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

Michael J. Somers[1], Arnaud Devresse[2], Richard Willey[3], Desmond Murphy[3], Anne-Laure Sellier-Leclerc[4], Cristin Kaspar[3], Justine Bacchetta[5] on behalf of the study investigators

[1]Division of Pediatric Nephrology, Boston Children's Hospital, Boston, MA, USA; [2]Department of Nephrology, Cliniques Universitaires Saint-Luc, Brussels, Belgium; [3]Alnylam Pharmaceuticals, Cambridge, MA, USA; [4]Division of Pediatric Nephrology-Rheumatology, Hôpital Femme-Mère-Enfant, Lyon, France; [5]Lyon Est Medical School, Hospices Civils de Lyon, Lyon, France

Presented at: Pediatric Academic Societies (PAS) 2025; April 24-28, 2025; Honolulu, Hawaii

MED-ALL-GO1-2500022: 21 April 2025

Disclosures

Michael J. Somers: Consultancy fees from Alnylam Pharmaceuticals and Dicerna Pharmaceuticals, and scientific review committee chair for ongoing clinical trial with Novo Nordisk

Arnaud Devresse: Principal investigator for Alnylam Pharmaceuticals; received consultancy fees from Alnylam Pharmaceuticals

Richard Willey and Desmond Murphy: Employees of and shareholders in Alnylam Pharmaceuticals

Anne-Laure Sellier Leclerc: Consultancy fees from Alnylam Pharmaceuticals and Dicerna Pharmaceuticals, and principal investigator for research funded by OxThera

Cristin Kaspar: Employee of Alnylam Pharmaceuticals

Justine Bacchetta: Consultancy fees from Alnylam Pharmaceuticals, Dicerna, and Biocodex

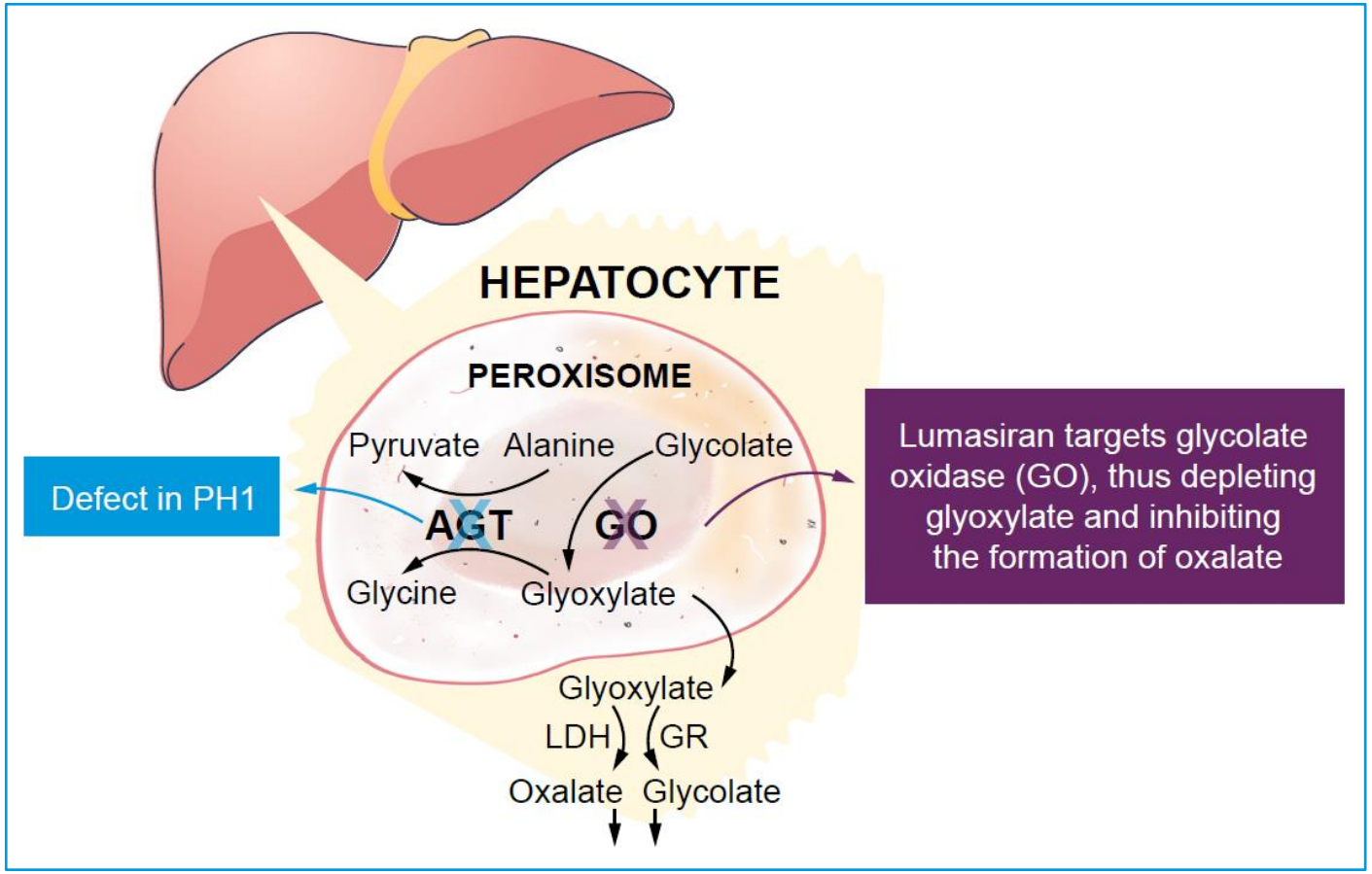
Acknowledgments: On behalf of the study investigators, we thank the patients, their families, investigators, study staff, and collaborators for their participation in the lumasiran clinical studies. Medical writing and editorial assistance was provided by Peloton Advantage, LLC, an OPEN Health company,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

