Lumasiran for Primary Hyperoxaluria Type 1 With Impaired Kidney Function: 24-Month Analysis of the Phase 3 ILLUMINATE-C Trial

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Conclusions

- POx reductions with lumasiran were maintained through 24 months of treatment with an acceptable safety profile in PH1 patients with CKD stages 3b–5, including those on HD, and in patients with isolated kidney transplant
- The 4 patients who underwent isolated kidney transplant remain on lumasiran treatment, with a functioning kidney graft
- Noninvasive indicators of systemic oxalosis appear largely stable after 2 years of treatment in this study population
- The most common treatment-related AEs were mild injection site reactions (24%); there were no lumasiran-related severe or serious AEs, discontinuations, or withdrawals

Introduction

- PH1 is a rare genetic disorder in which hepatic oxalate overproduction can lead to CKD[1]
- POx increases with declining kidney function; in CKD stages 3b–5, elevated POx increases the risk of systemic oxalosis (oxalate deposition throughout the body),[1,2] which may involve the heart, bones, and eyes, among other organs[3-9]
- Lumasiran, an RNA interference therapeutic that reduces hepatic oxalate production, is approved in the United States for the treatment of PH1 to lower UOx and POx levels in pediatric and adult patients[10] and in the European Union for the treatment of PH1 in all age groups[11]
- In the ILLUMINATE-C trial (ClinicalTrials.gov: NCT04152200; EudraCT: 2019-001346-17), lumasiran administration decreased POx with acceptable safety at 6 months (primary analysis)[12] and at 12 months in patients with PH1 and CKD 3b–5[13]
- Here we report Month 24 results from ILLUMINATE-C

Methods

- ILLUMINATE-C is an ongoing multicenter, single-arm Phase 3 study in which a 54-month extension period follows the 6-month primary analysis period
- Eligible patients had a genetically confirmed diagnosis of PH1, POx level of ≥20 µmol/L, and eGFR of ≤45 mL/min/1.73m² if age ≥12 months or increased serum creatinine level if age <12 months at screening
- Patients were assigned to 1 of 2 cohorts based on HD treatment status at study enrollment (Cohort A, not receiving HD; Cohort B, receiving HD)
- Lumasiran was administered subcutaneously using a weight-based dose and regimen

Results

- Of 21 patients who entered the study, 5/6 (83%) assigned at study entry to Cohort A (no HD) and 12/15 (80%) assigned to Cohort B (on HD) completed the Month 24 visit
- Baseline characteristics for the cohorts are presented in **Table 1**

