

Kidney Function and Isolated Kidney Transplant Outcomes in Primary Hyperoxaluria Type 1 Treated With Long-term Lumasiran

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Conclusions

- Annual eGFR decline over 30 to 48 months was minimal in patients with PH1 treated with lumasiran in clinical trials encompassing a range of baseline kidney function and age groups.
- Lumasiran treatment effectively lowered POx to allow for isolated kidney transplantation in 5 patients with end-stage kidney disease by Month 36.
- All patients who had isolated kidney transplantation remained dialysis-free, had no oxalate nephropathy, and continued lumasiran treatment.

Introduction

- PH1, a rare autosomal recessive disorder associated with hepatic oxalate overproduction, leads to progressive kidney damage, with poor historical graft survival rates after isolated kidney transplantation.¹⁻³
- Prior to availability of the RNA interference therapeutic lumasiran, which is indicated for the treatment of PH1, decline in kidney function in patients with PH1 and CKD was notably rapid in more advanced stages of kidney failure.³
- A Phase 2 trial^{4,5} and three Phase 3 trials (ILLUMINATE-A,⁶⁻⁸ ILLUMINATE-B,⁹⁻¹¹ and ILLUMINATE-C^{12,13}) (Table) have shown sustained reductions in UOx and POx and acceptable safety with lumasiran across a wide range of ages and baseline kidney function in data presented to date, reporting up to 54 months (Phase 2⁵), 36 months (ILLUMINATE-A⁸), 30 months (ILLUMINATE-B¹¹), and 24 months (ILLUMINATE-C¹³) of treatment.
- In long-term follow-up, lumasiran treatment has demonstrated robust efficacy for reducing UOx and POx, with relative preservation of kidney function in patients with mild-to-moderate CKD^{5,7,13} and with low enough POx to allow isolated kidney transplant with favorable clinical outcomes to date.¹³

Table. Lumasiran Clinical Trial Overview

	Phase 2 ⁵	ILLUMINATE-A ⁶⁻⁸	ILLUMINATE-B ⁹⁻¹¹	ILLUMINATE-C ^{12,13}
ClinicalTrials.gov	NCT03350451	NCT03681184	NCT03905694	NCT04152200
Phase	2	3	3	3
Design	Open-label extension study including patients from the single-blind, placebo-controlled Phase 1/2 trial (NCT02706888), ⁴ Part B (patients with PH1)	Randomized, double-blind, placebo-controlled study with extension period	Single-arm, open-label study with extension period	Single-arm, 2-cohort, open-label study with extension period
Patients, N	20	39	18	21
Inclusion criteria	<ul style="list-style-type: none">PH1Age 6–64 yearseGFR >45 mL/min/1.73m²24-hour UOx excretion >0.7 mmol/24h/1.73m²Completed Phase 1/2 study, Part B	<ul style="list-style-type: none">PH1Age ≥6 yearseGFR ≥30 mL/min/1.73m²24-hour UOx excretion >0.7 mmol/24h/1.73m²	<ul style="list-style-type: none">PH1All ages eligibleeGFR >45 mL/min/1.73m² if age ≥12 months or normal serum creatinine if age <12 monthsUOx:Cr greater than ULN for age	<ul style="list-style-type: none">PH1All ages eligibleeGFR ≤45 mL/min/1.73m² if age ≥12 months or elevated serum creatinine if age <12 monthsPOx ≥20 μmol/LNot on hemodialysis at study start (Cohort A) or on stable hemodialysis regimen (Cohort B)
Primary endpoint	Incidence of AEs	% change in 24-hour BSA-corrected UOx at 6 months	% change in UOx at 6 months	% change in POx at 6 months (in Cohort B, % change in predialysis POx)
Total duration	Up to 54 months	Up to 60 months	Up to 60 months	Up to 60 months
Study status	Completed	Completed	Active, not recruiting	Active, not recruiting

