Long-term Efficacy and Safety of Lumasiran in Patients With Primary Hyperoxaluria Type 1: Final Analysis of the ILLUMINATE-A Trial

Jeffrey M. Saland[1], John C. Lieske[2], Richard Willey[3], Yaacov Frishberg[4], Martin Coenen[5], Julien Hogan[6], Cristin Kaspar[3], Sally-Anne Hulton[7]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA; [3]Alnylam Pharmaceuticals, Cambridge, MA, USA; [4]Division of Pediatric Nephrology, Shaare Zedek Medical Center, Jerusalem, Israel Faculty of Medicine, Hebrew University, Jerusalem, Israel; [5]Institute of Clinical Chemistry and Clinical Pharmacology, University of Bonn, Bonn, Germany; [6]Pediatric Nephrology Department, Hôpital Robert-Debré, APHP, Paris, France; [7]Department of Nephrology, Birmingham Women's and Children's Hospital, Birmingham, UK

For US HCPs only
Scan to view congress materials

Conclusions

- Treatment of PH1 patients with lumasiran for 54 to 60 months led to sustained reductions in UOx with an acceptable safety profile.
- Clinical outcomes data included low rates of eGFR decline, minimal kidney stone events, and, in a number of patients, improved medullary nephrocalcinosis.

Introduction

- PH1 is a rare genetic disorder characterized by hepatic oxalate overproduction, increased kidney oxalate excretion, and calcium oxalate crystal formation in kidneys and urinary tract.[1]
  - Patients may experience nephrolithiasis and/or nephrocalcinosis, which can ultimately progress to kidney failure and systemic oxalosis.[1]
- Lumasiran, an RNAi therapeutic, targets and promotes degradation of the mRNA encoding glycolate oxidase, reducing hepatic oxalate production.[2]
  - Lumasiran is approved in the US and European Union for the treatment of PH1.[3,4]
- Here we report data from the final, 60-month analysis of the ILLUMINATE-A study of lumasiran in PH1 (ClinicalTrials.gov: NCT03681184; EudraCT: 2018-001981-40).

Methods

- ILLUMINATE-A was a multinational (Europe, Middle East, North America) Phase 3 trial conducted from November 27, 2018, to January 12, 2024.
  - Eligible patients were ≥6 years old with confirmed PH1 and an eGFR ≥30 mL/min/1.73m^2.
  - Lumasiran 3 mg/kg was administered as a loading dose once monthly for 3 doses, followed by a maintenance dose every 3 months beginning 1 month after the last loading dose, consistent with the US prescribing information.[3]
  - A pivotal 6-month, double-blind, randomized, placebo-controlled period was followed by an extension period of up to 54 months in which all patients received open-label lumasiran.
- Endpoint analyses
  - Primary: percent change in 24-hour UOx excretion from baseline to Month 6.
  - Secondary: proportion of patients with 24-hour UOx ≤1.5 × ULN at Month 6, change in POx and eGFR from baseline to Month 6, and change in 24-hour UOx excretion and eGFR during the extension period.
  - Exploratory: change in plasma glycolate, kidney stone event rate, and nephrocalcinosis as assessed by ultrasound, all from baseline to Month 6.
  - Post hoc: change in POx, plasma glycolate, kidney stone event rate, and nephrocalcinosis, and proportion of patients with 24-hour UOx 1.5 × ULN, all during the extension period.
  - Baseline is defined as the period prior to the first lumasiran dose; hence, the lumasiran/lumasiran sequence has 6 more months of on-lumasiran follow-up than the placebo/lumasiran sequence.
  - Annual rates of change were derived by dividing the mean change from baseline at Month 48 by 4 (eGFR) or overall events divided by overall patient exposure time (kidney stone events).

Results

- Of 39 patients enrolled in the pivotal study, 13/13 (placebo/lumasiran) and 24/26 (lumasiran/lumasiran) completed treatment in the open-label extension.
- Baseline characteristics were generally well balanced between groups (**Table 1**).

