Kidney Function, Isolated Kidney Transplant, and Health-Related Quality-of-Life Outcomes in Primary Hyperoxaluria Type 1 Treated With Long-term Lumasiran

Michael J. G. Somers[1]; Arnaud Devresse[2]; Weiming Du[3]; Desmond Murphy[3]; Cristin Kaspar[3]; Anne-Laure Sellier-Leclerc[4]; Justine Bacchetta[5]

[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

For US HCPs Only
Scan to View Congress Material Presented

Conclusions

- In patients with PH1, long-term lumasiran treatment resulted in minimal eGFR decline, demonstrating eGFR stabilization across a range of ages and kidney function levels.
- Five patients in whom sufficient POx reduction was observed by Month 36 underwent isolated kidney transplantation at their investigators' discretion; kidney graft survival without oxalate nephropathy has been demonstrated in 3 to 29 months of post-transplant follow-up.
- All patients who had isolated kidney transplantation remained dialysis-free, had no oxalate nephropathy, and continued lumasiran treatment.
- Patient and caregiver HRQoL measures showed improvements in symptoms and the overall burden of kidney disease, along with decreased concerns about progression and worsening of PH1.

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] (NCT03350451, N=20, age 6-64 years, and eGFR >45 mL/min/1.73m^2) and three Phase 3 trials (ILLUMINATE-A,[5] NCT03681184, N=39, age ≥6 years, and eGFR ≥30 mL/min/1.73m^2; ILLUMINATE-B,[6,7] NCT03905694, N=18, age <6 years, and eGFR >45 mL/min/1.73m^2 if age ≥12 months or normal serum creatinine if age <12 months; and ILLUMINATE-C,[8,9] NCT04152200, N=21, all ages, and eGFR ≤45 mL/min/1.73m^2 if age ≥12 months or elevated serum creatinine if age <12 months) have shown sustained reductions in UOx and POx and consistent safety with lumasiran across a wide range of ages.
- In long-term follow-up (range: 24-60 months), lumasiran treatment has demonstrated robust efficacy for reducing UOx and POx, with relative preservation of kidney function in patients with mild-to-moderate CKD[4-7,9] and with low enough POx to allow isolated kidney transplant with favorable clinical outcomes to date.[9]

Methods

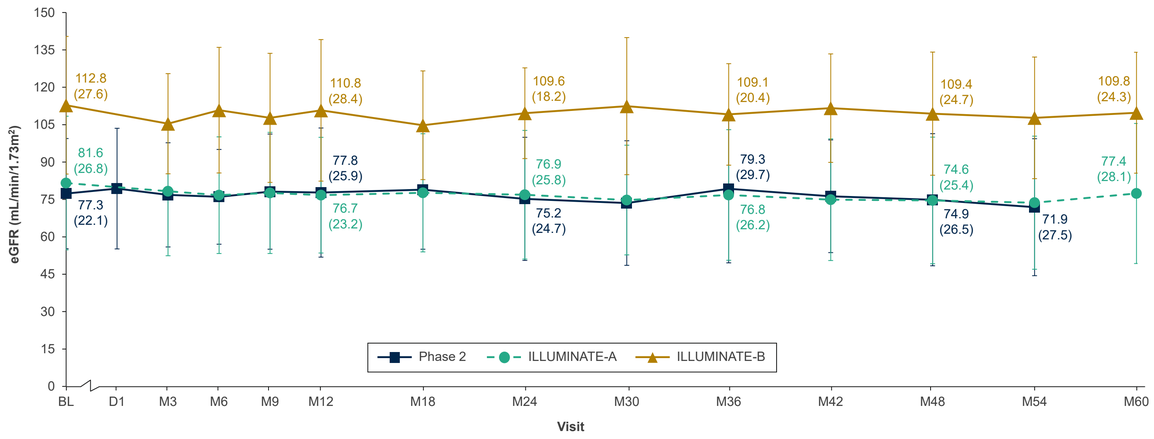
- Descriptive kidney function data from lumasiran clinical trials were summarized.
  - Change in eGFR per year was calculated using simple linear regression (slope) at Month 54 for Phase 2, Month 60 for ILLUMINATE-A, and Month 60 for ILLUMINATE-B.
  - For ILLUMINATE-C, there were 6 patients in Cohort A and 15 patients in Cohort B (on hemodialysis at study start). Data were analyzed through the Month 36 data cutoff date.
- Outcomes in patients enrolled in ILLUMINATE-C who underwent isolated kidney transplant were compiled in this post hoc analysis.
- HRQoL results were reported in patients assessed at both baseline and follow-up visits for the ILLUMINATE-A (KDQOL, completed by patients ≥18 years of age at screening; PedsQL, generic core scales completed by patients ≥2 to <18 years of age at screening; and Patient Experience Survey) and ILLUMINATE-B (Caregiver Experience Survey and VABS [developmental]) trials, as the final data analysis was available in both studies.

