Long-Term Efficacy and Safety in the Phase 3 ILLUMINATE-B Trial of Lumasiran for Primary Hyperoxaluria Type 1 in Infants and Young Children

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Conclusions

- Infants and young children with PH1 had sustained reduction in UOx and POx with consistent safety through Month 60.
- Infants and children with PH1 had stable eGFR through Month 60.
- Medullary nephrocalcinosis improved in the majority of patients.
- Kidney stone event rates were low through Month 60.

Introduction

- PH1 is a genetic disorder resulting in excess hepatic oxalate production, which can lead to urolithiasis, nephrocalcinosis, and ultimately chronic kidney disease, kidney failure, and systemic oxalosis.[1]
- Lumasiran, the first liver-directed RNAi therapeutic administered to infants and children age ≤6 years, targets hydroxyacid oxidase 1 (HAO1) mRNA through RNA interference, thus decreasing glycolate oxidase (GO) levels, depleting glyoxylate, and inhibiting the formation of oxalate.[2]
- We previously reported that lumasiran demonstrated sustained efficacy with no unexpected safety signals over 30 months in infants and children age ≤6 years with PH1 participating in ILLUMINATE-B (NCT03905694).[3-6]
- Here, we present final efficacy and safety outcomes in patients treated with lumasiran through Month 60 of ILLUMINATE-B.

Methods

- ILLUMINATE-B was a Phase 3, multinational, open-label, single-arm study (**Figure 1**).
- A primary analysis conducted at 6 months[4] was followed by an extension period of up to 54 months.

Figure 1. ILLUMINATE-B Study Design

PATIENT POPULATION (N=18)

- Children age <6 years
- Confirmed PH1 diagnosis
- UOx:Cr >ULN for age for ≥2 of 3 samples
- eGFR >45 mL/min/1.73m^2 if age ≥12 months or normal SCr if age <12 months without extrarenal systemic oxalosis
- If taking vitamin B6 (pyridoxine), stable regimen for ≥90 days pre-screening and maintained through at least Month 6

6-MONTH PRIMARY ANALYSIS PERIOD FOLLOWED BY 54-MONTH EXTENSION PERIOD

Loading Dose

<10 kg: 6 mg/kg once monthly for 3 doses

10 to <20 kg: 6 mg/kg once monthly for 3 doses

≥20 kg: 3 mg/kg once monthly for 3 doses

Maintenance Dose

<10 kg: 3 mg/kg once monthly, beginning 1 month after last loading dose

10 to <20 kg: 6 mg/kg once quarterly, beginning 1 month after last loading dose

≥20 kg: 3 mg/kg once quarterly, beginning 1 month after last loading doses

- The primary endpoint was percentage change in spot UOx:Cr from baseline to Month 6.[4]
- Secondary endpoints included absolute and percentage change from baseline in UOx excretion, proportion of patients with UOx excretion ≤ULN and ≤1.5 × ULN for age, absolute and percentage change from baseline in POx, and change from baseline in eGFR.
- Changes in nephrocalcinosis and kidney stone event rates were exploratory endpoints.

Results

- All 18 patients enrolled in ILLUMINATE-B completed the 60-month study.
- All patients were ≤6 years of age (median age in months, 50.1; range, 3-72; **Table 1**).

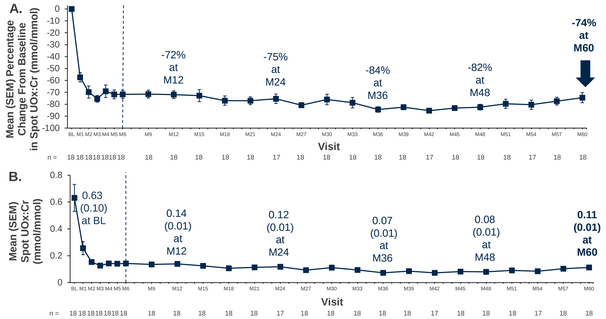
Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	All Treated (N=18)
Age at consent, median (range), months	50.1 (3-72)
Age at diagnosis, median (range), months	16.3 (0-44)
Time from diagnosis to first dose date, median (range), months	23.5 (4-56)
Genotype,[a] n (%)	
PR/*	3 (17)
M/M or M/N	10 (56)
N/N	5 (28)
Pyridoxine use, n (%)	11 (61)
Spot UOx:Cr, median (range), mmol/mmol[b,c]	0.469 (0.166-1.708)
POx, median (range), µmol/L[d]	11.5 (6.6-30.6)
eGFR, median (range), mL/min/1.73m^2[e]	111 (65-174)
At least 1 kidney stone event in the 12 months prior to informed consent, n (%)	3 (16.7)
Presence of medullary nephrocalcinosis, n (%)	14 (77.8)