Methods

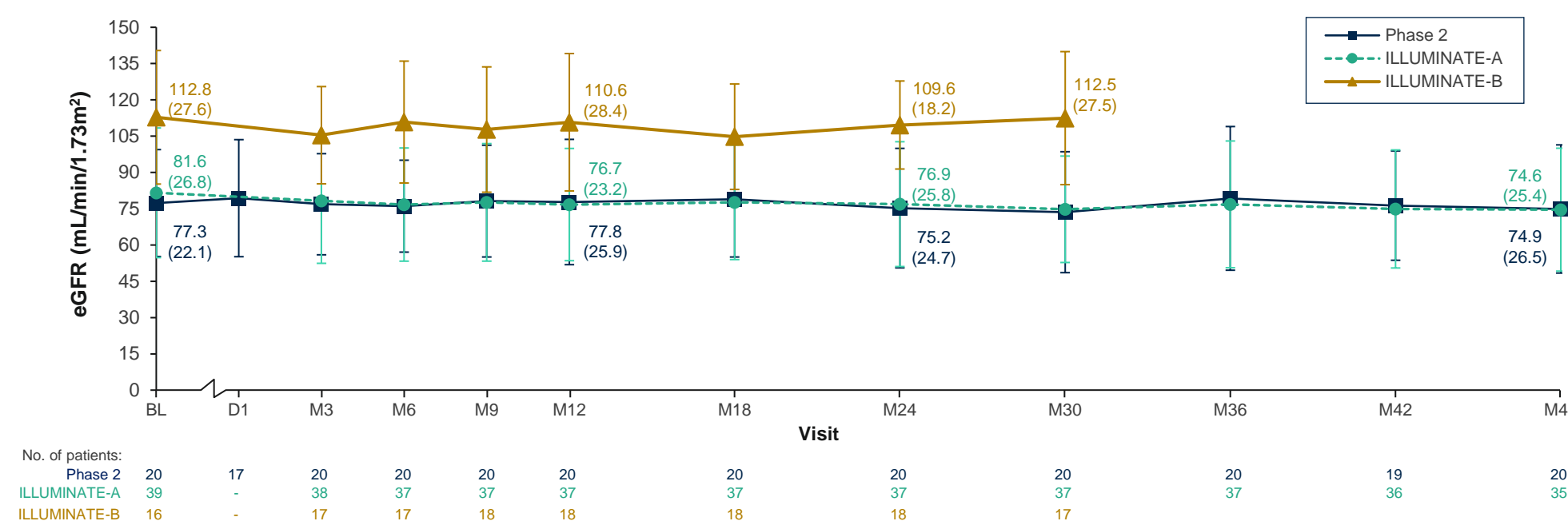
- Descriptive kidney function data from lumasiran clinical trials were summarized.
 - Mean annual rates of eGFR change (a secondary endpoint in all trials) were calculated at Month 48 for Phase 2 and ILLUMINATE-A and Month 30 for ILLUMINATE-B; these timepoints maximize eGFR follow-up duration and available data for each trial.
 - For ILLUMINATE-C, eGFR data were summarized for the 5 patients in Cohort A (not on hemodialysis at study start) remaining in the study at Month 36.
 - At baseline, there were 6 patients in Cohort A and 15 patients in Cohort B (on hemodialysis).
- Outcomes in patients enrolled in ILLUMINATE-C who underwent isolated kidney transplant were compiled in this post hoc analysis.

Results

eGFR Change in Lumasiran Clinical Trials

- Mean (SD) eGFR actual values over time in the Phase 2, ILLUMINATE-A, and ILLUMINATE-B trials are displayed in Figure 1.
 - The range of baseline eGFR values was 32 to 174 mL/min/1.73m² among patients enrolled in the 3 trials.
 - Median (range) ages at baseline were 11.5 (6–43), 14.0 (6–60), and 4.2 (0.3–6) years, respectively.