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/1.73m^2 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



No. of patients:

Phase 2	20	17	20	20	20	20	20	20	20	20	19	20	16	-
ILLUMINATE-A	39	-	38	37	37	37	37	37	37	37	36	35	29	18
ILLUMINATE-B	16	-	17	17	18	18	18	18	17	18	18	18	18	18

eGFR was calculated based on the Schwartz Bedside Formula in patients <18 years of age at screening, and ≥12 months of age at the time of the assessment. eGFR was calculated based on the MDRD formula for patients ≥18 years of at screening.

- Change in eGFR (slope) in lumasiran-treated patients with PH1 ranged from –0.6 to 0.3 mL/min/1.73m^2 per year over 54 to 60 months of follow-up during these 3 trials.
- In ILLUMINATE-C, Cohort A, 5 of 6 patients remained in the study.
  - Three patients, who had the lowest baseline eGFR (8.6-16.5 mL/min/1.73m^2) in the cohort, began hemodialysis.
  - Two patients remaining in Cohort A without hemodialysis (baseline eGFR 24.0 and 34.1 mL/min/1.73m^2) had annual rates of eGFR decline of –2.3 and –0.9 mL/min/1.73m^2 per year, respectively.

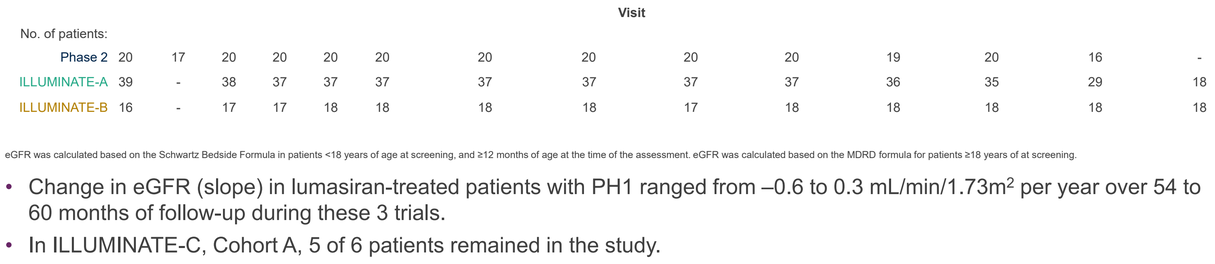
Isolated Kidney Transplantation

- In ILLUMINATE-C, Cohort B, 5 of 15 enrolled patients underwent isolated kidney transplant (**Figure 2A-E**).
  - Prior to transplant, patients had a median 6 dialysis sessions/week, for a median 4 hours/session.
  - Transplant decisions were made at the discretion of the individual investigators.
- All 5 patients had reductions in POx from baseline prior to transplantation; further reductions post-transplant indicate improved POx clearance with functioning kidney grafts.

