.6	15.5±7.3	15.0±7.4
Kidney-function measures			
eGFR — ml/min/1.73 m^2¶	83.0±25.5	78.9±26.8	81.6±25.7
eGFR category — no. (%)			
≥90 ml/min/1.73 m^2	9 (35)	4 (31)	13 (33)
60 to <90 ml/min/1.73 m^2	13 (50)	6 (46)	19 (49)
30 to <60 ml/min/1.73 m^2	4 (15)	3 (23)	7 (18)

* Plus–minus values are means ±SD.
† Race was reported by the patient or the patient's parent or guardian. "Other" included 1 patient in the placebo group who reported more than one race and 2 patients in the lumasiran group who reported "other."
‡ The baseline value is the median of the values from all valid 24-hour urine samples obtained before the first dose of lumasiran or placebo. The upper limit of the normal range for 24-hour urinary oxalate is 0.514 mmol per 24 hours per 1.73 m^2 of body-surface area. To convert values to milligrams per 24 hours per 1.73 m^2, multiply by 90.
§ The upper limit of the normal range is 12.11 μmol per liter. The plasma oxalate analysis set included 23 patients in the lumasiran group and 10 patients in the placebo group.
¶ The estimated glomerular filtration rate (eGFR) was calculated with the Modification of Diet in Renal Disease formula for patients 18 years of age or older and with the Schwartz Bedside Formula for patients 6 to less than 18 years of age.

oxalate excretion from baseline to month 6 was –0.98 mmol per 24 hours per 1.73 m^2 (95% CI, –1.18 to –0.77; P<0.001) (Table 2 and Fig. S4). At month 6, 84% of lumasiran-treated patients had 24-hour urinary oxalate levels no higher than 1.5 times the upper limit of the normal range, as compared with 0% of patients who received placebo (P<0.001); in addition, 52% of lumasiran-treated patients had 24-hour urinary oxalate levels that were equal to or lower than the upper limit of the normal range, as compared with 0% of patients who received placebo (P=0.001) (Table 2 and Fig. S5). Patients with lower 24-hour urinary oxalate excretion at baseline (≤1.70 mmol per 24 hours per 1.73 m^2) were more likely to attain these thresholds (Table S3), but patients with higher baseline levels often had slightly larger percent reductions. The least-squares mean difference (lumasiran minus placebo) in the percent change in the 24-hour urinary oxalate: creatinine ratio from baseline to month 6 was –51.8 percentage points (95% CI, –64.3 to –39.3; P<0.001) (Table 2 and Fig. S6).

The decline in plasma oxalate levels was significantly greater among patients treated with lumasiran than among those who received placebo, with levels remaining relatively unchanged over time in the latter group. Among the 33 pa-