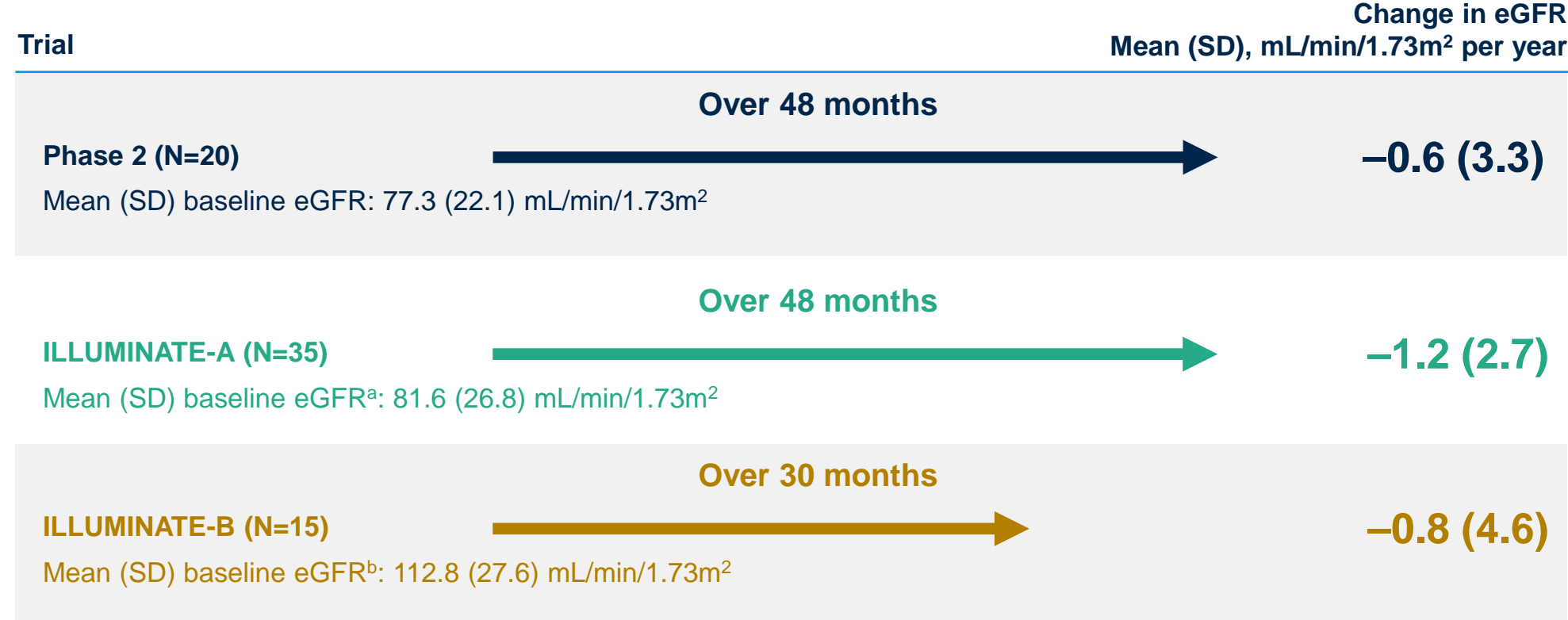
Figure 1. Mean (SD) eGFR Actual Values Over Time in Lumasiran Clinical Trials



ILLUMINATE-B: The eGFR was calculated based on the Schwartz Bedside Formula in patients ≥12 months of age at the time of the assessment. ILLUMINATE-A and Phase 2: The eGFR was calculated from serum creatinine based on the Modification of Diet in Renal Disease formula for patients ≥18 years of age and the Schwartz Bedside Formula for patients <18 years of age at screening.

- Mean annual rates of eGFR change in lumasiran treated patients with PH1 ranged from –0.6 to –1.2 mL/min/1.73m² per year over 30 to 48 months of follow-up during these 3 trials (Figure 2).