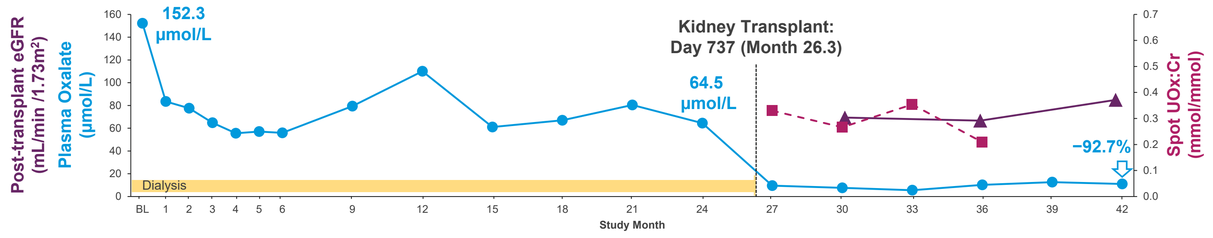
Figure 2. Patients With Isolated Kidney Transplant: POx, UOx:Cr, and Post-transplant eGFR

A. Patient 1 (age 44 years at study entry; pyridoxine-responsive genotype)[a]

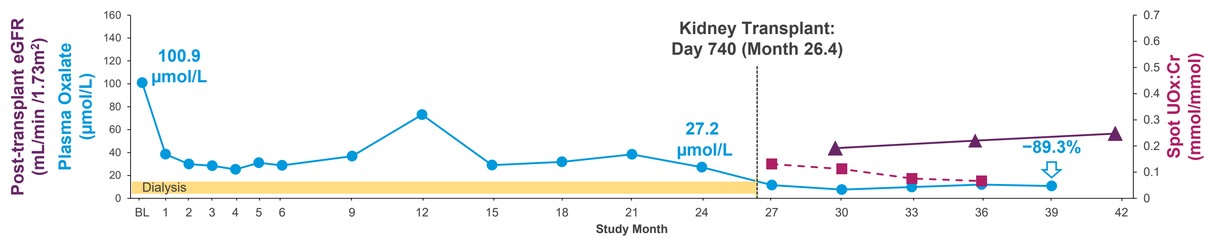
B. Patient 2 (age 2 years at study entry; non-pyridoxine-responsive genotype)[b]



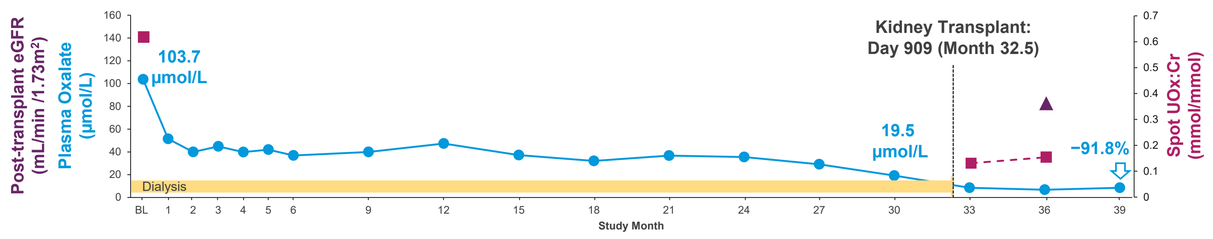
C. Patient 3 (age 0.9 years at study entry; non-pyridoxine-responsive genotype)[c]



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]



