



For US HCPs Only
Scan to View Congress
Material Presented

Final 60-Month Efficacy, Safety, and Kidney Stone Outcomes of a Phase 3 Trial of Lumasiran for Primary Hyperoxaluria Type 1 in Infants and Young Children

David J. Sas¹, Mini Michael², Yaacov Frishberg³, Wesley Hayes⁴, Efrat Ben-Shalom³, Hadas Shasha-Lavsky⁵, Anne-Laure Sellier-Leclerc⁶, Julien Hogan⁷, Weiming Du⁸, Desmond Murphy⁸, Cristin Kaspar⁸, Daniella Magen⁹ on behalf of the ILLUMINATE-B study investigators

¹Mayo Clinic, Rochester, MN, USA; ²Texas Children's Hospital, Houston, TX, USA; ³Shaare Zedek Medical Center, Jerusalem, Israel; ⁴Great Ormond Street Hospital for Children NHS, London, UK; ⁵Galilee Medical Center, Nahariya, Israel; ⁶Hôpital Femme Mère Enfant, Bron, France; ⁷Robert Debré Hospital, APHP, Paris, France; ⁸Alnylam Pharmaceuticals, Cambridge, MA, USA; ⁹Pediatric Nephrology Institute, Haifa, Israel

Conclusions

- Infants and young children with PH1 had sustained reduction in UOx and POx with lumasiran treatment through Month 60.
- eGFR was stable through Month 60 in these patients with PH1, a population in which eGFR decline would be expected.
- Nephrocalcinosis grade improved in the majority of patients.
- KSE rates were low through Month 60.
- 4 patients with KSEs had UOx reductions and changes in nephrocalcinosis grade consistent with those of other trial patients.
- Consistent safety was seen with lumasiran treatment through Month 60.