[a]M=missense; N=nonsense; PR=pyridoxine-responsive; *=any genotype of PR, M, or N. PR was defined as NM_000030.3(AGXT):c.508G>A (p.Gly170Arg) or NM_000030.3(AGXT):c.454T>A (p.Phe152Ile). M and N were defined based on a publication by Mandrile et al.[7] [b]1 mmol/mmol=0.796 mg/mg.
[c]Age-related reference ranges in spot UOx:Cr: <1 year, 0.015–0.26 mmol/mmol; 1 to <5 years, 0.011–0.12 mmol/mmol; 5 to 12 years, 0.006–0.15 mmol/mmol.[1,8]
[d]ULN=12.11 µmol/L for POx, as determined based on data from 75 healthy adults.
[e]eGFR was calculated based on the Schwartz Bedside formula[8] for patients ≥12 months, N=16; eGFR was not calculated for 2 patients because their age at baseline was <12 months.

- Mean spot UOx:Cr decreased from 0.63 at baseline to 0.11 at Month 60; mean percentage change from baseline was −74% (**Figure 2**).
- Overall, 100% of patients had a spot UOx:Cr ≤ULN at one or more post-baseline visit.

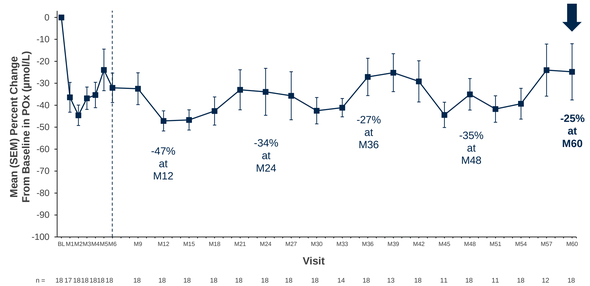
Figure 2. Change from Baseline in Spot UOx:Cr Ratio



(A) Percentage change from baseline at each visit, and (B) Actual values at each visit. The baseline value represents the mean of all assessments collected prior to the first dose of lumasiran; 1 mmol/mmol = 0.796 mg/mg; 1 mmol/mmol = 1000 mmol/mol. Labels on graph show mean (SEM) at baseline and at 12-month intervals; end-of-study appears in bold. End of the primary analysis period is represented by the vertical dashed line; error bars show standard error of the mean (SEM). The ULN for spot UOx:Cr is age-dependent.[10] Age-related reference ranges in spot UOx:Cr: <1 year, 0.015-0.26 mmol/mmol; 1 to <5 years, 0.011-0.12 mmol/mmol; 5 to 12 years, 0.06-0.15 mmol/mmol.[8] Oxalate assessments were evaluated by validated liquid chromatography–tandem mass spectrometry assays at a central laboratory.

- Mean POx decreased from 13.2 µmol/L at baseline (ULN = 12.11 µmol/L) to 8.2 µmol/L at Month 60; mean percentage change from baseline was −25% (**Figure 3**).

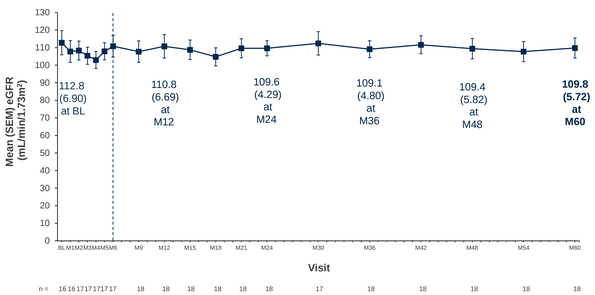
Figure 3. Percentage Change from Baseline in POx



The baseline value represents the mean of all assessments collected prior to the first dose of lumasiran. End of the primary analysis period is represented by the vertical dashed line; error bars show standard error of the mean (SEM). The lower limit of quantification is 5.55 µmol/L. Oxalate assessments were evaluated by validated liquid chromatography–tandem mass spectrometry assays at a central laboratory.

- eGFR remained stable through Month 60 (**Figure 4**).
- The annual change (slope) in mean eGFR over 60 months was +0.26 (SEM 0.8) mL/min/1.73m^2/y.

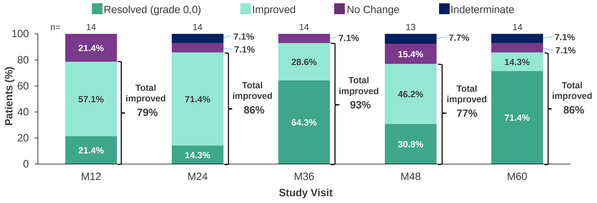
Figure 4. eGFR



Baseline is the last non-missing value collected prior to the first dose of lumasiran. Labels on graph show mean (SEM) at baseline and at 12-month intervals; end-of-study appears in bold. End of the primary analysis period is represented by the vertical dashed line; error bars show standard error of the mean (SEM). eGFR is calculated based on the Schwartz Bedside formula[8] in patients ≥12 months of age at the time of the assessment. Baseline values are not available for 2 patients who were <12 months of age at that time point.

