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Efficacy and Safety of Lumasiran for Advanced Primary Hyperoxaluria Type 1: 24-Month Follow-Up of the Phase 3 Illuminate-C Trial

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Efficacy and Safety of Lumasiran for Advanced Primary Hyperoxaluria Type 1: 24-Month Follow-Up of the Phase 3 Illuminate-C Trial

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To the Editor:

Primary hyperoxaluria type 1 (PH1) is a rare autosomal recessive disorder caused by hepatic alanine-glyoxylate aminotransferase deficiency, leading to oxalate overproduction which results in progressive kidney damage and increased urinary oxalate (UOx) and plasma oxalate (POx) levels.[1,2] Oxalate accumulation can result in kidney stones, nephrocalcinosis, and kidney failure.[2] In chronic kidney disease stages 3b−5, elevated POx increases the risk of calcium oxalate deposition (systemic oxalosis) in the heart, bones, eyes, and other organs.[3]

Managing patients with PH1 and kidney failure is extremely challenging. Patients may require dialysis followed by combined or sequential liver-kidney transplantation, which represents curative treatment.[2,3] Isolated kidney transplant is typically only considered for a subset of patients who are homozygous for the *AGXT* p.Gly170Arg or p.Phe152Ile mutations, which confer responsiveness to pyridoxine treatment.[1,3]

Lumasiran is an RNA interference therapeutic that reduces hepatic oxalate production via inhibiting expression of the enzyme glycolate oxidase.[4] Lumasiran is approved in several countries, including in the European Union and the United States, for the treatment of PH1 to lower UOx and POx levels in pediatric and adult patients.[4,5] In the ongoing phase 3, open-label, single-arm ILLUMINATE-C trial (NCT04152200; 6-month primary; 54-month extension period) in patients with PH1 and advanced kidney disease, lumasiran treatment reduced POx from baseline to 6 months (primary endpoint).[6] Here, we summarize efficacy and safety results at Month 24 (M24).

ILLUMINATE-C enrolled 21 patients with PH1; estimated glomerular filtration rate ≤45 mL/min/1.73m^2 (age ≥12 months) or increased serum creatinine level (age <12 months); POx ≥20 μmol/L; and, if taking pyridoxine, on a stable regimen.[6] Patients not on hemodialysis at

screening were assigned to Cohort A (N=6) and those on hemodialysis, to Cohort B (N=15). Subcutaneous lumasiran was administered monthly or quarterly, based on body weight (**Item S1**, Methods). Endpoints are summarized using descriptive statistics (**Item S2**).

All 21 enrolled patients entered the extension period (**Figure S1**). At baseline, patients were aged 4 months to 59 years and 57% were using pyridoxine; mean (SEM) POx (μmol/L) was 64.7 (16.9) in Cohort A and 108.4 (7.6) in Cohort B (pre-dialysis) (**Table S1**). Baseline organ-specific oxalosis measures revealed echocardiogram abnormalities in 24% of patients for left ventricular ejection fraction (LVEF); 86% had evidence of skeletal oxalosis. Among 12 evaluated patients, 42% had ocular oxalosis abnormalities.

In Cohort A, 2 patients (33%) initiated dialysis by M24. In Cohort B, 2 patients (13%) underwent kidney-only transplantation by M24 and remained in the study, and 3 patients (20%) withdrew during the extension (2 due to liver-kidney transplantation).

At M24, mean (SEM) POx in Cohort A had decreased to 27.9 (9.6), a reduction of 60.5% from baseline; in Cohort B, pre-dialysis POx was 67.6 (7.6) at M24, a reduction of 30.6% (**Figure 1**).