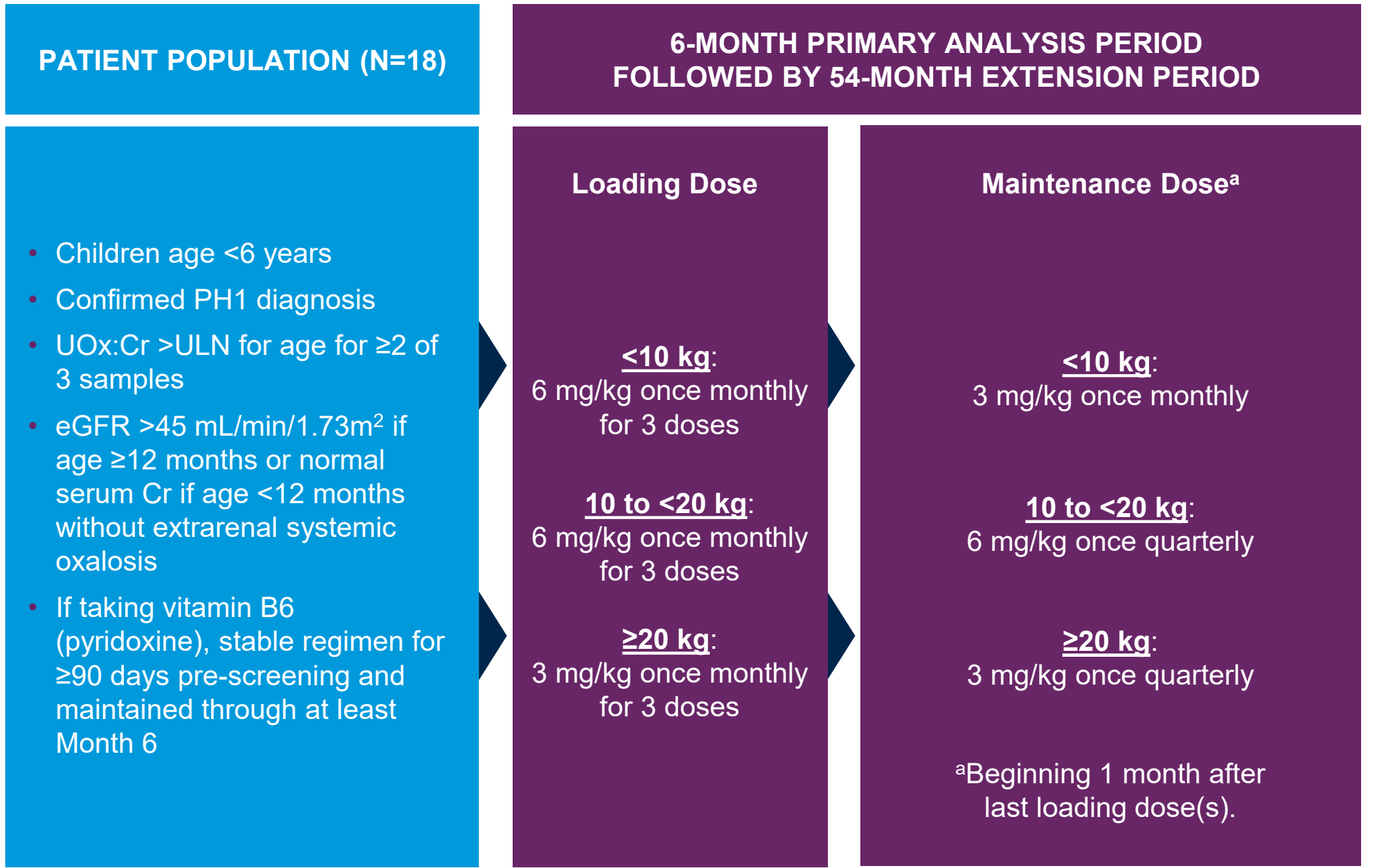
Introduction

- PH1 is a genetic disease resulting in excess hepatic oxalate production, which can lead to urolithiasis, nephrocalcinosis, and ultimately chronic kidney disease, kidney failure, and systemic oxalosis.¹
- Lumasiran, the first liver-directed RNAi therapeutic for PH1 administered to infants and children age ≤6 years, targets hydroxyacid oxidase 1 (HAO1) mRNA through RNA interference, thus decreasing glycolate oxidase (GO) levels, depleting glyoxylate, and inhibiting the formation of oxalate.²
- Previously reported data showed that lumasiran demonstrated sustained efficacy with no unexpected safety signals over 30 months in infants and children aged ≤6 years with PH1 participating in ILLUMINATE-B (NCT03905694).³⁻⁵
- This report presents the final efficacy and safety outcomes through Month 60 of ILLUMINATE-B, including results for patients who had kidney stone events.

Methods

- ILLUMINATE-B was a Phase 3, multinational, open-label, single-arm study (Figure 1).
- A primary analysis conducted at 6 months⁴ was followed by an extension period of up to 54 months.

Figure 1. ILLUMINATE-B Study Design



- The primary endpoint was percentage change in spot UOx:Cr from baseline to Month 6.
- Secondary endpoints included absolute and percentage change from baseline in UOx excretion, proportion of patients with UOx excretion ≤ULN and ≤1.5 × ULN for age, absolute and percentage change from baseline in POx, and change from baseline in eGFR.
- Changes in nephrocalcinosis and kidney stone event rates were exploratory endpoints.

Results

- All 18 patients enrolled in ILLUMINATE-B completed the 60-month study.
- All patients were ≤6 years of age (median age at consent in months, 50.1; range, 3-72; Table 1).