Table 1. Baseline Demographic and Clinical Characteristics

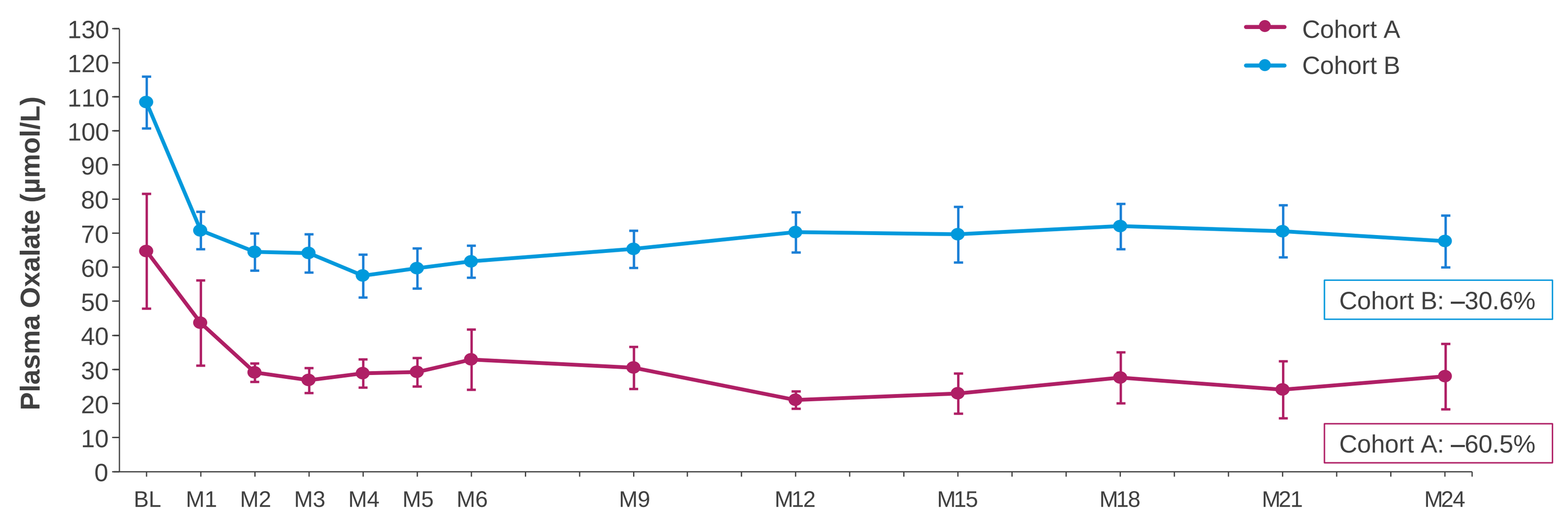
Baseline Characteristic	Cohort A (N=6)	Cohort B (N=15)	All Treated (N=21)
Age at consent, median (range), years	9 (0–40)	6 (1–59)	8 (0–59)
Female, n (%)	3 (50)	6 (40)	9 (43)
Pyridoxine (vitamin B6), n (%)	5 (83)	7 (47)	12 (57)
Genotype[a], n (%)			
PR/*	0 (0)	5 (33)	5 (24)
M/M or M/N	5 (83)	7 (47)	12 (57)
N/N	1 (17)	3 (20)	4 (19)
POx, median (range),[b] µmol/L	58 (23–134)	104 (56–167)	101 (23–167)
Plasma glycolate, median (range), µmol/L	239 (48–457)	273.5 (74–655)	273.5 (48–655)
eGFR,[c] median (range), mL/min/1.73m²	N=5[c] 16.5 (9–34)	NA	N=5[c] 16.5 (9–34)
Dialysis sessions per week, median (range)	NA	6 (3–7)	NA
Evidence of bone oxalosis,[d] n (%)	5 (83)	13 (87)	18 (86)
Evidence of retinal crystalline deposits,[e] n (%)	N=4 1 (25)	N=5 2 (40)	N=9 3 (33)
Baseline abnormality in LVEF,[f] n (%)	1 (17)	4 (27)	5 (24)
Baseline abnormality in GLS,[f] n (%)	1 (17)	3 (20)	4 (19)

[a]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.[14] The asterisk (*) denotes any genotype of PR, M, or N. M, missense; N, nonsense; PR, pyridoxine-responsive. [b]ULN =12.11 µmol/L for POx, as determined based on data from 75 healthy adults. [c]eGFR was calculated only in patients age ≥12 months. [d]Evidence of bone oxalosis at baseline is defined as a Grade 1 or higher assessment for ribs, spine, hands, hips, knees, and/or humeri on the Alnylam Bone Oxalosis Grading Scale. [e]Any evidence of retinal crystalline deposits appearing as pinpoint whitish gray and/or yellow lesions, and occurring as either isolated or widespread throughout the fundus. [f]Definitions of abnormality: Echo LVEF: <55%; Echo GLS: |GLS| <15%.

- In Cohort A, mean (SEM) POx decreased from 64.7 (16.9) µmol/L at baseline to 27.9 (9.6) at Month 24. In Cohort B, mean (SEM) POx decreased from 108.4 (7.6) µmol/L at baseline to 67.6 (7.6) at Month 24 (**Figure 1**)

Results (cont'd)

Figure 1. POx Mean (SEM) Actual Values Through Month 24



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

In Cohort A, baseline was defined as the mean of all POx samples (µmol/L) collected prior to the first dose of lumasiran in Cohort B, baseline was defined as the mean of the last 4 predialysis POx samples (µmol/L) collected prior to the first dose of lumasiran. Observations occurring after a liver transplant, initiation of hemodialysis in Cohort A, or discontinuation of hemodialysis in Cohort B were censored.