Figure 2. Mean Annualized Rates of eGFR Change in Lumasiran Clinical Trials



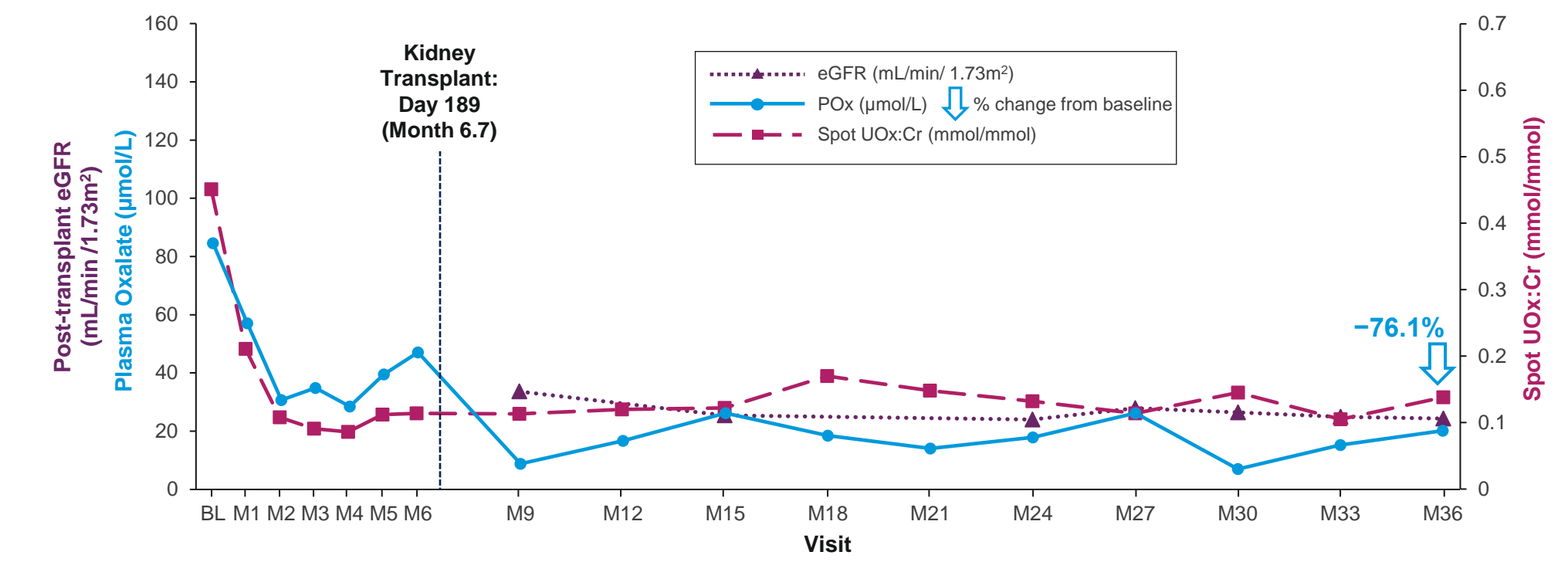
^aILLUMINATE-A: Baseline eGFR was assessed in all 39 enrolled patients.
^bILLUMINATE-B: Baseline eGFR was assessed in 16 of 18 enrolled patients.

- In ILLUMINATE-C, Cohort A (not on hemodialysis at study start), 5 of 6 patients remained in the study as of Month 36.
 - Three patients, who had the lowest baseline eGFR (8.6–16.5 mL/min/1.73m²) in the cohort, began hemodialysis by the Month 36 data cutoff.
 - Two patients remaining in Cohort A without hemodialysis (baseline eGFR 24.0 and 34.1 mL/min/1.73m²) had annual rates of eGFR decline of –2.3 and –0.9 mL/min/1.73m² per year, respectively, over 36 months.

Isolated Kidney Transplantation

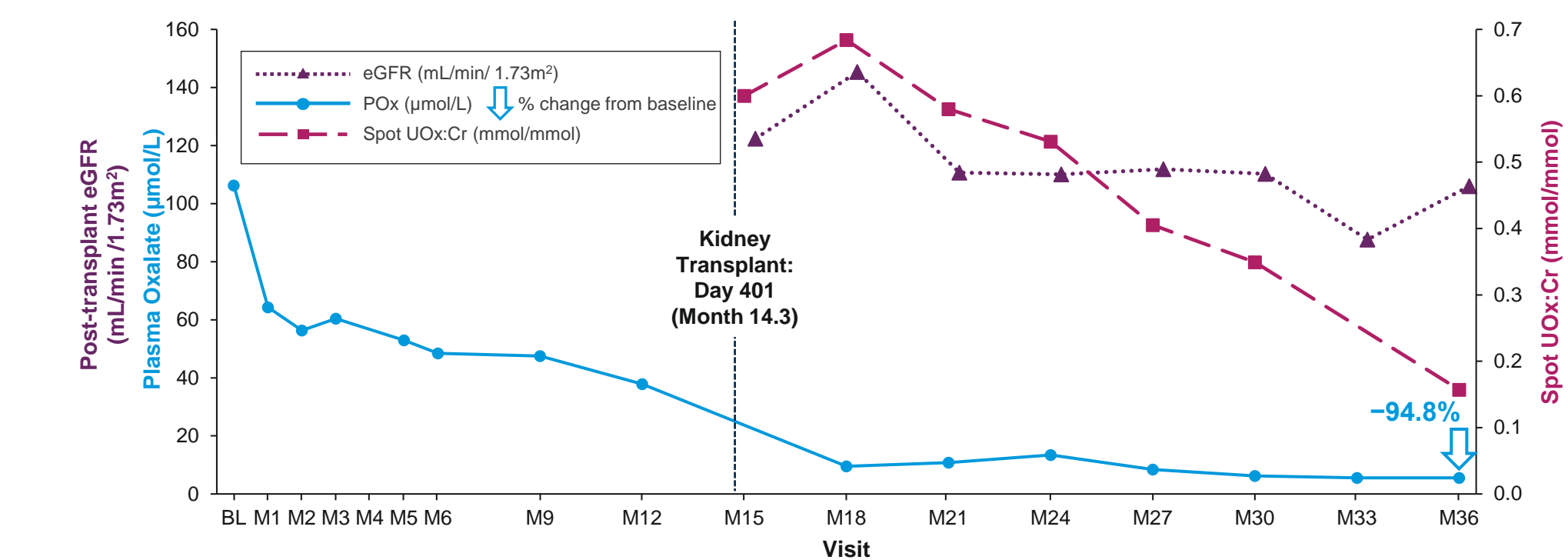
- In ILLUMINATE-C, Cohort B (on hemodialysis at study start), 5 of the 15 enrolled patients underwent isolated kidney transplant as of Month 36 (Figure 3A-E).
 - Transplant decisions were made at the discretion of the individual investigators.