[a]The patient experienced non-serious AEs of graft failure and BK virus nephropathy 102 days post-transplant, which both resolved; a renal graft biopsy performed 122 days after transplantation associated with this AE showed evidence of BK virus nephropathy without calcium oxalate nephropathy. Two additional mild post-transplant AEs determined to be unrelated to lumasiran were reported (COVID-19 infection and nasopharyngitis); both resolved.
[b]Hemodialysis was initiated over 3 different periods post-transplant, 1) POD 0-2, CVVHDF for prophylactic purposes; 2) POD 3-4, CVVHDF due to SAEs of obstructive acute renal failure, unrelated to lumasiran, in addition to concurrent AEs of fever, graft complication, and urinoma; and 3) POD 17-35, acute intermittent hemodialysis due to acute renal injury. Hemodialysis did not resume through data cutoff. The patient also had ureteral stent insertion and replacement on POD 4 and 15, and a collection drainage procedure on POD 19 to treat a uretero-ureteral anastomosis leak, blockage of ureteral stent, and urinoma. In addition, the patient experienced herpes simplex virus infection on POD 21 and was treated with acyclovir. A mild, unrelated, asymptomatic case of nephrolithiasis was reported on POD 59 and did not meet the criteria for KSE. A planned renal transplant biopsy was performed on POD 216 (study day 617) and was reported to have evidence of rare intratubular crystals with absence of refringence in polarized light (calcium oxalate crystals typically appear as brightly birefringent, needle-like crystals under polarized light[10]). The patient experienced 3 more AEs of acute renal failure associated with gastroenteritis up to data cutoff at POD 233, 292, and 453, which resolved.
[c]The patient experienced AEs of hypomagnesemia and urinary tract infection not related to lumasiran on POD 1 and 14, respectively, and recovered. The patient experienced SAEs of hypogammaglobulinemia (not recovered) starting POD 108, gastroenteritis on POD 178, otitis on POD 214 and 234, pneumonia on POD 305, and PTLD (not recovered) on POD 367. PTLD was treated with intravenous immunoglobulin, rituximab, and cyclophosphamide. Additional post-transplant non-serious AEs included small intestinal perforation (severe), and moderate AEs of upper respiratory infection, hyponatremia, dyspepsia, and anemia. All post-transplantation AEs were unrelated to lumasiran, and the patient's eGFR remained normal.
[d]Within the first month post-transplantation, the patient experienced non-serious AEs of diarrhea on POD 2 and BK virus infection (not recovered) on POD 29, both unrelated to lumasiran.
[e]Within the first month post-transplantation, the patient experienced 2 moderate AEs (*Clostridium difficile* infection and incision site discharge) and 1 mild AE (perinephric collection), all of which resolved and were unrelated to lumasiran. Additional AEs requiring hospitalization were gastroenteritis adenovirus (POD 84) and herpes virus infection (Epstein-Barr virus, human herpes virus 6, and human herpes virus 7; POD 177).

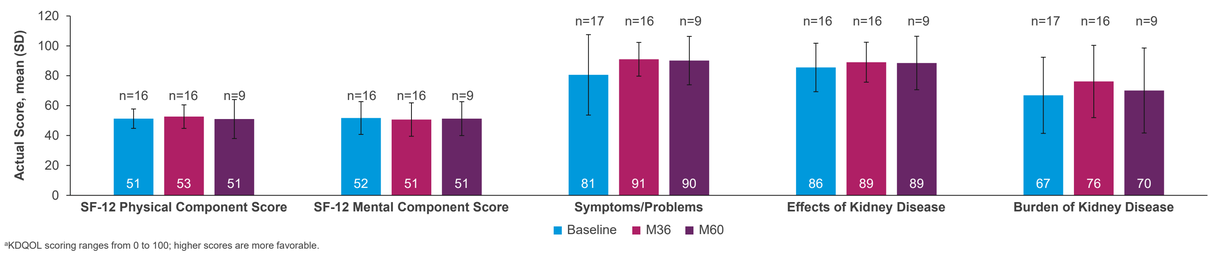
Isolated Kidney Transplantation: Clinical Outcomes

- 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 on lumasiran, and none had restarted chronic hemodialysis.