- Four patients, all in Cohort B, underwent kidney-only transplantation (**Figure 2**)
  - In Patients 1, 3, and 4, HD was stopped within 2 days after kidney transplant
    - All 3 patients remain in the study with functional renal allografts after 2 to 21 months of post-transplant follow-up at the data cutoff
    - AEs occurring after transplant included COVID-19 infection in 1 patient, BK virus (human polyomavirus 1) infection, diarrhea, urticaria in 1 patient, and hypogammaglobulinemia in 1 patient
  - In Patient 2, HD was stopped 36 days after transplant; during this period, the patient had AEs of renal allograft obstruction and urine leakage, pyrexia, acute kidney injury, and herpes simplex infection
    - Post-transplant AEs also included acute gastroenteritis with acute kidney injury and electrolyte disturbances
    - Renal ultrasound 2 months post-transplant revealed asymptomatic renal lithiasis; planned renal allograft biopsy at 7 months post-transplant showed rare intratubular crystals in the medullary parenchyma without refringence in polarized light, findings that are not characteristic of calcium oxalate
    - This patient remains in the study with functional renal allograft 16 months post-transplant at the data cutoff
  - POx values immediately prior to kidney transplant were <70 µmol/L in all 4 patients. Post-transplant POx values in the isolated kidney transplant patients ranged from 6.2 to 26.2 µmol/L, comparable to the post-transplant values of 2 patients in Cohort B who had combined liver-kidney transplant, then discontinued lumasiran and withdrew from the study (range 14.4–44.8 µmol/L)

Plasma Glycolate

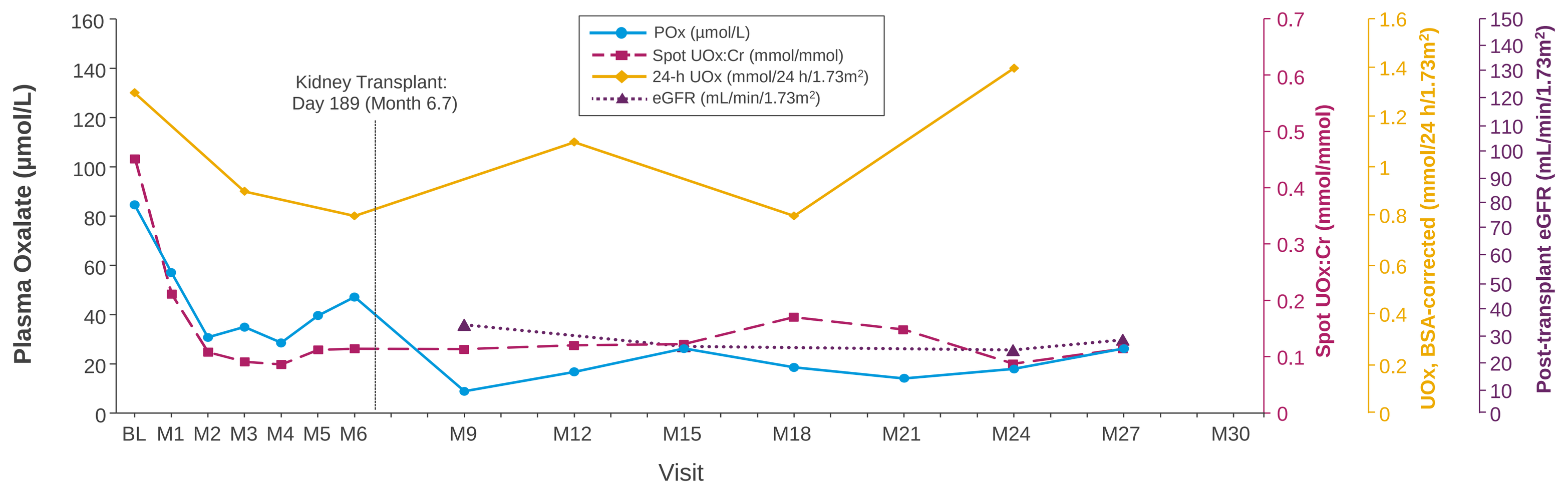
- Plasma glycolate levels increased during the primary analysis period (through Month 6), then were relatively stable during the extension period through Month 24 (**Figure 3**)
- The maximum measured plasma glycolate levels were 923 µmol/L (Cohort A) and 2240 µmol/L (Cohort B); the majority of measured levels were <1000 µmol/L