Both patients who received an isolated kidney transplant had reduced POx with concurrent long-term lumasiran treatment (**Figure 2**). Relative to baseline, POx was reduced 78.8% in Patient 1 and 87.4% in Patient 2. Both continued lumasiran post-transplant and had functioning grafts and minimal change in eGFR at M24 (17 and 9 months, respectively, of post-transplant follow-up). In Cohort B patients who did not undergo transplantation by M24 (N=11), 8 had unchanged hemodialysis frequency (range: 3-7 sessions/week). In 3 patients, frequency changed by 1 session/week (1 increase [reason: preparation for iKT]; 2 decreases [reasons: reduced oxalemia and family requirements]).

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Skeletal and ocular oxalosis measurements remained largely unchanged through M24. No Cohort A patients remaining in the study at M24 met criteria for worsening LVEF (**Table S2**). Of the Cohort B patients remaining in the study at M24, 2 of the 3 patients with an abnormal baseline LVEF met criteria for important LVEF improvement by M24. Small sample size and lack of placebo control limit evaluation of correlation of POx with oxalosis and restrict results to descriptive reports.

The most frequently reported adverse events (AEs) were pyrexia (38%), diarrhea (29%), and injection site reactions (ISRs; 24%). ISRs were the most common treatment-related AEs; all 6 events (5 patients) were mild in severity. No severe AEs were considered related to lumasiran (**Table S3**). See **Tables S4-S5** and **Figures S2-S5** for additional clinical data through M24.

Limitations include the lack of a control group and small sample size, and insufficient follow-up for interpretation of oxalosis data. In PH1, elevated oxalate levels may persist from efflux of extra-renal stores (particularly skeletal) in addition to hepatic oxalate synthesis[1]. Bone improvements can evolve over more than 3-4 years after liver transplant.[7,8] Ascertaining the impact of lumasiran treatment on manifestations arising from long-term oxalate deposition in body tissues requires longer follow-up. A report of oxalosis findings is planned when data are mature.

In conclusion, in ILLUMINATE-C, POx reductions were sustained through 24 months of lumasiran treatment with an acceptable safety profile in adults and children with PH1 and advanced kidney disease, including patients on hemodialysis and those receiving isolated kidney transplants.

Supplementary Material

Supplementary File 1 (PDF)

Figures S1-S5, Items S1-S2, Tables S1-S5.

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Supplementary File 2 (PDF)
Alnylam Bone Oxalosis Grading Scale.

Article Information

Authors' Contributions: Research idea and study design: JMG, YF, CM; data acquisition: FGE, JCL, IG, AD, R Singer, SB, DM, ES; data analysis/interpretation: FGE, JMG, JCL, RW, NM, AD, YF, MM, JWG, SB, CK, ALSL, DM, R Saqan, HSL; statistical analysis: RW; supervision or mentorship: FGE, JMG. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's 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.
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Data Sharing: Access to anonymized individual participant data that support these results is made available 12 months after study completion and not less than 12 months after the product

and indication have been approved in the US and/or the EU. Data 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.

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Figure 1. Plasma Oxalate Mean (SEM) Values at Each Visit Through Month 24**.** Data labels show actual mean (SEM) plasma oxalate values at BL and M24, and percent reduction relative to the baseline mean value. In Cohort A, baseline was defined as the mean of all plasma oxalate samples (µmol/L) collected prior to the first dose of lumasiran; in Cohort B, baseline was defined as the mean of the last 4 pre-dialysis plasma oxalate samples (µmol/L) collected prior to the first dose of lumasiran. Oxalate data collected after liver transplant, hemodialysis initiation (Cohort A), or hemodialysis discontinuation (Cohort B) were censored. The upper limit of normal is 12.11 µmol/L for POx, as determined based on data from 75 healthy adults.[9]
BL, baseline; M, month.