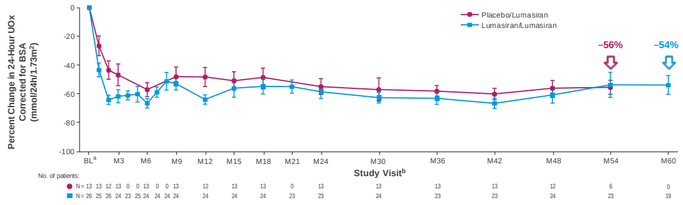
Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Placebo/Lumasiran (N=13)	Lumasiran/Lumasiran (N=26)
Age at informed consent, mean (range), years	17.0 (6–60)	18.7 (6–47)
Male, n (%)	8 (62)	18 (69)
Race, n (%)		
Asian	3 (23)	3 (12)
White	9 (69)	21 (81)
Other, or >1 race	1 (8)	2 (8)
24-hour UOx excretion corrected for BSA, mean (SD), mmol/24h/1.73m^2[a,b]	1.6 (0.7)	1.8 (0.6)
POx, mean (SD), µmol/L[c,d]	19.3 (9.5)	14.8 (7.6)
eGFR, mean (SD), mL/min/1.73m^2[c]	78.8 (30.0)	83.0 (25.5)
Patients reporting history of kidney stone events, n (%)		
Lifetime	10 (77)	23 (88)
12 Months prior to consent	4 (31)	11 (42)

[a]For the lumasiran/lumasiran group, baseline is the median of all valid 24-hour urine assessments collected prior to the first dose date/time of lumasiran without any non-protocol-related sample issues. For the placebo/lumasiran group, baseline is the median of all valid 24-hour urine assessments at Month 6 without any non-protocol-related sample issues (or, if the patient did not have 2 valid 24-hour urine pharmacodynamic assessments at Month 6, then the baseline was calculated using the latest 3 valid 24-hour urine pharmacodynamic collections prior to the first dose date/time of lumasiran). [b]ULN is 0.514 mmol/24h/1.73m^2 = 45 mg/24h/1.73m^2 (1 mmol/24h/1.73m^2 = 90 mg/24h/1.73m^2). [c]Baseline is defined as the last non-missing value prior to the first dose of lumasiran (all-lumasiran-treated set). [d]ULN is 12.11 µmol/L.

- Mean 24-hour UOx reductions at end of study relative to baseline: 56% (placebo/lumasiran) and 54% (lumasiran/lumasiran) (**Figure 1**).

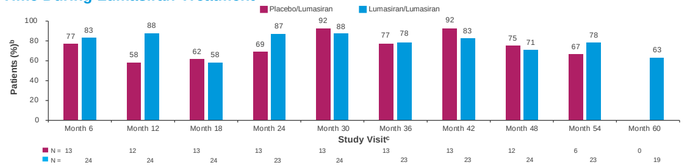
Figure 1. Mean (SEM) Percent Change in 24-Hour UOx Levels Over Time During Lumasiran Treatment



[a]For the lumasiran/lumasiran group, baseline is the median of all valid 24-hour urine assessments collected prior to the first dose date/time of lumasiran without any non-protocol-related sample issues. For the placebo/lumasiran group, baseline is the median of all valid 24-hour urine assessments at Month 6 without any non-protocol-related sample issues (or, if the patient did not have 2 valid 24-hour urine pharmacodynamic assessments at Month 6, then the baseline was calculated using the latest 3 valid 24-hour urine pharmacodynamic collections prior to the first dose date/time of lumasiran). [b]Visit is relative to the first dose of lumasiran.

- Beginning 2 months after lumasiran treatment initiation, ≥50% of patients in each group achieved 24-hour UOx excretion ≤1.5 × ULN (**Figure 2**).