Systemic Oxalosis

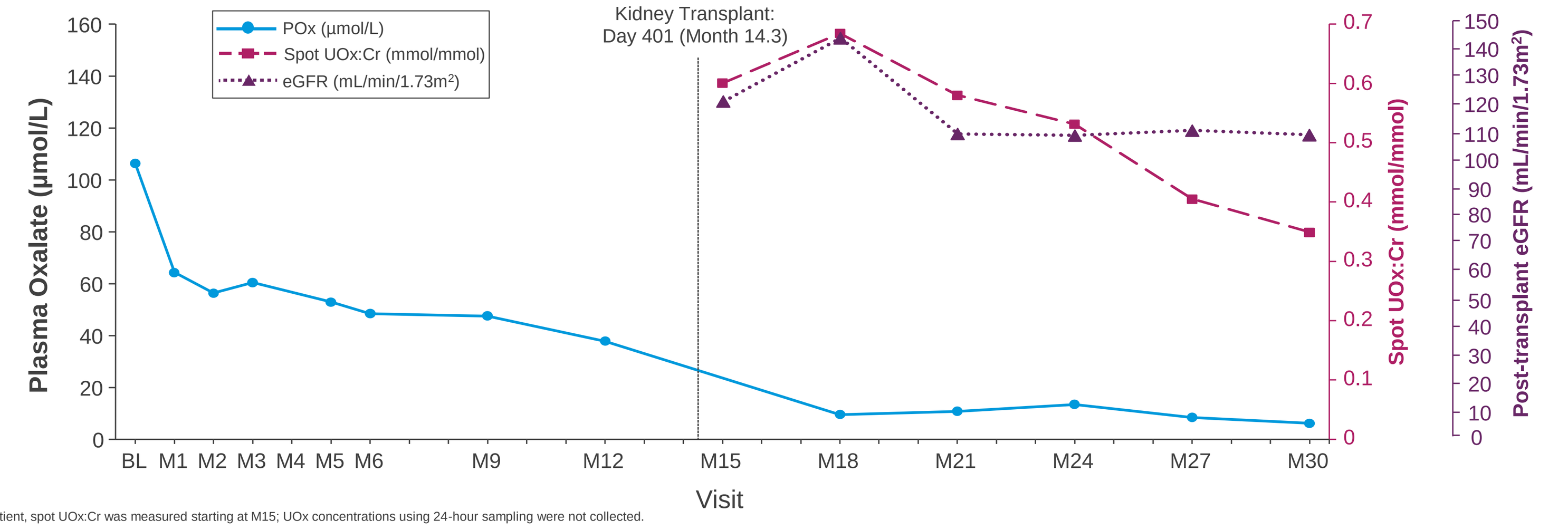
- Cardiac systemic oxalosis measures (LVEF, GLS) were stable at Month 24
  - Of the 5 patients with LVEF <55% at baseline, 3 remained in the study at Month 24; of these, 2 had improvement of ≥5% at Month 24; no patient met criteria for LVEF worsening (>10% decline from baseline to a value <50%)
  - One patient in Cohort A without baseline abnormality in GLS had worsening GLS at Month 24 (concurrent LVEF 61%); the other Cohort A patients had no important change
  - Three patients in Cohort B had abnormal GLS at baseline (absolute value of GLS <15%), 1 of whom also had baseline LVEF abnormality; all 3 of these patients showed improvement in GLS (increase of >2% in GLS absolute value) at Month 24
- Assessments of skeletal systemic oxalosis as measured by a novel bone oxalosis scale were largely unchanged from baseline at Month 24
- Of the patients who had available baseline and post-baseline color fundus photography and ocular tomography assessments, the majority of results were unchanged post-baseline for measures of ocular oxalosis, including evidence of retinal crystalline deposits, fibro-atrophic lesions, intra-/sub-retinal hemorrhage, and evidence of irregular retinal pigment epithelium, sub-retinal and intra-retinal fluid, and sub-retinal pigment epithelium hyperreflective deposits