Correspondence: Michael J. Somers – Michael.Somers@childrens.harvard.edu

Funding: This study was funded by Alnylam Pharmaceuticals

Introduction

- Primary hyperoxaluria type 1 (PH1) is a rare autosomal recessive disorder associated with hepatic oxalate overproduction, leading to progressive kidney damage



- Historically, PH1 manifests clinically with nephrolithiasis, nephrocalcinosis, and steady decline in eGFR
- Prior to RNA interference therapy with lumasiran, kidney function decline was more rapid as CKD stage advanced
  - Many PH1 patients developed ESKD and required kidney-liver transplantation as treatment
- Lumasiran treatment has demonstrated robust efficacy in reducing urinary oxalate (UOx) and plasma oxalate (POx) and in attenuating kidney injury from PH1, which has spurred reconsideration of expectations for clinical course in CKD and approaches to transplantation in ESKD

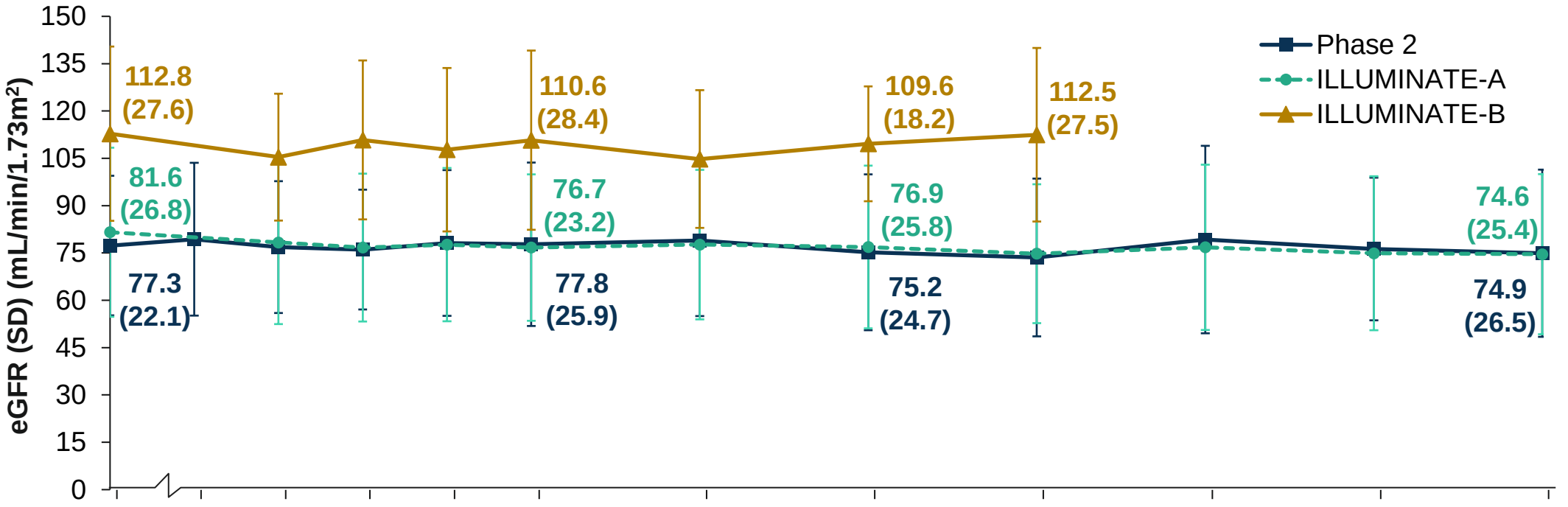
Objective

- In this *post hoc* analysis of lumasiran clinical trials data, we aimed to:
  - Evaluate rates of eGFR change after lumasiran initiation
  - Describe post-transplant outcomes following isolated kidney transplant with ongoing lumasiran therapy

Lumasiran Clinical Trials

	Phase 2	ILLUMINATE-A	ILLUMINATE-B	ILLUMINATE-C
Design	Open-label extension study including patients from the single-blind, placebo-controlled Phase 1/2 trial, Part B (in PH1)	Phase 3, randomized, double-blind, placebo-controlled study with extension period	Phase 3, single-arm, open-label study with extension period	Phase 3, single-arm, 2-cohort, open-label study with extension period
Patients, N	20	39	18	21 (6 in Cohort A, 15 in Cohort B)
Inclusion criteria	• PH1 • Age 6-64 years • **eGFR >45 mL/min/1.73m^2** • 24-hour UOx excretion >0.7 mmol/24h/1.73m^2 • Completed Phase 1/2 study, Part B	• PH1 • Age ≥6 years • **eGFR ≥30 mL/min/1.73m^2** • 24-hour UOx excretion >0.7 mmol/24h/1.73m^2	• PH1 • Age <6 years • **eGFR >45 mL/min/1.73m^2 if age ≥12 months or normal serum creatinine if age <12 months** • UOx:Cr greater than ULN for age	• PH1 • All ages eligible • **eGFR ≤45 mL/min/1.73m^2 if age ≥12 months or elevated serum creatinine if age <12 months** • POx ≥20 µmol/L • Not on HD at study start (Cohort A); stable HD 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 pre-dialysis POx)
Total duration	Up to 54 months	Up to 60 months	Up to 60 months	Up to 60 months

eGFR Over Time in Phase 2, ILLUMINATE-A, and ILLUMINATE-B



No. of patients:	BL	D1	M3	M6	M9	M12	M18	M24	M30	M36	M42	M48
Phase 2	20	17	20	20	20	20	20	20	20	20	19	20
ILLUMINATE-A	39	-	38	37	37	37	37	37	37	37	36	**35**
ILLUMINATE-B	16	-	17	17	18	18	18	18	17			