Figure 3. Patients With Isolated Kidney Transplant: POx, UOx:Cr, and Post-transplant eGFR. A. Patient 1 (age 44 years at study entry; pyridoxine-responsive genotype)^a

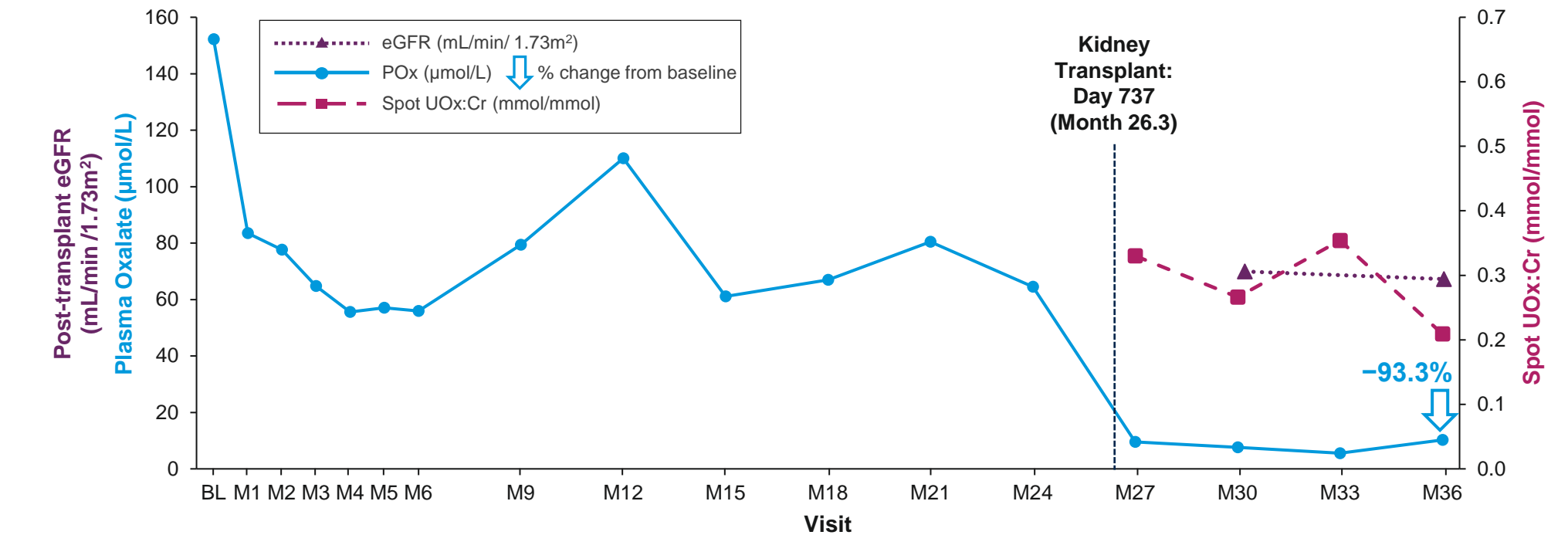


- All 5 patients had reductions in POx from baseline prior to transplantation (range: –37.5 to –87.8 μmol/L); further reductions post-transplant indicate improved POx clearance with functioning kidney grafts.
 - Baseline POx values ranged from 84.6 to 152.3 μmol/L.