Figure 2. Patients With Kidney-Only Transplant

A. Patient 1 (age 44 years at study entry): POx, UOx:Cr, 24-hour UOx, and post-transplant eGFR

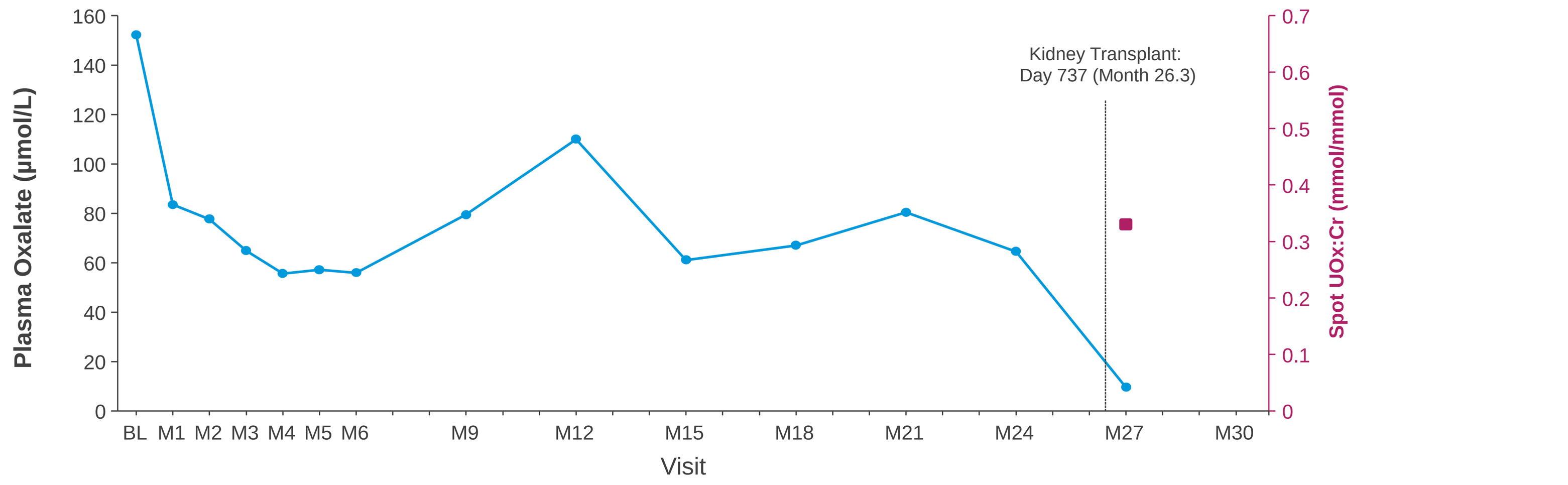


B. Patient 2 (age 2 years at study entry): POx, UOx:Cr, and post-transplant eGFR



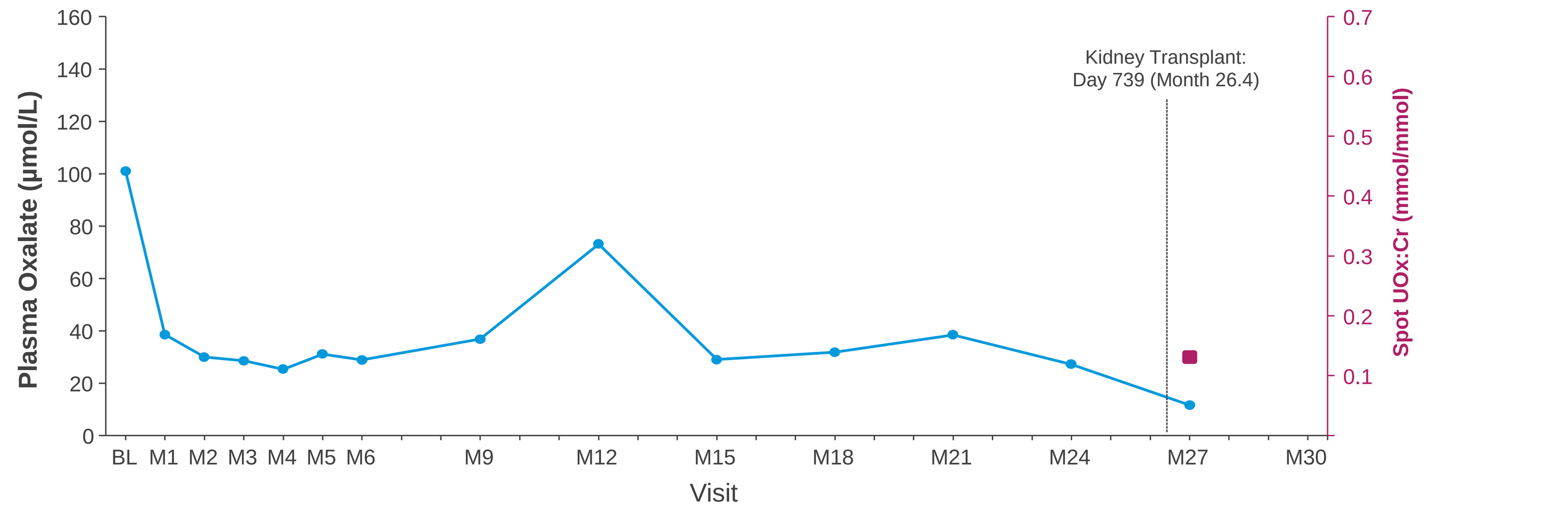
For this patient, spot UOx:Cr was measured starting at M15; UOx concentrations using 24-hour sampling were not collected.