- The range of baseline eGFR values was 32 to 174 mL/min/1.73m^2 among patients enrolled in these 3 trials
- Median (range) ages at baseline were 11.5 (6-43) years in Phase 2, 14.0 (6-60) years in ILLUMINATE-A, and 4.2 (0.3-6) years in ILLUMINATE-B

Rates of eGFR Change in Lumasiran Clinical Trials

- Mean annualized rates of eGFR change ranged from –0.6 to –1.2 mL/min/1.73m^2 per year up to 48 months

Trial	Change in eGFR Mean (SD), mL/min/1.73m^2 per year
Phase 2 (N=20) Mean (SD) baseline eGFR: 77.3 (22.1) mL/min/1.73m^2	Over 48 months → **–0.6 (3.3)**
ILLUMINATE-A (N=35) Mean (SD) baseline eGFR[a]: 81.6 (26.8) mL/min/1.73m^2	Over 48 months → **–1.2 (2.7)**
ILLUMINATE-B (N=15) Mean (SD) baseline eGFR[b]: 112.8 (27.6) mL/min/1.73m^2	Over 30 months → **–0.8 (4.6)**

Rates of eGFR Change in ILLUMINATE-C

- In ILLUMINATE-C, the 6 Cohort A patients were pre-dialysis with eGFR <45 mL/min/1.73m^2 at study initiation
  - Three patients (study initiation eGFRs all <16.5 mL/min/1.73m^2) progressed to need to start dialysis
  - In 2 of 3 patients remaining off dialysis with baseline eGFR data, a relatively modest annualized decline in eGFR was seen through Month 36 while on lumasiran therapy

Cohort A: Patients Remaining Off Dialysis at Month 36

Patient	Baseline eGFR	Month 36 eGFR	Annualized eGFR Decline
1	24.0	17.2	−2.3
2	34.1	31.3	−0.9

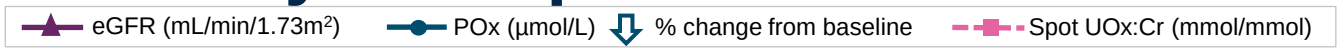
Isolated Kidney Transplant Outcomes in ILLUMINATE-C

Cohort B: Kidney Transplant by Month 36

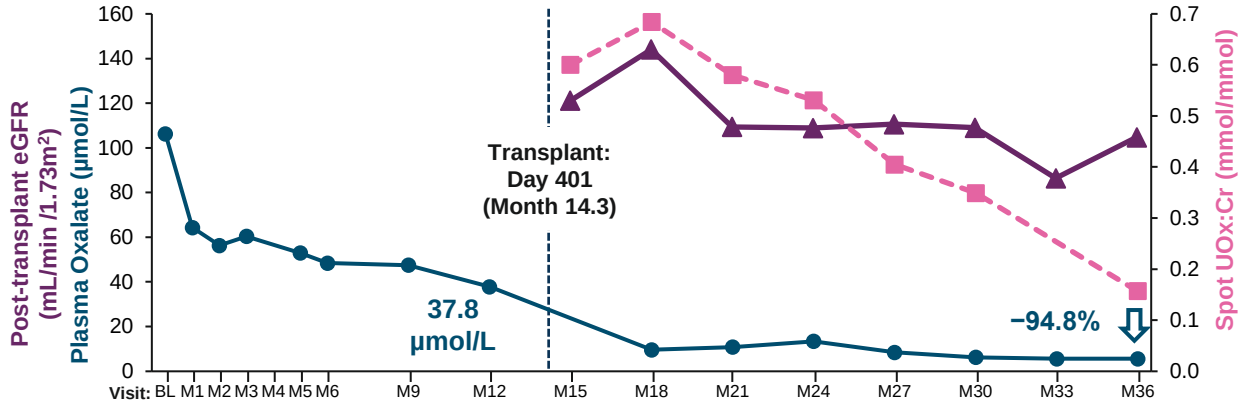
Patient	Age at Baseline (Years)	POx at Baseline (µmol/L)	Months of Lumasiran Treatment Until Transplant	POx Pre-transplant (µmol/L)	Months of Post-transplant Follow-up to Month 36	Overall % Decline in POx from Baseline
1	44	84.6	6.7	47.1	29.3	−76.1%
2	2	106.3	14.3	37.8	21.7	−94.8%
3	0.9	152.3	26.3	64.5	9.7	−93.3%
4	18	100.9	26.4	27.2	9.6	−88.1%
5	1	103.7	32.5	19.2	3.6	−93.4%