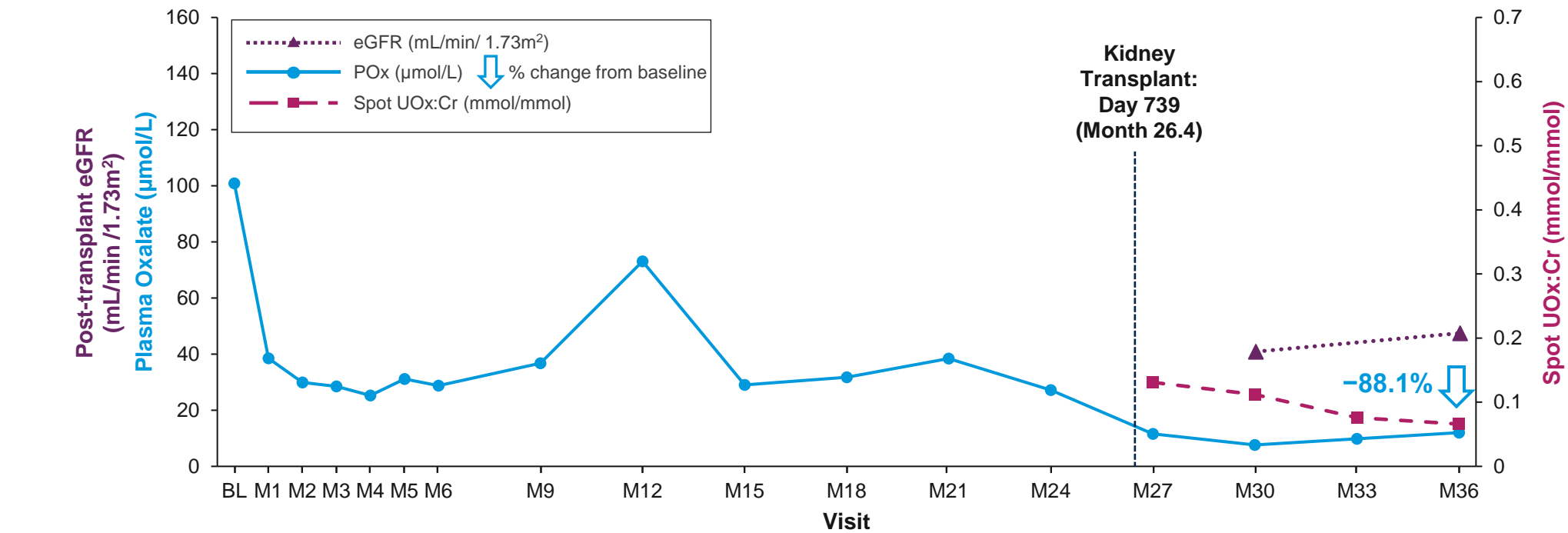
B. Patient 2 (age 2 years at study entry; non-pyridoxine-responsive genotype)^b