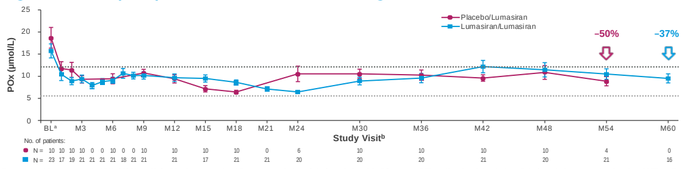
Figure 2. Percentage of Patients With 24-Hour UOx Corrected for BSA ≤1.5 × ULN[a] Over Time During Lumasiran Treatment



[a]ULN is 0.514 mmol/24h/1.73m^2 = 45 mg/24h/1.73m^2 (1 mmol/24h/1.73m^2 = 90 mg/24h/1.73m^2). [b]Percentages are based upon the number of patients having 24-hour UOx corrected for BSA data at the visit. [c]Visit is relative to the first dose of lumasiran (all-lumasiran-treated set).

- Mean POx reductions at end of study relative to baseline: 50% (placebo/lumasiran) and 37% (lumasiran/lumasiran) (**Figure 3**).

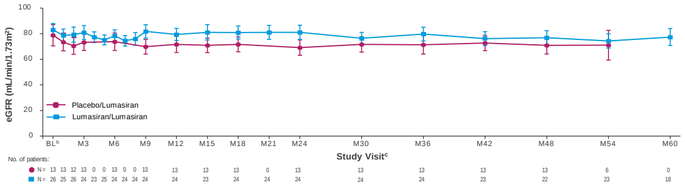
Figure 3. Mean (SEM) POx Levels Over Time During Lumasiran Treatment



Top gray dotted line represents the ULN of 12.11 µmol/L for POx; Bottom gray dotted line represents the lower limit of quantitation of the POx assay at 5.55 µmol/L; values below the lower limit of quantitation were assigned a value of 5.55 µmol/L. [a]For the lumasiran/lumasiran group, baseline is defined as the mean of all measurements prior to the first dose date/time of lumasiran. For the placebo/lumasiran group, baseline is the mean of the last 2 non-missing measurements prior to the first dose date/time of lumasiran. [b]Visit is relative to the first dose of lumasiran.

- Plasma glycolate increased during the first 6 months of lumasiran treatment (mean change from baseline: 154% [placebo/ lumasiran] and 119% [lumasiran/lumasiran]), then plateaued and remained stable.
- eGFR remained stable through end of study: mean (SEM) change from baseline, −12.86 (3.89) mL/min/1.73m^2 (placebo/ lumasiran) and −2.89 (2.75) mL/min/1.73m^2 (lumasiran/lumasiran) (**Figure 4**).
- Overall, in the all-lumasiran-treated set, the mean annual rate of eGFR change per year at Month 48 was −1.19 mL/min/1.73m^2.

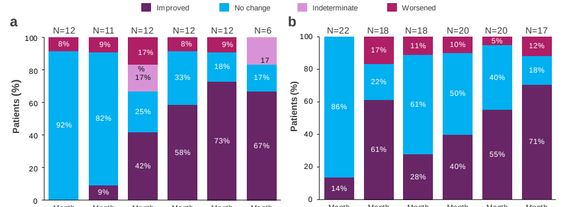
Figure 4. Mean (SEM) eGFR[a] Over Time During Lumasiran Treatment



[a]eGFR was calculated with the Modification of Diet in Renal Disease formula for patients ≥18 years of age at screening and the Schwartz Bedside Formula for patients 6 to <18 years of age at screening. [b]Baseline is the last assessment collected prior to the first dose date/time of lumasiran. [c]Visit is relative to the first dose of lumasiran.

- Kidney stone event rates were low during lumasiran treatment:
  - All months: 0.54/PY (placebo/lumasiran) and 0.47/PY (lumasiran/lumasiran)
  - Final 6 months: 0.68/PY (placebo/lumasiran) and 0.09/PY (lumasiran/lumasiran)
- Zero kidney stone events occurred during lumasiran treatment in 8/13 (62%) placebo/lumasiran patients and 13/26 (50%) lumasiran/lumasiran patients.
- Medullary nephrocalcinosis grade generally improved or remained stable (no change) (**Figure 5**).
  - Among patients who had medullary nephrocalcinosis at baseline (N=20), medullary nephrocalcinosis grade improved in 16 (80%) patients.