- Of 15 patients enrolled in Cohort B (on HD at study start), 5 underwent isolated kidney transplant as of Month 36
- All 5 patients had reductions in POx from baseline prior to transplantation (range of POx reduction: −37.5 to −87.8 µmol/L)
  - POx at baseline, range: 84.6 to 152.3 µmol/L; POx at last visit prior to iKT, range: 19.2 to 64.5 µmol/L
- Further reductions post-transplant indicate improved POx clearance with functioning kidney grafts (POx at Month 36, range: 5.6 [LLOQ] to 20.2 µmol/L)

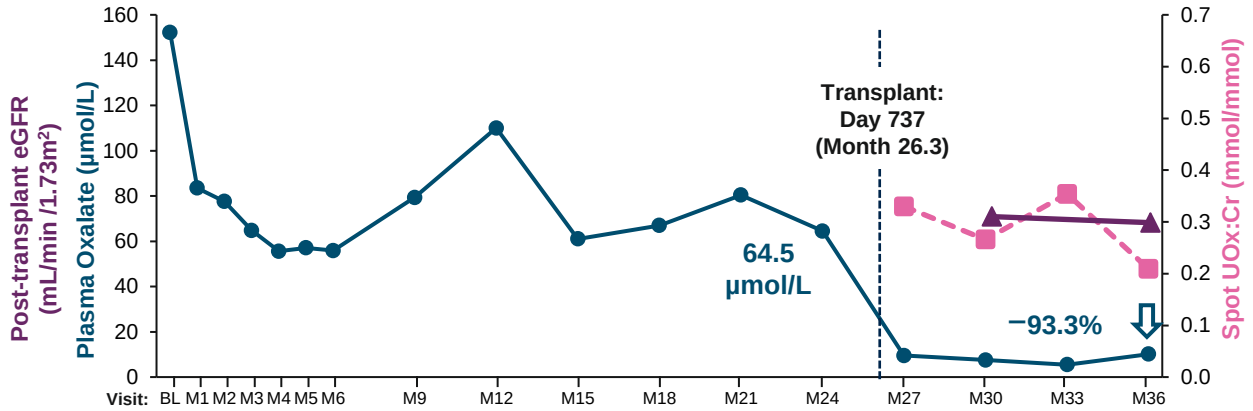
Pediatric Isolated Kidney Transplant Outcomes in ILLUMINATE-C