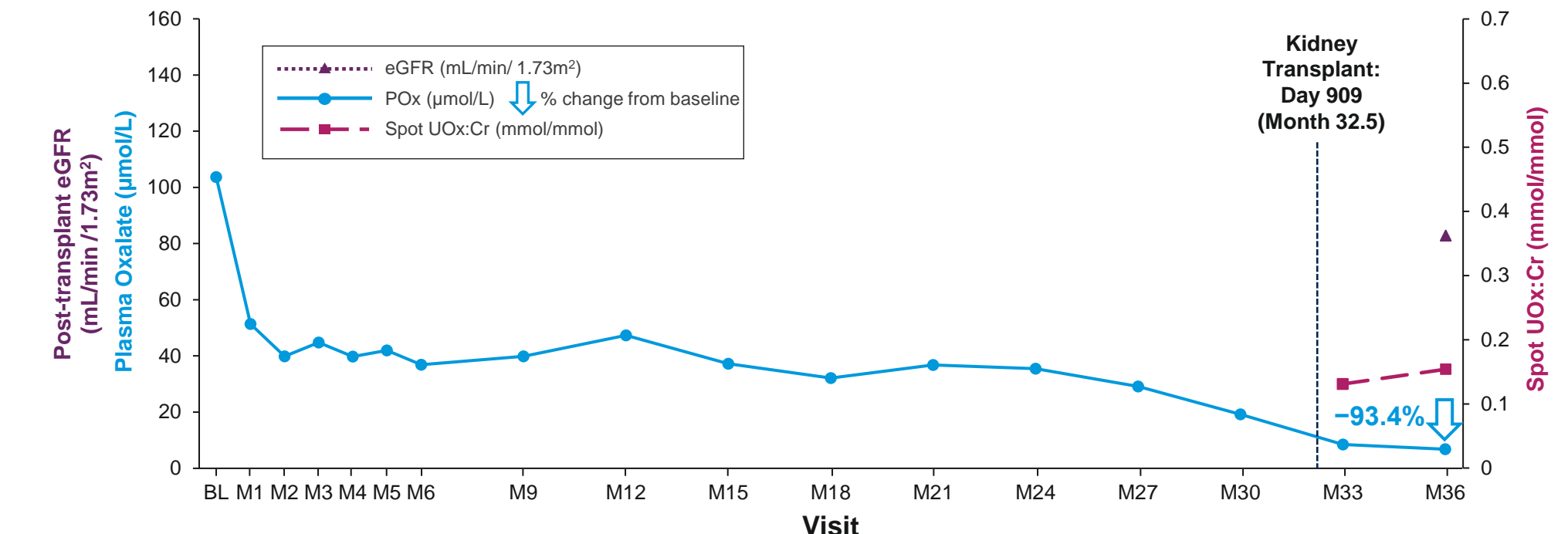
C. Patient 3 (age 0.9 years at study entry; non-pyridoxine-responsive genotype)^c



D. Patient 4 (age 18 years at study entry; non-pyridoxine-responsive genotype)^d



E. Patient 5 (age 1 year at study entry; pyridoxine-responsive genotype)^e



^aPatient 1 experienced a post-transplantation AE of graft failure which resolved; a renal graft biopsy performed 6 weeks after transplantation associated with this AE showed evidence of BK virus nephropathy without calcium oxalate nephropathy.
^bPatient 2's hemodialysis was stopped 36 days after transplant; the reason for the continuation of dialysis after transplantation was not reported. However, within the first month after transplant, the patient experienced several AEs (severe, not related to the study drug) of pyrexia 13 days after the transplant; graft complication, urinoama, and acute kidney injury 14 days after the transplant; and herpes simplex infection 21 days after the transplant.
^cPatient 3 experienced urinary tract infection (mild, not related to the study drug) 14 days after the transplant and recovered from the event. Other complications that occurred within 3 months to 1 year after the transplant and required hospitalization included hypogammaglobulinemia (moderate); gastroenteritis, pneumonia, and post-transplant lymphoproliferative disorder (all severe); and ear infection.
^dPatient 4 experienced 2 moderate AEs (diarrhea and BK virus infection), which were both not related to the study drug, within the first month post-transplantation; both events were not resolved at time of the datacut.
^ePatient 5 experienced 2 moderate AEs (*Clostridium difficile* infection and incision site discharge) within the first month post-transplantation, from which the patient recovered, along with 1 mild AE (perinephric collection), which was not resolved; all 3 AEs were not related to the study drug.

Isolated Kidney Transplantation: Clinical Outcomes

- Post-transplant AEs were frequent and included transplant-related complications (not related to study drug), highlighting the risks associated with organ transplantation.
- No patients experienced oxalate nephropathy post-transplantation.
- All 5 patients remained hemodialysis-free and continued lumasiran treatment post-transplant as of study Month 36.

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Abbreviations: AE, adverse event; BL, baseline; BSA, body surface area; CKD, chronic kidney disease; D1, Day 1; eGFR, estimated glomerular filtration rate; M, month; PH1, primary hyperoxaluria type 1; POx, plasma oxalate; SD, standard deviation; ULN, upper limit of normal; UOx, urinary oxalate; UOx:Cr, urinary oxalate to creatinine ratio.

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