Figure 2. Patients With Isolated Kidney Transplant: POx, UOx, and Post-transplant eGFR Through Month 24. (A) Patient 1. (B) Patient 2.
Patient 1: (Cohort B; 44 years old at study entry)
Per genetic assessment, Patient 1 had a pyridoxine-responsive genotype; this patient was taking pyridoxine at baseline. Patient 1 stopped hemodialysis 1 day after transplant. This patient, who received a kidney from a >50-year-old donor, had suboptimal graft function, with a postoperative course complicated by a BK virus graft nephropathy that was successfully treated by reducing immune suppression. Postoperative biopsy showed no recurrence of oxalate nephropathy. Patient 1 received pyridoxine and crystallization inhibitor therapy after transplant. Postoperative eGFR remained low but stable after transplant at 24–34 mL/min/1.73m^2.
Patient 2: (Cohort B; 2 years old at study entry)
In Patient 2, spot UOx:Cr was measured starting at M15; urinary oxalate concentrations (using 24-hour sampling) were not assessed. Patient 2 was taking pyridoxine at baseline; however, per genetic assessment, Patient 2 did not have a pyridoxine-responsive genotype. Patient 2 continued hemodialysis for 36 days after transplant. Adverse events (AEs) recorded by the site during the post-transplantation period (not required by protocol) included: a readmission to hospital for fever and graft dilation 1 day after discharge from the transplant hospitalization; HSV infection; occurrence of a urinoma; and acute renal injury. All AEs were considered recovered/resolved and not caused by the study drug by the investigator. As interpreted by the Sponsor, these AEs are consistent with the known complications associated with organ transplantation and are likely the cause of the acute kidney injury AE reported during the interval that the post-transplant hemodialysis occurred. Renal ultrasound 2 months post-transplant showed an asymptomatic nephrolithiasis, which resolved; a planned transplant biopsy performed at postoperative month 7 showed rare intratubular crystals in the medullary parenchyma without refringence in polarized light, findings that are not characteristic of calcium oxalate. Patient 2 received pyridoxine and crystallization inhibitor treatment after transplant. The first post-transplant eGFR (M15) was 120 mL/min/1.73m^2; eGFR at M24 was 115 mL/min/1.73m^2.
BL, baseline; eGFR, estimated glomerular filtration rate; M, month; POx, plasma oxalate; UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio. Data labels (blue) show actual POx values at BL and M24, and percent reduction relative to the baseline value.

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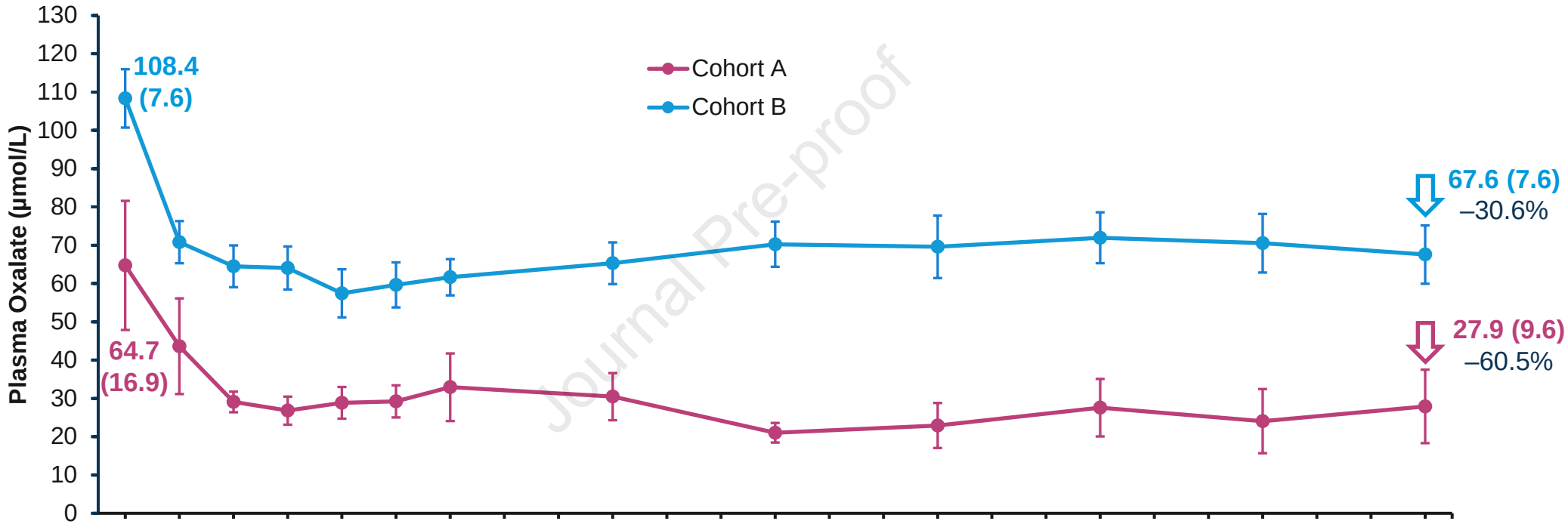