Health-Related Quality of Life

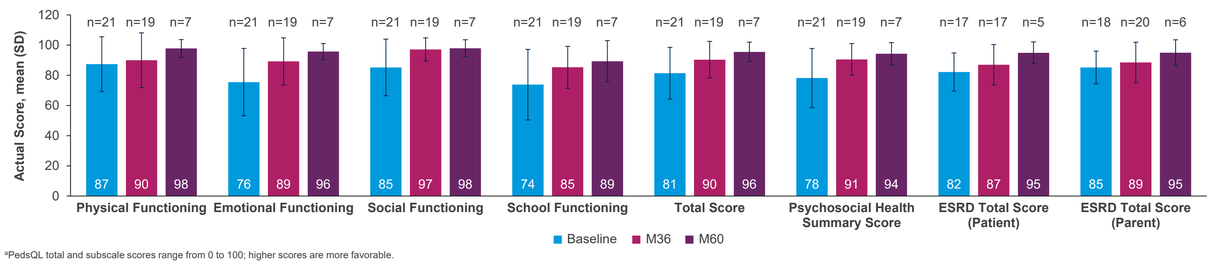
- At Month 60, scores in components of the KDQOL Instrument (**Figure 3**) and the PedQL (**Figure 4**) related to the symptoms and burden of kidney disease improved from baseline by 15% to 43%.
- Physical and mental component scores were maintained over long-term treatment.
- In ILLUMINATE-B, patients generally maintained their developmental level as assessed with the VABS.

Figure 3. ILLUMINATE-A Kidney Disease Quality of Life (KDQOL)[a]



[a]KDQOL scoring ranges from 0 to 100; higher scores are more favorable.

Figure 4. ILLUMINATE-A Pediatric Quality of Life (PedsQL)[a]



[a]PedsQL total and subscale scores range from 0 to 100; higher scores are more favorable.

- Assessments of patient experience in ILLUMINATE-A (**Figure 5**) and caregiver experiences in ILLUMINATE-B (**Figure 6**) indicated improvement, including reductions in concern about disease burden and worsening of PH1.

Figure 5. ILLUMINATE-A Patient Experience

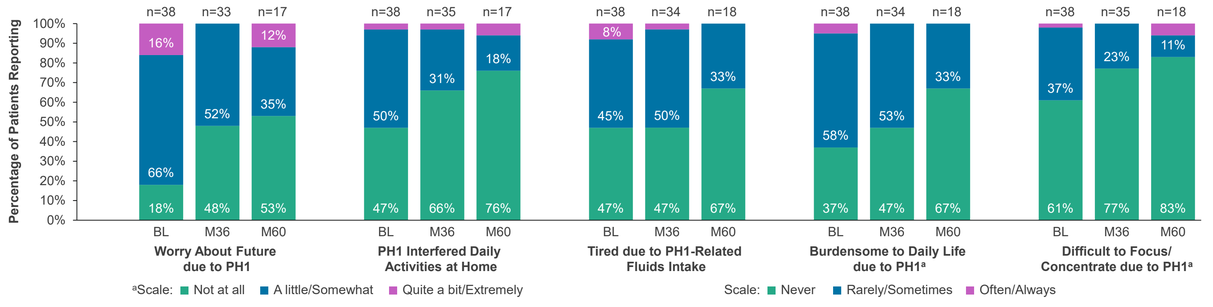
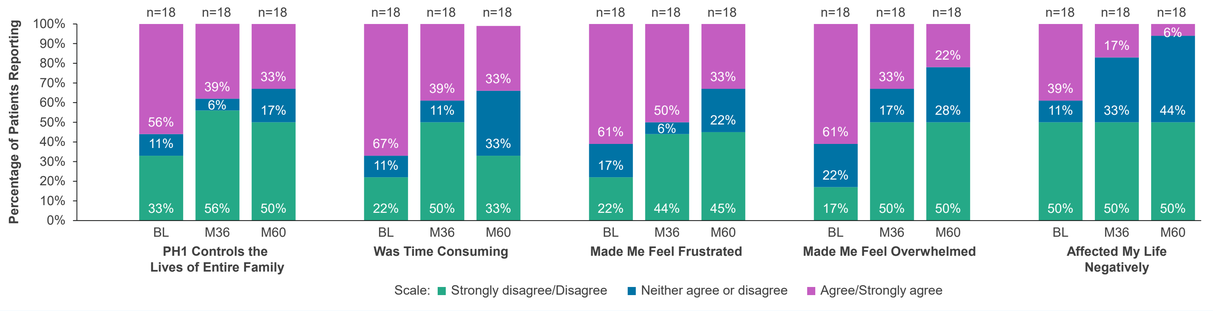