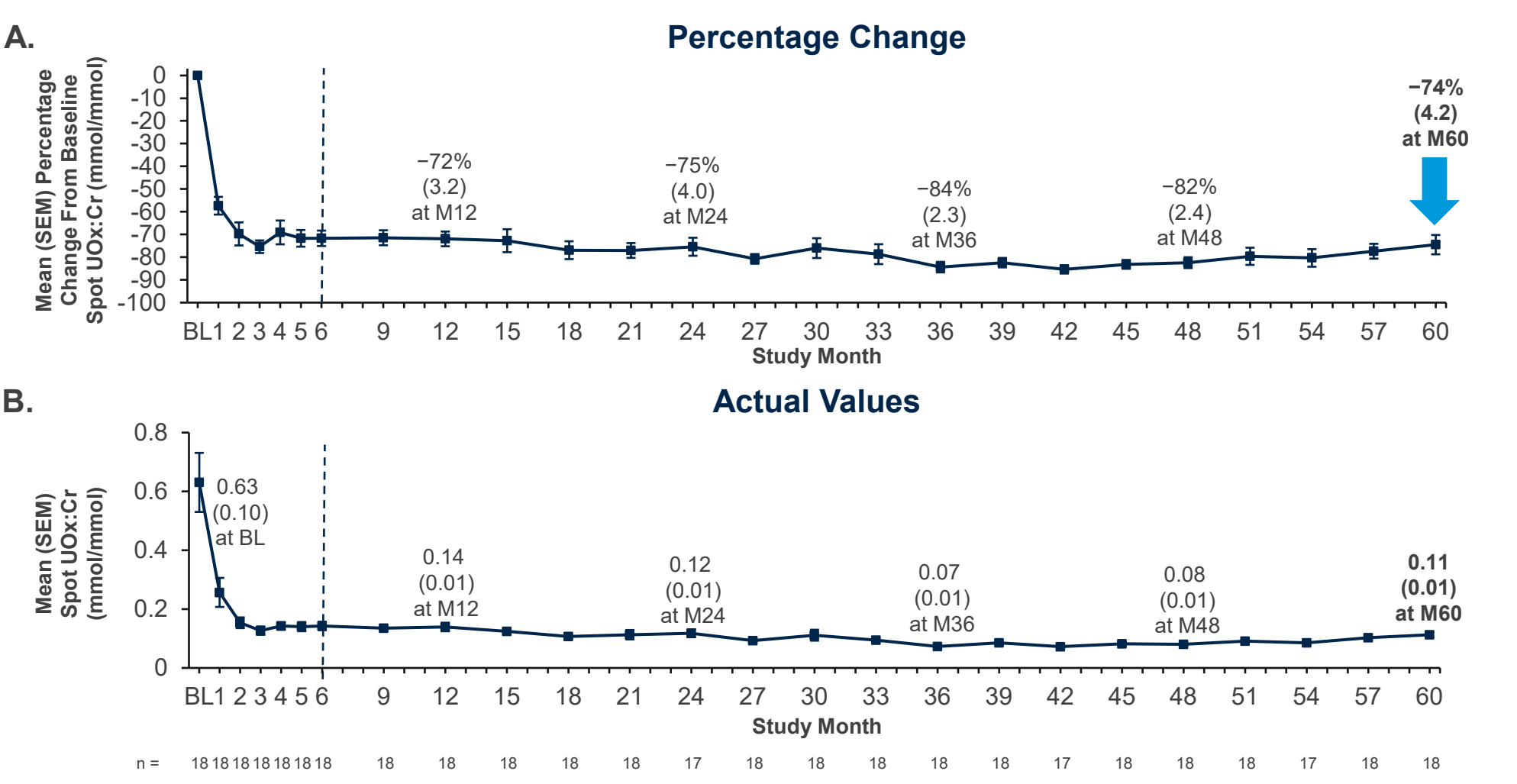
Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	All Treated (N=18)
Age at consent, median (range), months	50.1 (3-72)
Age at PH1 diagnosis, median (range), months	16.3 (0-44)
Time from diagnosis to first dose date, median (range), months	23.5 (4-56)
Genotype ^a , n (%)	
PR ^a	3 (17)
M/M or M/N	10 (56)
N/N	5 (28)
Pyridoxine use, n (%)	11 (61)
Spot UOx:Cr ^b , median (range), mmol/mmol	0.469 (0.166-1.708)
POx ^c , median (range), μmol/L	11.5 (6.6-30.6)
eGFR ^d , median (range), mL/min/1.73m ²	111 (65-174)
At least 1 kidney stone event in the 12 months prior to informed consent ^e , n (%)	3 (16.7)
Presence of medullary nephrocalcinosis, n (%)	14 (77.8)

^aM=missense; N=non-sense; PR=pyridoxine-responsive; ^bany genotype of PR, M, or N. PR was defined as NM_000030.3(AGXT):c.454T>A (p.Phe152Ile). M and N were defined based on a publication by Mandrile et al.⁶
^c1 mmol/mmol=0.796 mg/mg. Age-related reference ranges in spot UOx:Cr: <1 year, 0.015-0.26 mmol/mmol; 1 to <5 years, 0.011-0.12 mmol/mmol; 5 to 12 years, 0.009-0.15 mmol/mmol.⁷
^dULN=12.11 μmol/L for POx, as determined based on data from 75 healthy adults.
^eeGFR was calculated based on the Schwartz Bedside Formula⁸ for patients aged ≥12 months at the time of assessment, N=16; eGFR was not calculated for 2 patients because their age at baseline was <12 months.
^fThe annualized rate of kidney stones in the 12 months prior to informed consent was based on patient-reported history (recall) and was only calculated for patients aged ≥6 months.