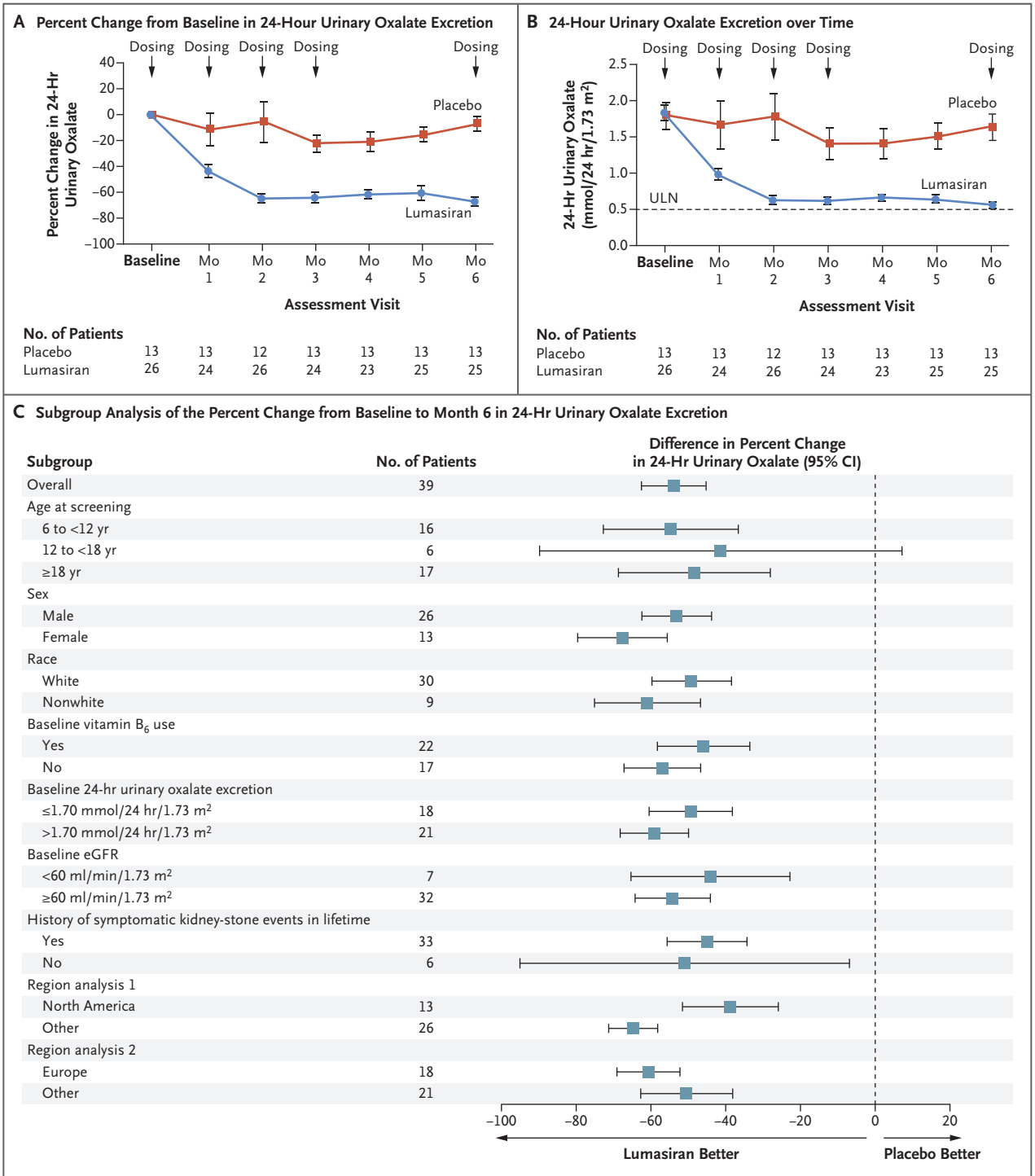

Figure 1. 24-Hour Urinary Oxalate Excretion.

Panel A shows observed percent changes in 24-hour urinary oxalate excretion, and Panel B shows absolute 24-hour urinary oxalate excretion values. In both panels, data points are means and I bars indicate the standard error. Panel C shows between-group differences (lumasiran minus placebo) based on the mixed-effects model for repeated-measures analysis of the percent reduction from baseline in 24-hour urinary oxalate excretion overall and in prespecified subgroups. Race was reported by the patient or the patient's parent or guardian; "nonwhite" included Asian, more than one race, and "other." All measurements of urinary oxalate excretion were corrected for body-surface area. CI denotes confidence interval, eGFR estimated glomerular filtration rate, and ULN upper limit of the normal range.

Table 2. Primary End Point and Hierarchically Tested Secondary End Points.

End Point	Lumasiran (N = 26)	Placebo (N = 13)	Difference, Lumasiran Minus Placebo	P Value
Primary end point: percent change in 24-hour urinary oxalate excretion from baseline to month 6 (95% CI)*†	−65.4 (−71.3 to −59.5)	−11.8 (−19.5 to −4.1)	−53.5 (−62.3 to −44.8)	<0.001
Secondary end points				
Absolute change in 24-hour urinary oxalate excretion from baseline to month 6 (95% CI) — mmol/24 hr/1.73 m^2*†	−1.24 (−1.37 to −1.12)	−0.27 (−0.44 to −0.10)	−0.98 (−1.18 to −0.77)	<0.001
Percent change in 24-hour urinary oxalate:creatinine ratio from baseline to month 6 (95% CI)†	−62.5 (−70.7 to −54.4)	−10.8 (−21.6 to 0.0)	−51.8 (−64.3 to −39.3)	<0.001
Percent change in plasma oxalate level from baseline to month 6 (95% CI)†‡	−39.8 (−45.8 to −33.8)	−0.3 (−9.1 to 8.5)	−39.5 (−50.1 to −28.9)	<0.001
Percentage of patients with 24-hour urinary oxalate excretion ≤1.5×ULN at month 6 (95% CI)*§	84 (64 to 95)	0 (0 to 25)	84 (55 to 94)¶	<0.001‖
Percentage of patients with 24-hour urinary oxalate excretion ≤ULN at month 6 (95% CI)*§	52 (31 to 72)	0 (0 to 25)	52 (23 to 70)¶	0.001‖
Absolute change in plasma oxalate level from baseline to month 6 (95% CI) — μmol/liter†‡	−7.5 (−9.0 to −5.9)	1.3 (−1.0 to 3.5)	−8.7 (−11.5 to −6.0)	<0.001