- In 14 patients with medullary nephrocalcinosis at baseline, nephrocalcinosis grade improved in 86% (12/14), and no patient worsened at Month 60 (**Figure 5**).
- The 4 patients without nephrocalcinosis at baseline remained nephrocalcinosis-free at Month 60.

Figure 5. Change in Medullary Nephrocalcinosis (NC) Grade in Patients with NC at Baseline



Resolved (grade 0,0) denotes bilateral grade of '0,0' (both kidneys), **Improved** denotes grade lower than baseline (unilateral improvement if one side improved and other side did not change), **Indeterminate** denotes improvement on one side and worsening on the other. **Worsened** denotes grade higher than baseline (no patients worsened).

- Kidney stone event rates remained low (0.11/person-years [95% CI, 0.06-0.21]) through Month 60.
  - Overall, 9 kidney stone events (in 4 patients) were reported during the entire study period; all events were mild or moderate in severity.
  - Fourteen patients (77.8%) had no kidney stone events during ILLUMINATE-B.
- Median (range) exposure to lumasiran was 55.5 (54.5-56.1) months.
- Five (28%) patients had AEs considered related to lumasiran by the investigator, none of which were severe or serious (**Table 2**).
  - The most common lumasiran-related AEs were mild, transient injection site reactions (3 patients [17%]); symptoms included erythema, hematoma, and pain at the injection site, and urticaria.
- There were no clinically relevant changes in laboratory measures, vital signs, or electrocardiograms related to lumasiran.

Table 2. Safety Data for ILLUMINATE-B

Event, n (%)	All Treated (N=18)
AEs	18 (100)
Treatment-related AEs[a]	5 (28)
Severe treatment-related AEs	0
AEs leading to treatment discontinuation	0
AEs leading to study withdrawal	0
Serious AEs	2 (11)[b]
Death	0

[a]Treatment-related AEs included injection site reactions, blood bilirubin increase, and headache.
[b]One patient had a serious AE of viral infection (moderate in severity; considered unrelated to lumasiran by the investigator) during the 6-month primary analysis period, which was reported previously.[4] The other patient had a serious AE of ear pain and ear hemorrhage (severe; considered unrelated to lumasiran by the investigator) during the extension period. In both patients, lumasiran dosing was not changed.

- The data suggest no unexpected safety signals.

Acknowledgments: On behalf of the study investigators, we thank the patients, their families, investigators, study staff, and collaborators for their participation in the lumasiran clinical studies. Medical writing and editorial assistance was provided by Peloton Advantage, LLC, an OPEN Health company, in accordance with Good Publication Practice (GPP 2022) guidelines and funded by Alnylam Pharmaceuticals.

Funding: This study was funded by Alnylam Pharmaceuticals.

Presented at: the National Kidney Foundation (NKF) Congress; April 10-13, 2025; Boston, MA

Disclosures: YF: Consultancy fees from Alnylam Pharmaceuticals and membership in the safety review committee. **WH:** Principal investigator for Alnylam Pharmaceuticals; consultancy fees, travel and accommodation. **EB-S:** Principal investigator for Alnylam Pharmaceuticals. **HSL:** Principal investigator for Alnylam Pharmaceuticals; travel and accommodation expenses to attend international investigators' meetings. **DJS:** Grants and other from Alnylam Pharmaceuticals, and personal fees from Advicenne. **MM:** Principal investigator for Alnylam Pharmaceuticals; advisory board member for Novo Nordisk Inc; and speaker fees for session/symposium from Alnylam Pharmaceuticals and Novo Nordisk. **ALSL:** Consultancy fees from Alnylam Pharmaceuticals and Dicerna Pharmaceuticals, and principal investigator for research funded by OxThera. **JH:** Consultancy fees from Alnylam Pharmaceuticals. **WD:** Alnylam Pharmaceuticals – employee and shareholder. **CK:** Alnylam Pharmaceuticals – employee. **DMurphy:** Alnylam Pharmaceuticals – employee and shareholder. **DMagen:** Research funding, consultancy fees, and non-financial support from Alnylam Pharmaceuticals.

Abbreviations: AE, adverse event; BL, baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; LC-MS/MS, liquid chromatography-tandem mass spectrometry; M, month; NC, nephrocalcinosis; PH1, primary hyperoxaluria type 1; POx, plasma oxalate; SCr, serum creatinine; ULN, upper limit of normal; UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio.

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