- Mean spot UOx:Cr decreased from 0.63 mmol/mmol at baseline to 0.11 mmol/mmol at Month 60; mean (SEM) percentage change from baseline was -74% (4.2) (Figure 2).
- Overall, 100% of patients had a spot UOx:Cr ≤ULN at one or more post-baseline visit.

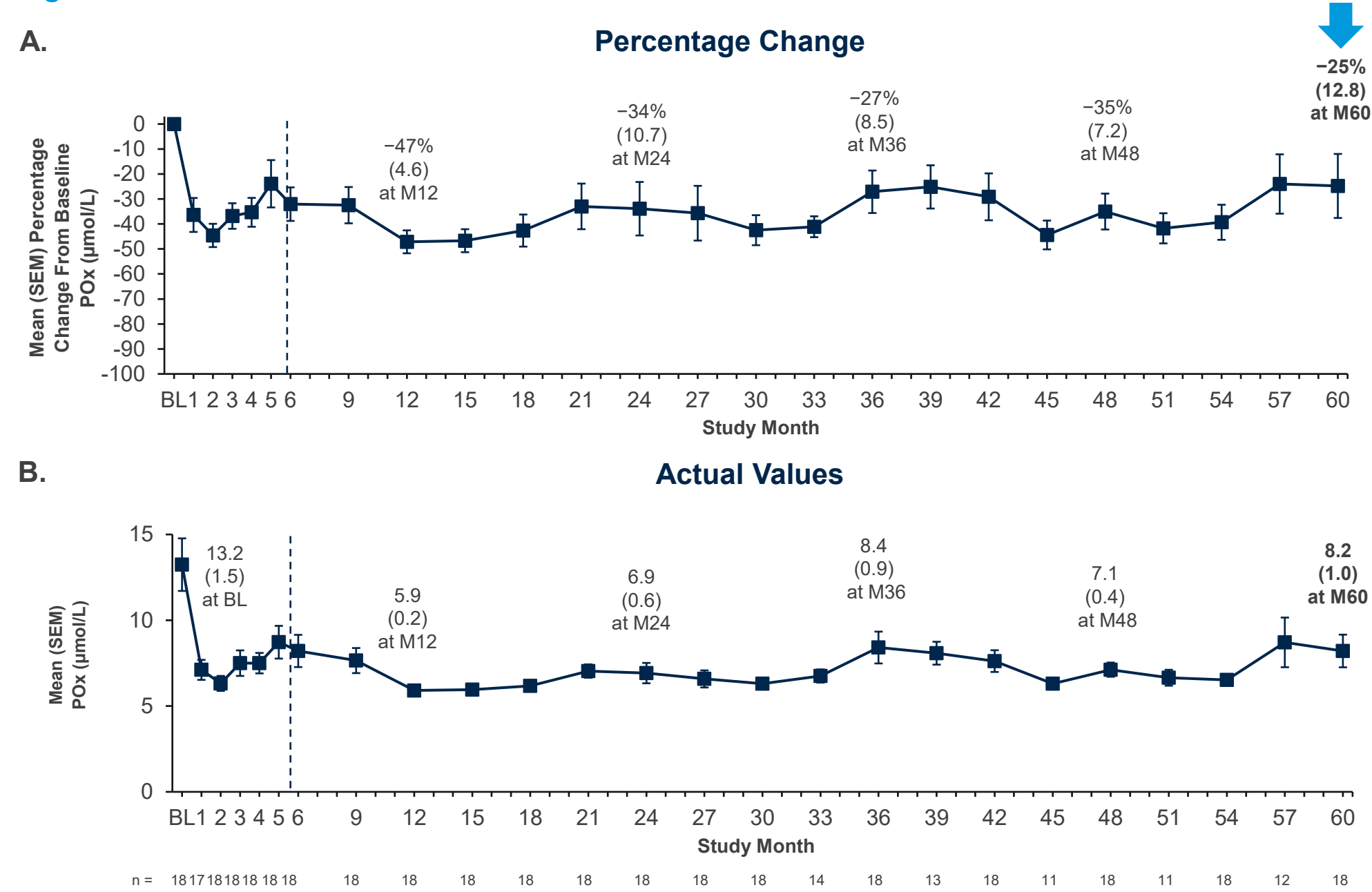
Figure 2. Change From Baseline in Spot UOx:Cr