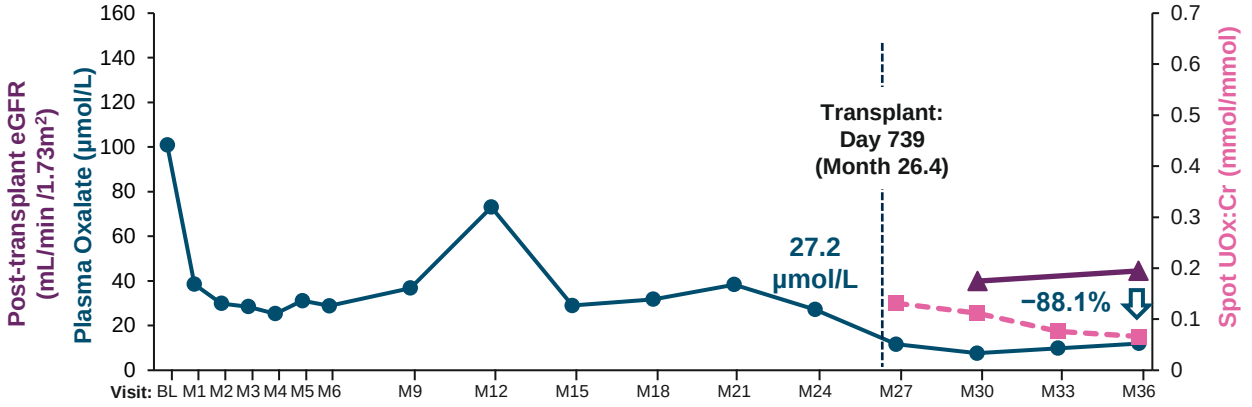
Patient 2 (age 2 years at study entry; non-pyridoxine-responsive genotype)



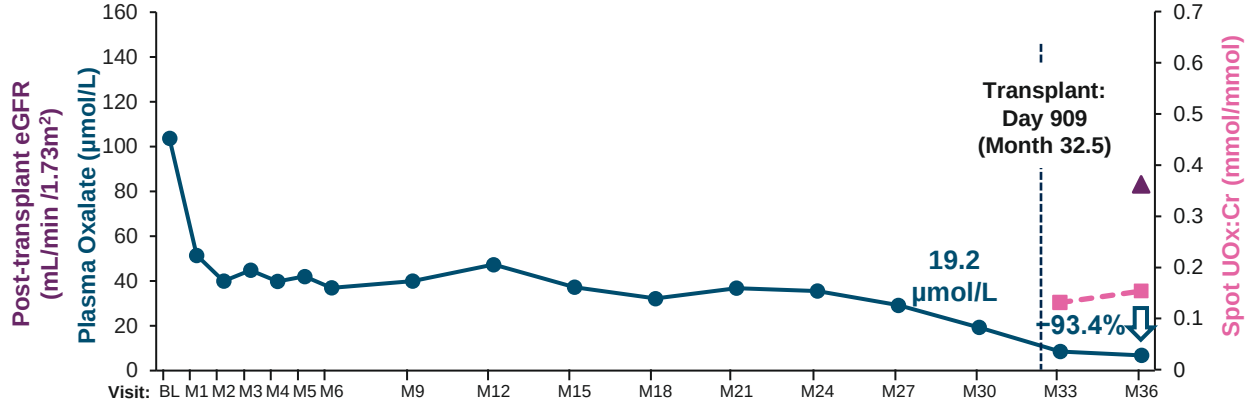
Patient 3 (age 0.9 years at study entry; non-pyridoxine-responsive genotype)



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



Patient 5 (age 1 year at study entry; pyridoxine-responsive genotype)



- Post-isolated kidney transplant with ongoing lumasiran therapy, plasma oxalate declined to low levels and remained in a range without systemic risk of oxalate deposition
- Urinary oxalate levels declined over time post-transplant, reflecting improved oxalate homeostasis and systemic oxalate burden
- eGFR remained satisfactory and in expected post-transplant range
- Reported adverse events post-transplant were all unrelated to lumasiran and reflected typical post-transplant clinical events
- Results in Patient 1 (age 44 at study entry) were generally consistent with those in pediatric patients

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 (baseline age range: 3 months to 60 years)

Lumasiran treatment effectively lowered plasma oxalate to allow for consideration of isolated kidney transplantation with end-stage kidney disease

Post-transplant adverse events were frequent and included transplant-related complications (not related to study drug), highlighting the risks associated with organ transplantation

All patients who had isolated kidney transplantation remained dialysis-free, had no oxalate nephropathy, and continued lumasiran treatment post-transplant as of the Month 36 data cut in ILLUMINATE-C

Thank you!

For US HCPs only
Scan to view
congress materials

Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the lumasiran clinical studies