Figure 5. Change From Baseline in Medullary Nephrocalcinosis in the (a) Placebo/Lumasiran Group and (b) Lumasiran/Lumasiran Group[a,b]



[a]All-lumasiran-treated set. [b]The degree of medullary nephrocalcinosis in each kidney was graded using a validated 4-point scale[5]: stable (no change in either kidney), improving (both kidneys improving or 1 kidney improving and 1 with no change), worsening (both kidneys worsening or 1 kidney worsening and 1 with no change), and indeterminate (1 kidney improving and 1 worsening).

- Overall, 95% (37/39) of patients had AEs (**Table 2**).
  - The most common lumasiran-related AEs were injection site reactions (36% of patients); all were mild.

Table 2. Safety Profile of Lumasiran[a]

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

[a]All-lumasiran-treated set. [b]Abdominal pain (N=2), dysuria (N=1), follicular lymphoma (N=1), postprocedural complication (N=1), postprocedural infection (N=1), renal impairment (N=1), urinary tract infection (N=1), and urosepsis (N=1), all considered not related to lumasiran by the investigator. [c]Acute pyelonephritis (N=1), follicular lymphoma (N=1), postprocedural complication (N=1), postprocedural infection (N=1), urinary tract infection (N=1), and urosepsis (N=1), all considered not related to lumasiran by the investigator. [d]Fatigue and disturbance in attention, considered not related to lumasiran by the investigator, which began during the double-blind period. [e]All were transient, considered mild in severity, and resolved without sequelae.

References: 1. Cochat P, Rumsby G. *N Engl J Med.* 2013;369:649-658. **2.** Liebow A, et al. *J Am Soc Nephrol.* 2017;28:494-503. **3.** Oxlumo [package insert]. Cambridge, MA: Alnylam Pharmaceuticals; 2022. **4.** Oxlumo [summary of product characteristics]. Amsterdam, Netherlands: Alnylam Netherlands; 2022. **5.** Dick PT, et al. *Pediatr Radiol.* 1999;29:68-72.

Acknowledgments: We thank and collaborators for their participation in the ILLUMINATE-A clinical study, Medical writing and editorial assistance was provided by Karyn Liu, PhD, of Peloton Advantage, LLC, an OPEN Health company, in accordance with Good Publication Practice (GPP 2022) guidelines and funded by Alnylam Pharmaceuticals.
We thank Nune Makarova, MD, MPH of Alnylam Pharmaceuticals for safety review.
Presented at: ASN Kidney Week; October 24–27, 2024; San Diego, CA

Abbreviations: AE, adverse event; BL, baseline; BSA, body surface area; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; mRNA, messenger ribonucleic acid; M, month; PH1, primary hyperoxaluria type 1; POx, plasma oxalate; PY, patient-years; RNAi, ribonucleic acid interference; ULN, upper limit of normal; UOx, urinary oxalate.

Disclosures: JMS: Alnylam Pharmaceuticals – grants, personal fees, and nonfinancial support. **JCL:** Alnylam Pharmaceuticals, Arbor, BioMarin, Dicerna Pharmaceuticals, Retrophin, OxThera, and Siemens – grants; Novobiome and Orfan-Bridgefilm – other; Allena and Syntiogic – grants and other. **RW** and **CK:** employees of and shareholders in Alnylam Pharmaceuticals. **YF:** Alnylam Pharmaceuticals – consultancy fees and membership in the safety review committee. **MC:** Nothing to disclose. **JH:** Alnylam Pharmaceuticals and Traversa – consultant; Biocodex – travel fees; CareDx – research grant. **S-AH:** Travel expenses to participate in clinical research meetings, consultancy fee from 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.