(A) Percentage change from baseline at each visit, and (B) Actual values at each visit. The baseline value represents the mean of all assessments collected prior to the first dose of lumasiran; 1 mmol/mmol=0.796 mg/mg; 1 mmol/mmol=1000 mmol/mol. End of the primary analysis period is represented by the vertical dashed line; error bars show standard error of the mean (SEM). The ULN for spot UOx:Cr is age-dependent.⁹ Age-related reference ranges in spot UOx:Cr: <1 year, 0.015-0.26 mmol/mmol; 1 to <5 years, 0.011-0.12 mmol/mmol; 5 to 12 years, 0.009-0.15 mmol/mmol.⁷ Oxalate assessments were evaluated by validated liquid chromatography-tandem mass spectrometry assays at a central laboratory.

- Mean POx decreased from 13.2 μmol/L at baseline (ULN=12.11 μmol/L) to 8.2 μmol/L at Month 60; mean (SEM) percentage change from baseline was -25% (12.8) (Figure 3).

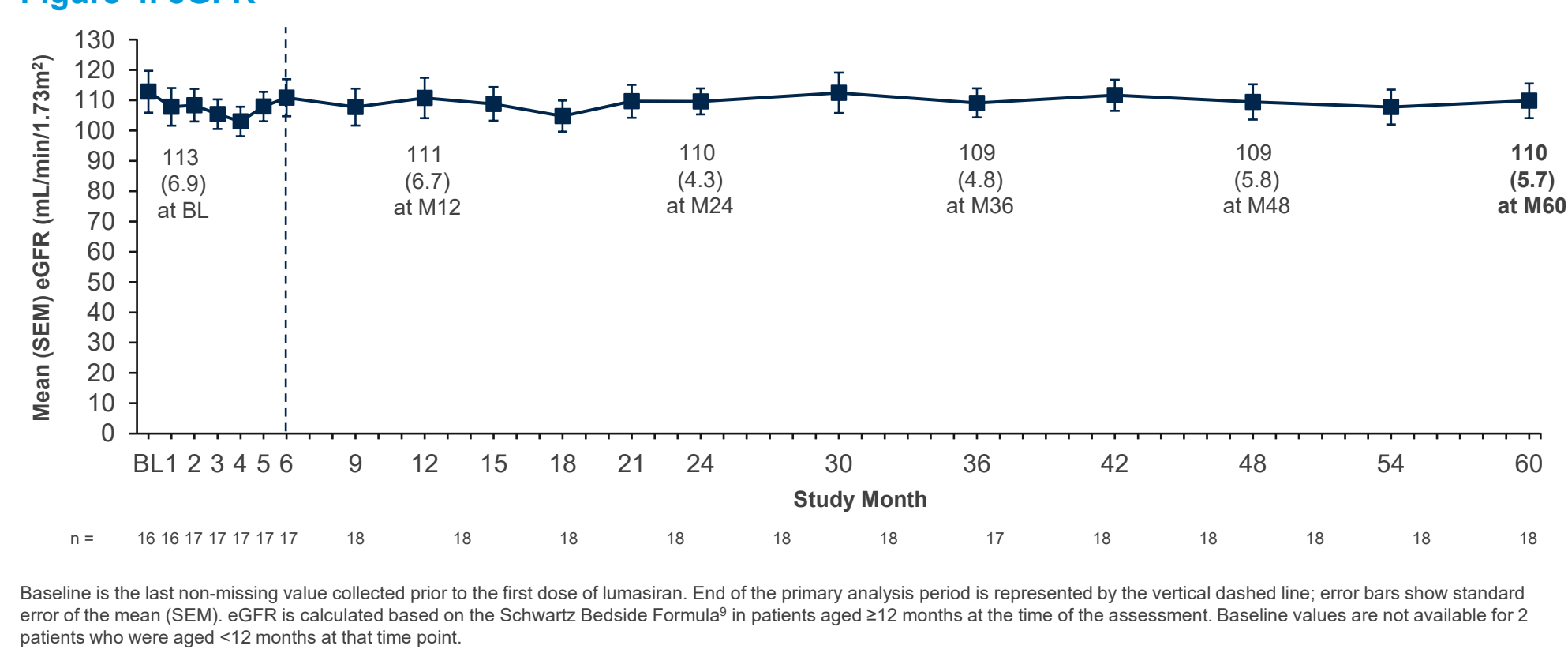
Figure 3. Plasma Oxalate



The baseline value represents the mean of all assessments collected prior to the first dose of lumasiran. End of the primary analysis period is represented by the vertical dashed line; error bars show standard error of the mean (SEM). The lower limit of quantification is 5.55 μmol/L. Oxalate assessments were evaluated by validated liquid chromatography-tandem mass spectrometry assays at a central laboratory.