* Measurements of urinary oxalate excretion were corrected for body-surface area.
† The change from baseline to month 6 was calculated as the mean change or mean percent change across months 3 through 6. The least-squares mean, between-group difference in the least-squares mean, 95% confidence intervals, and P value for comparisons of lumasiran and placebo were derived with a mixed model for repeated measures. A difference of less than 0 represents a favorable outcome for lumasiran.
‡ The plasma oxalate analysis set included 23 patients in the lumasiran group and 10 patients in the placebo group.
§ Data were available for 25 patients in the lumasiran group and 13 patients in the placebo group. The upper limit of the normal range (ULN) is 0.514 mmol per 24 hours per 1.73 m^2. The confidence interval is a Clopper–Pearson exact confidence interval.
¶ The confidence interval was calculated by the Newcombe method on the basis of the Wilson score.
‖ P value was based on a Cochran–Mantel–Haenszel test stratified according to baseline 24-hour urinary oxalate excretion corrected for body-surface area (≤1.70 vs. >1.70 mmol/24 hr/1.73 m^2).

tients with a baseline plasma oxalate level of at least 1.5 times the lower limit of quantitation, the least-squares mean difference (lumasiran minus placebo) in the percent change in the plasma oxalate level from baseline to month 6 was −39.5 percentage points (95% CI, −50.1 to −28.9; P<0.001) (Table 2 and Fig. S7) and the least-squares mean difference in the absolute change in the plasma oxalate level from baseline to month 6 was −8.7 μmol per liter (95% CI, −11.5 to −6.0; P<0.001) (Table 2 and Fig. 2A). The eGFR remained stable in both treatment groups during the 6-month treatment period (Fig. 2B).

Exploratory End Points

Urinary oxalate:creatinine ratios measured in spot urine samples were reduced in lumasiran-treated patients at the first postdose assessment visit (week 2), and steady-state reductions in the range of 60 to 68% were reached by the end of the loading-dose phase (Table S4 and Fig. S8). By contrast, expected month-to-month variability with no clear trend was observed among the patients who received placebo. Plasma glycolate levels and 24-hour urinary glycolate:creatinine ratios initially increased and then plateaued in the lumasiran group (Fig. S9), a finding consistent with a reduction in hepatic glycolate oxidase activity mediated by lumasiran.

In a preliminary assessment of potential disease-modifying activity, kidney ultrasonography was performed to evaluate nephrocalcinosis. Among the patients with both baseline and month 6 kidney ultrasound results, nephrocalcinosis grade improved in 3 of 22 patients in the lumasiran group as compared with 0 of 12 in the placebo group. The nephrocalcinosis grade worsened in 1 of 12 patients in the placebo group as compared with no patients in the lumasiran group (Table S5).

The calculated rate of kidney-stone events in the lumasiran group decreased from a reported rate of 3.19 per person-year (95% CI, 2.57 to 3.96) over the 12 months before consent was obtained to an observed rate of 1.09 per person-year (95% CI, 0.63 to 1.87) during the treatment period (Table S6). In the placebo group, kidney-stone event rates remained stable, with a reported rate of 0.54 per person-year (95% CI, 0.26 to 1.13) over the 12 months before consent was obtained and an observed rate of 0.66 per person-year (95% CI, 0.25 to 1.76) during the treatment period (Table S6).