No. of Patients:	BL	M1	M2	M3	M4	M5	M6	M9	M12	M15	M18	M21	M24
Cohort A	6	6	6	6	6	6	6	5	4	4	4	4	4
Cohort B	15	15	15	15	13	13	15	12	12	9	9	10	10

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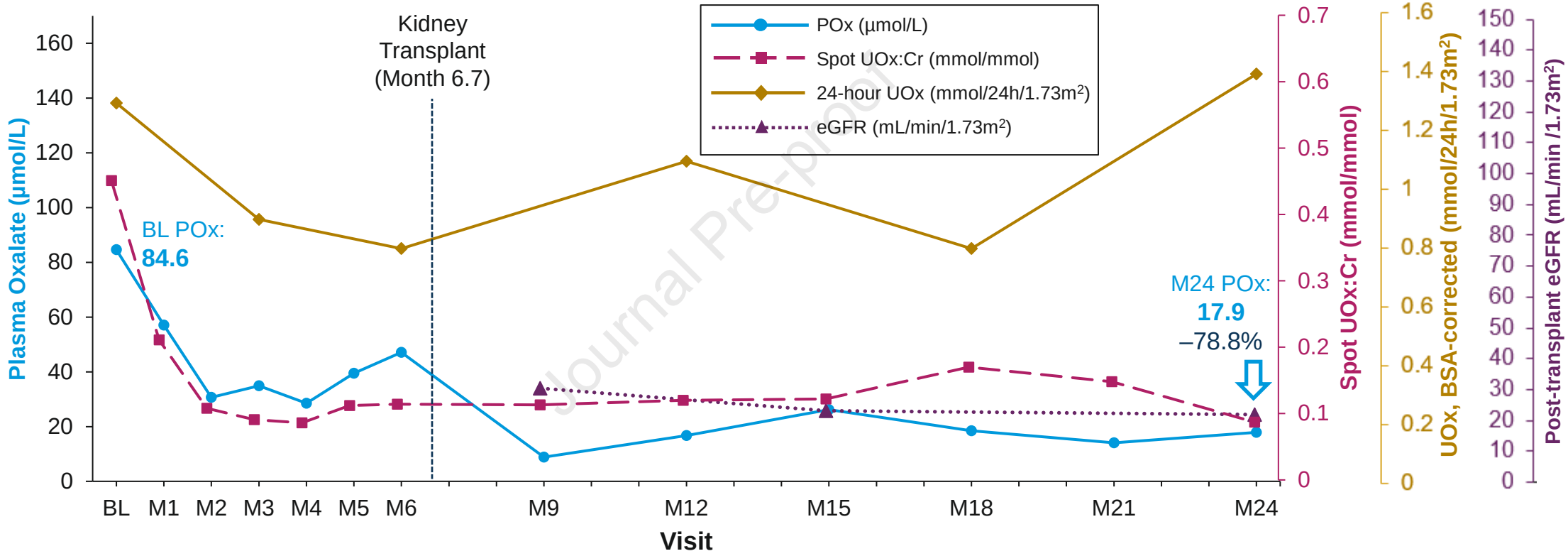

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