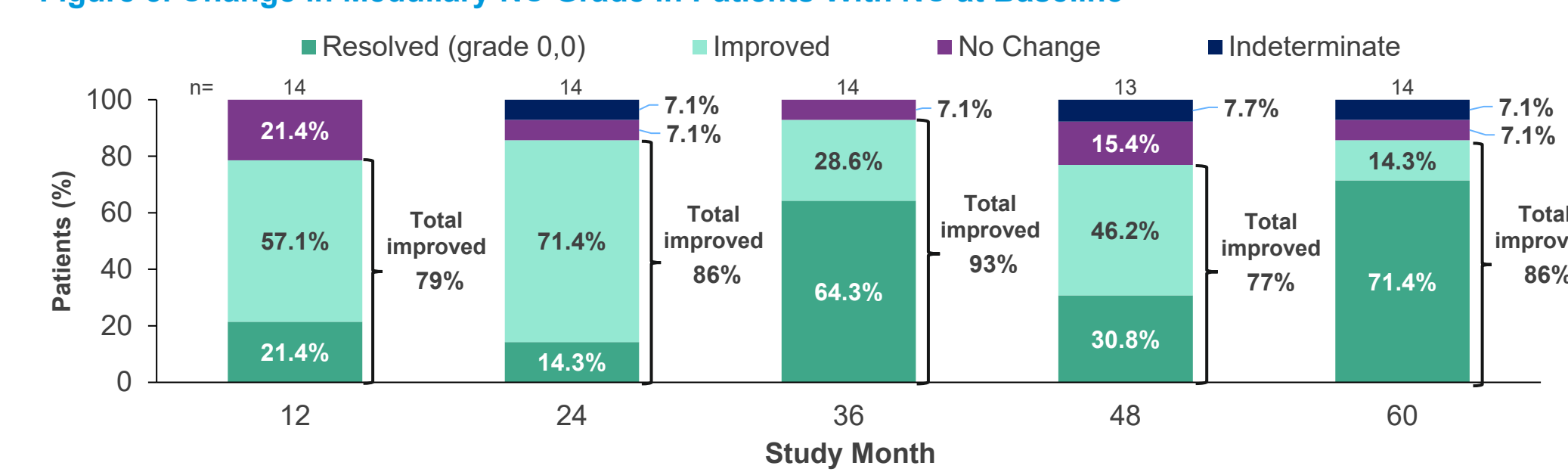
- eGFR remained stable through Month 60 (Figure 4).
- The annual rate of change (slope) in mean (SEM) eGFR over 60 months was +0.26 (0.8) mL/min/1.73m²/y.

Figure 4. eGFR



- In 14 patients with medullary nephrocalcinosis at baseline, nephrocalcinosis grade improved in 86% (12/14), and no patient worsened at Month 60 (Figure 5).
- The 4 patients without nephrocalcinosis at baseline remained nephrocalcinosis-free at Month 60.

Figure 5. Change in Medullary NC Grade in Patients With NC at Baseline



Improved denotes grade lower than baseline (unilateral improvement if one side improved and other side did not change). Resolved (grade 0/0) denotes bilateral grade of 0/0 (both kidneys). Indeterminate denotes improvement on one side and worsening on the other. Worsened denotes grade higher than baseline (no patients worsened). Images are graded in comparison to the baseline ultrasound image.

Kidney Stone Events

- KSE was defined as ≥1 of the following: visit to healthcare provider because of a kidney stone, medication for renal colic, stone passage, or macroscopic hematuria due to a kidney stone.
- KSE rates remained low (0.11/person-year [95% CI, 0.06-0.21]) through Month 60.
- Fourteen patients (77.8%) had no KSEs during ILLUMINATE-B.
- Overall, 9 KSEs were reported in 4 patients, whose spot UOx:Cr change ranged from -75% to -93% at Month 60. All events were mild or moderate in severity.
 - 1 patient (1 KSE) with baseline NC grade 1/1 had complete resolution (0/0) at Month 60.
 - 1 patient (1 KSE) with baseline NC grade 0/0 had no change (0/0) at Month 60.
 - 1 patient (5 KSEs) with baseline NC grade 3/3 had complete resolution (0/0) at Month 60.
 - 1 patient (2 KSEs) with baseline NC grade 3/3 had no change (3/3) at Month 60.