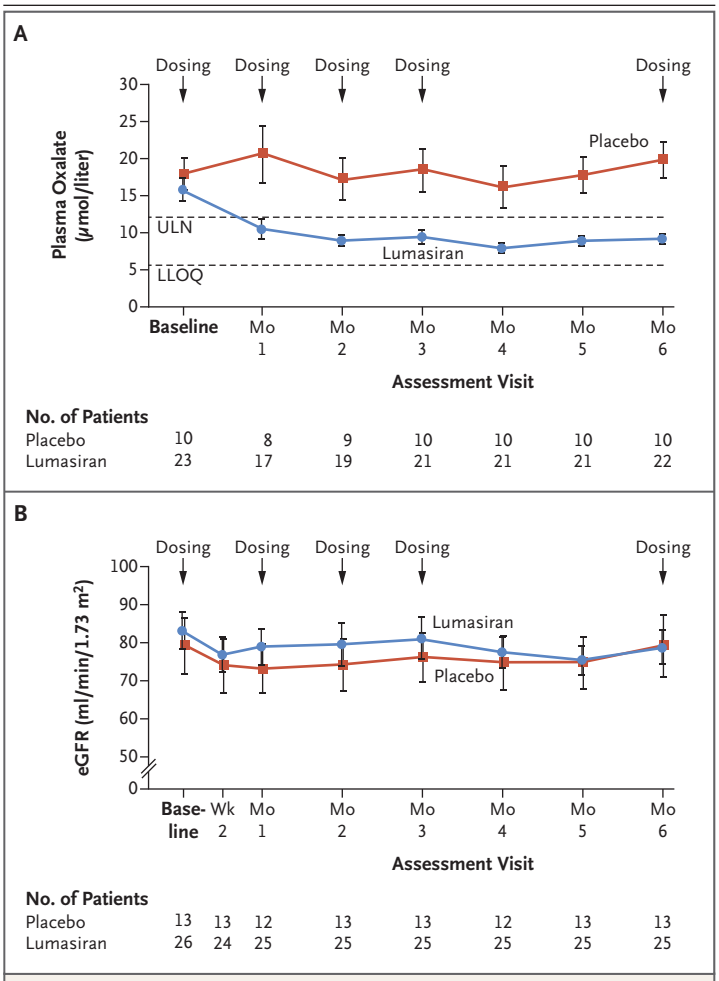

Figure 2. Observed Values for Plasma Oxalate and eGFR from Baseline to Month 6.

Panel A shows observed plasma oxalate levels. The ULN for plasma oxalate is 12.11 μmol per liter, and the lower limit of quantitation (LLOQ) is 5.55 μmol per liter. Panel B shows the eGFR from baseline to month 6. In both panels, data points are means and I bars indicate the standard error.

One patient tested positive for antidrug antibodies (with a low titer [1:50]) at month 6. This finding had no observable effect on efficacy or safety.

SAFETY

Overall, 85% of the patients who received lumasiran and 69% of the patients who received placebo reported adverse events (Table 3), all of which were mild or moderate in severity. There were no severe or serious adverse events or deaths. One patient in the lumasiran group dis-

Table 3. Safety.

Event	Lumasiran (N=26)	Placebo (N=13)
	no. of patients (%)	
Any adverse event	22 (85)	9 (69)
Adverse events occurring in ≥10% of patients in either group		
Injection-site reactions*	10 (38)	0
Headache	3 (12)	3 (23)
Rhinitis	2 (8)	2 (15)
Upper respiratory infection	2 (8)	2 (15)
Adverse event leading to discontinuation of lumasiran or placebo	1 (4)	0
Adverse event leading to withdrawal from the trial	0	0
Death	0	0
Any serious adverse event	0	0
Any severe adverse event	0	0

* This category includes adverse events of injection-site reaction, injection-site pain, injection-site erythema, and injection-site discomfort.

continued treatment because of adverse events of fatigue and disturbance in attention (Table 3).

The most common adverse events that occurred more frequently with lumasiran than with placebo were injection-site reactions (38% vs. 0%). All injection-site reactions were mild and transient and did not result in discontinuation of treatment. The most frequently reported symptoms were erythema, pain, pruritus, and discomfort. No hepatic adverse events were reported in either treatment group. There were no clinically relevant changes in laboratory measures (including hematologic measures, blood chemical measures, liver-function tests, and renal measures), vital signs, physical examinations, or electrocardiograms.

DISCUSSION

Oxalate is the key toxic metabolite in PH1, and reductions in hepatic oxalate production, measured with the use of plasma and urinary oxalate, have long-term clinical benefits, including preservation of kidney function in patients who undergo liver transplantation before the development of end-stage kidney disease.[11,14,16-20] We found that the percentage reduction in 24-hour urinary oxalate excretion was 53.5 percentage points greater with lumasiran than with placebo during the 6-month double-blind treatment period and that most patients who received lumasiran had normal or near-normal urinary oxalate levels at month 6. The treatment effect of lumasiran was robust and consistent across all subgroups, irrespective of age, baseline urinary oxalate excretion, pyridoxine use, or kidney function. A reduction in urinary oxalate excretion with lumasiran was observed as early as the first postdose assessment visit (week 2 for the spot urinary oxalate:creatinine ratio and month 1 for 24-hour urinary oxalate excretion); steady-state reductions were attained by the end of the loading-dose period.