Figure 6. ILLUMINATE-B Caregiver Experience



Abbreviations: AE, adverse event; BL, baseline; BSA, body surface area; CKD, chronic kidney disease; CVVHDF, continuous venovenous hemodiafiltration; eGFR, estimated glomerular filtration rate; M, month; HRQoL, health-related quality of life; KDQOL, Kidney Disease Quality of Life Questionnaire; MDRD, Modification of Diet in Renal Disease; PedsQL, Pediatric Quality of Life Inventory; PH1, primary hyperoxaluria type 1; POD, postoperative day; POx, plasma oxalate; PTLD, post-transplant lymphoproliferative disorder; SAE, serious adverse event; SD, standard deviation; SEM, standard error of the mean; ULN, upper limit of normal; UOx, urinary oxalate, UOx:Cr, urinary oxalate to creatinine ratio, VABS, Vineland Adaptive Behavior Scale.

References: 1. Cochat P, Rumsby G. *N Engl J Med*. 2013;369:649-658. **2.** Milliner DS, et al. Primary Hyperoxaluria Type 1. *GeneReviews* 1993. https://www.ncbi.nlm.nih.gov/books/NBK1283/. Accessed: January 11, 2022. **3.** Harambat J, et al. *Clin J Am Soc Nephrol*. 2012;7:458-465. **4.** Frishberg Y, et al. Long-term treatment with lumasiran: final results from the phase 2 open-label extension study. Presented at European Renal Association; May 23-26, 2024; Stockholm, Sweden & Virtual. **5.** Saland JA, et al. Long-term efficacy and safety of lumasiran in patients with primary hyperoxaluria type 1 in a final analysis of the ILLUMINATE-A trial. Presented at Pediatric Academic Societies; April 24-28, 2025; Honolulu, Hawaii. **6.** Frishberg Y, et al. Long-term efficacy and safety in the phase 3 ILLUMINATE-B trial of lumasiran for primary hyperoxaluria type 1 in infants and young children. Presented at National Kidney Foundation; April 10-13, 2025; Boston, MA. **7.** Frishberg Y, et al. Long-term efficacy and safety in the 60-month phase 3 ILLUMINATE-B trial of lumasiran in infants and young children with primary hyperoxaluria type 1. Presented at European Renal Association; June 4-7, 2025; Vienna, Austria & Virtual. **8.** Michael M, et al. *Am J Kidney Dis*. 2023;81:145-155. **9.** Lieske J, et al. Lumasiran for primary hyperoxaluria type 1 with impaired kidney function: 24-month analysis of the phase 3 ILLUMINATE-C trial. Presented at: Annual Meeting of the American Society of Nephrology; November 2-5, 2023; Philadelphia, PA. **10.** Geraghty R, et al. *Urolithiasis*. 2020;48:377-384.

Acknowledgment: 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.

Disclosures: MJS: Consultancy fees from Alnylam Pharmaceuticals and Dicerna Pharmaceuticals, and scientific review committee chair for ongoing clinical trial with Novo Nordisk. **AD:** Principal investigator for Alnylam Pharmaceuticals and consultancy fees from Alnylam Pharmaceuticals. **WD** and **DM:** Employees of and shareholders in Alnylam Pharmaceuticals. **CK**: Employee of Alnylam Pharmaceuticals. **A-LS-L:** Consultancy fees from Alnylam Pharmaceuticals and Dicerna Pharmaceuticals, and principal investigator for research funded by OxThera. **JB:** Consultancy fees from Alnylam Pharmaceuticals, Dicerna, and Biocodex.

Funding: This study was funded by Alnylam Pharmaceuticals.

Presented at: the 57th European Society for Paediatric Nephrology (ESPN) Annual Meeting; October 15-18, 2025; Athens, Greece