Safety

- Median (range) exposure to lumasiran was 55.5 (54.5-56.1) months.
- Five (28%) patients had treatment-related AEs, none of which were severe or serious (Table 2).
- The most common treatment-related AEs were mild, transient injection site reactions (3 patients [17%]); symptoms included erythema, discoloration, hematoma, pain, and urticaria at the injection site.
- There were no lumasiran-related clinically relevant changes in laboratory measures, vital signs, or ECGs.
- The data suggest no unexpected safety signals.

Table 2. Safety Data for ILLUMINATE-B

Patients With ≥ 1 Event	All Treated (N=18) n (%)
AEs	18 (100)
Treatment-related AEs ^a	5 (28)
Severe treatment-related AEs	0
AEs leading to treatment discontinuation	0
AEs leading to study withdrawal	0
Serious AEs	2 (11) ^b
Death	0

^aTreatment-related AEs included injection site hematoma (n=1), injection site reactions (n=3), injection site urticaria (n=1), blood bilirubin increase (n=1), and headache (n=1).
^bOne patient had a serious AE of viral infection (moderate in severity, considered unrelated to lumasiran by the investigator) during the 6-month primary analysis period, which was reported previously.¹⁰ The other patient had a serious AE of ear pain and ear hemorrhage (severe; considered unrelated to lumasiran by the investigator) during the extension period. Both serious AEs (n=2) were not related to lumasiran, and dosing was not changed.

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. **Funding:** This study was funded by Alnylam Pharmaceuticals. **Presented at:** the American Society of Nephrology (ASN) Congress; November 5-9, 2025; Houston, TX

Disclosures: DJS: Grants and other from Alnylam Pharmaceuticals, and personal fees from Advicene. MM: Principal investigator for Alnylam Pharmaceuticals; advisory board member for Novo Nordisk Inc; and speaker fees for association/symposium from Alnylam Pharmaceuticals and Novo Nordisk. YF: Consultancy fees from Alnylam Pharmaceuticals and membership in the safety review committee. WH: Principal investigator for Alnylam Pharmaceuticals; consultancy fees, travel and accommodation. EB-S: Principal investigator for Alnylam Pharmaceuticals; travel and accommodation expenses to attend international investigators' meetings. A-LS-L: Consultancy fees from Alnylam Pharmaceuticals and Dicerna Pharmaceuticals, and principal investigator for research funded by Oryza. JK: Consultancy fees from Alnylam Pharmaceuticals. WD: Alnylam Pharmaceuticals – employee and shareholder. DMurphy: Alnylam Pharmaceuticals – employee and shareholder. CK: Alnylam Pharmaceuticals – employee. DMagen: Research funding, consultancy fees, and non-financial support from Alnylam Pharmaceuticals.

Abbreviations: AE, adverse event; BL, baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; KSE, kidney stone event; LC-MS/MS, liquid chromatography-tandem mass spectrometry; M, month; NC, nephrocalcinosis; PH1, primary hyperoxaluria type 1; POx, plasma oxalate; SCR, serum creatinine; ULN, upper limit of normal; UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio. **References:** 1. Cochran P, Ramsby G. *N Engl J Med*. 2013;369:649-658. 2. Oulomo [package insert]. Cambridge, MA: Alnylam Pharmaceuticals; 2022. 3. Frishberg Y, et al. *Front Pediatr*. 2024;12. 4. 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 (NKF) Congress; April 10-13, 2025; Boston, MA. 5. 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 RA; June 4-7, 2025; Vienna, Italy & Virtual. 6. Mandrile G, et al. *Kidney Int*. 2014;86:1197-1204. 7. Barratt TM, et al. *Arch Dis Child*. 1991;66:501-503. 8. Schwartz GJ, et al. *J Am Soc Nephrol*. 2009;20:629-637. 9. Matos V, et al. *Am J Kidney Dis*. 1999;34(2):e1. 10. Sas DJ, et al. *Genet Med*. 2022;24:654-662.