Treatment with lumasiran also substantially reduced plasma oxalate levels, supporting the mechanism of action of lumasiran and its potential to favorably affect the development and progression of systemic oxalosis. (Plasma oxalate levels increase as kidney function worsens, especially in patients with an eGFR <30 ml per minute per 1.73 m^2.[27])

The observed percent reduction in urinary oxalate:creatinine ratios in random urine samples was similar to the corresponding percent reduction in 24-hour urinary oxalate excretion normalized to body-surface area. This finding adds to existing data that support the use of random urine samples for measuring changes in urinary oxalate excretion[28] in this patient population, in which the majority of oxalate derives from the liver as opposed to the diet.

For patients in the lumasiran group, plasma glycolate levels and 24-hour urinary glycolate:creatinine ratios initially increased and then reached a plateau by the end of the loading-dose phase. This had been anticipated on the basis of the mechanism of action of lumasiran, which inhibits glycolate oxidase production. Elevated levels of plasma glycolate have been reported in four cases of glycolate oxidase deficiency, with no apparent adverse clinical consequences.[29-32]

In both treatment groups, the eGFR remained stable during the 6-month double-blind period, a finding consistent with the natural history of the disease.[33] Spontaneous improvements in nephrocalcinosis are not expected in patients with PH1, although nephrocalcinosis can abate with normalization of urinary oxalate levels — for instance, after liver transplantation.[16]

The principal adverse events related to luma-

siran in our trial were mild, transient injection-site reactions that did not lead to discontinuation of treatment. There were no clinically relevant laboratory findings, including no imbalances in liver-function test results, in lumasiran-treated patients as compared with placebo recipients. One limitation of our trial is that patients younger than 6 years of age and patients with an eGFR of less than 30 ml per minute per 1.73 m^2 were excluded. Two additional, ongoing phase 3 trials are being conducted to comprehensively evaluate the effect of lumasiran in patients with PH1 across the full spectrum of age and disease severity. In ILLUMINATE-B (ClinicalTrials.gov number, NCT03905694), the efficacy and safety of lumasiran in patients younger than 6 years of age who have relatively preserved kidney function are being evaluated. In ILLUMINATE-C (NCT04152200), the efficacy and safety of lumasiran in patients of all ages who have advanced PH1, including patients undergoing hemodialysis, are being evaluated.

This phase 3 trial showed that lumasiran led to substantial reductions in urinary and plasma levels of oxalate, the disease-causing metabolite in PH1, with urinary oxalate levels in most patients reaching the normal or near-normal range.

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APPENDIX

The authors' affiliations are as follows: the Department of Pediatric Nephrology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam (S.F.G., J.W.G.); the Division of Pediatric Nephrology, Shaare Zedek Medical Center, Jerusalem (Y.F.); the Department of Nephrology, Birmingham Women's and Children's Hospital, Birmingham (S.A.H.), and the Department of Paediatric Nephrology, Great Ormond Street Hospital (W.G.H.), and UCL Department of Renal Medicine, Royal Free Hospital (S.H.M.), London — both in the United Kingdom; Jacksonville Center for Clinical Research, Jacksonville, FL (M.J.K.); eStudySite, San Diego, CA (W.D.O.); Center for Rare Renal Diseases and INSERM Pediatric Clinical Investigation Center–Hospices Civils de Lyon and Université de Lyon, Lyon (P.C.), and the Department of Pediatric Nephrology, Hôpital Robert-Debré, Paris (G.D.) — both in France; the Pediatric Nephrology Unit, Galilee Medical Center, Nahariya (H.S.-L.), and the Pediatric Nephrology Institute, Rambam Health Care Campus, Haifa (D.M.) — both in Israel; the Icahn School of Medicine at Mount Sinai, New York (J.M.S., K.A.M.); the Department of Nephrology and Hypertension, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland (D.G.F.); the University of Bonn, Bonn, Germany (G.S.); Al Jalila Children's Hospital, Dubai, United Arab Emirates (E.S.); the Divisions of Pediatric Nephrology and Hypertension (D.J.S.) and Nephrology and Hypertension (J.C.L.), Mayo Clinic, Rochester, MN; and Alnylam Pharmaceuticals, Cambridge, MA (J.L., M.T.S., P.P.G., A.K.V., J.M.G., T.L.M.).

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