C. Patient 3 (age 0.9 years at study entry): POx and UOx:Cr



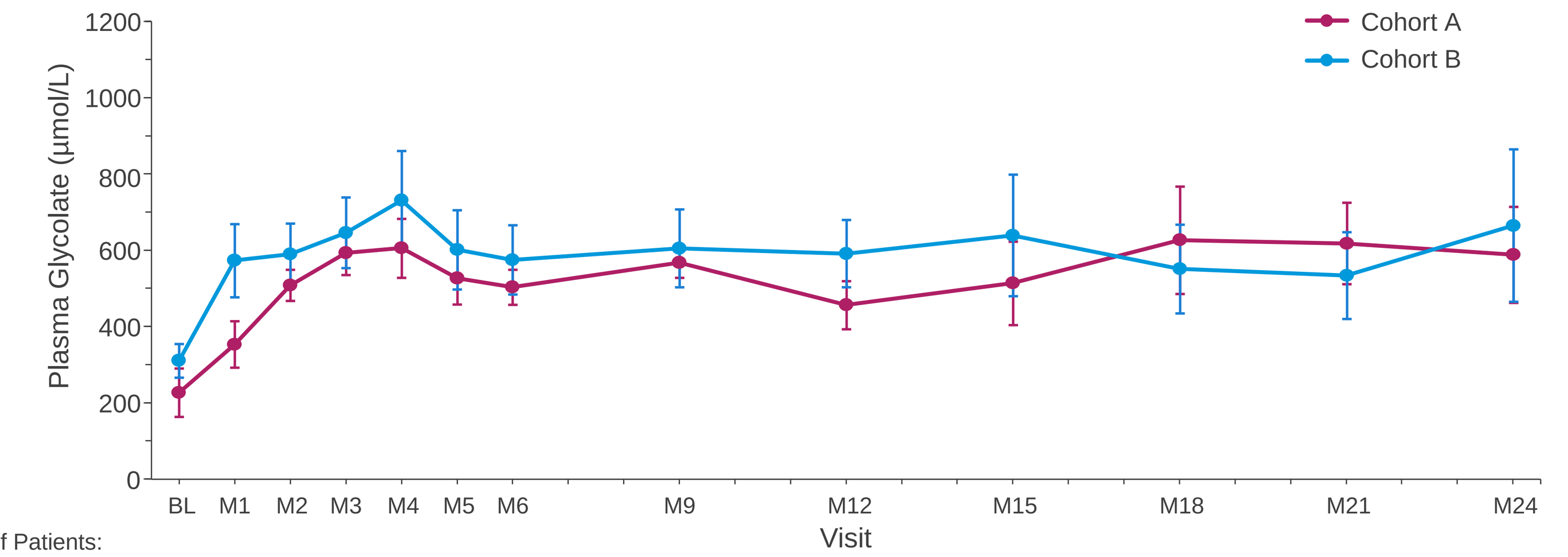
For this patient, spot UOx:Cr was measured starting at M15; UOx concentrations using 24-hour sampling were not collected. As of the data cutoff, no data are available for post-transplant eGFR; however, the patient had a functioning kidney transplant and was not receiving HD.

D. Patient 4 (age 18 years at study entry): POx and UOx:Cr



For this patient, spot UOx:Cr was measured at M27 only; UOx concentrations using 24-hour sampling were not collected. As of the data cutoff, no data are available for post-transplant eGFR; however, the patient had a functioning kidney transplant and was not receiving HD.

Figure 3. Plasma Glycolate Mean (SEM) Actual Values Through Month 24



No. of Patients:	BL	M1	M2	M3	M4	M5	M6	M9	M12	M15	M18	M21	M24
Cohort A	6	5	6	6	6	6	6	5	4	4	4	4	4
Cohort B	15	14	15	13	13	14	14	12	12	10	10	10	10

Baseline was defined as the mean of all plasma glycolate assessments prior to the first dose of lumasiran.

Safety

- The most frequently reported AEs were pyrexia (8/21; 38%), diarrhea (6/21; 29%), and injection site reactions (5/21; 24%) (**Table 2**)
- Treatment-related AEs were reported in 33% (7/21) of patients; the most common treatment-related AEs were mild injection site reactions (5/21; 24%)
- No treatment-emergent deaths or lumasiran-related severe or serious AEs, discontinuations, or withdrawals occurred

Table 2. Safety Overview[a]

	Original Assignment		After HD Change		All Treated
Treatment-Emergent Event, N (%)	Cohort A N=6 (PY 9.0)	Cohort B N=15 (PY 26.2)	Cohort A (On HD) N=2 (PY 1.4)	Cohort B (Off HD) N=5 (PY 3.3)	N=21 (PY 39.9)
Patients with ≥1 AE	6 (100)	15 (100)	1 (50)	5 (100)	21 (100)
AEs occurring in ≥3 patients in either cohort					
Pyrexia	1 (17)	7 (47)	0 (0)	0 (0)	8 (38)
Injection site reaction	1 (17)	4 (27)	0 (0)	0 (0)	5 (24)
Diarrhea	1 (17)	3 (20)	0 (0)	2 (40)	6 (29)
Anemia	1 (17)	2 (13)	1 (50)	0 (0)	4 (19)
Vomiting	2 (33)	1 (7)	0 (0)	1 (20)	4 (19)
Kidney transplant	0 (0)	3 (20)	0 (0)	1 (20)	4 (19)[b]
COVID-19	0 (0)	2 (13)	1 (50)	1 (20)	4 (19)
Cough	1 (17)	1 (7)	1 (50)	0 (0)	3 (14)
Upper respiratory tract infection	1 (17)	1 (7)	1 (50)	0 (0)	3 (14)
Gastroenteritis	1 (17)	1 (7)	0 (0)	1 (20)	3 (14)
AEs leading to treatment discontinuation and study withdrawal	0 (0)	2 (13)	0 (0)	0 (0)	2 (10)[c]
Severe AEs	3 (50)	8 (53)	0 (0)	0 (0)	11 (52)[d]
Serious AEs	3 (50)	11 (73)	0 (0)	4 (80)	15 (71)[e]
Death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

[a]Safety data during the extension period include all available data through the data cutoff date. "Original Assignment" columns display AEs prior to any change in HD status, ie, while not on HD for Cohort A/while on HD for Cohort B. "After HD Change" columns display AEs reported after patients in Cohort A initiated HD (N=2), and after patients in Cohort B went off HD (N=5). "All Treated" column displays total patients reporting AEs, regardless of cohort/HD status. [b]Two patients underwent kidney transplantation before Month 24, and 2 patients underwent kidney transplantation after Month 24. [c]AEs led to both treatment discontinuation and study withdrawal in 2 patients; both were due to liver-kidney transplant and were not related to lumasiran. [d]No severe AEs were determined to be related to lumasiran. [e]Serious AEs of pyrexia occurred in 6 patients; serious AEs of renal transplant occurred in 4 patients; and serious AEs of liver-kidney transplant occurred in 2 patients. No serious AEs were determined to be related to lumasiran.

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Abbreviations: AE, adverse event; BL, baseline; BSA, body surface area; CKD, chronic kidney disease; Cr, creatinine; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; HD, hemodialysis; LVEF, left ventricular ejection fraction; NA, not applicable; PH1, primary hyperoxaluria type 1; POx, plasma oxalate; PY, patient-years; SEM, standard error of the mean; ULN, upper limit of normal; UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio.

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