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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

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Disclosures

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Yaacov Frishberg: Consultancy fees from Alnylam Pharmaceuticals and membership in the safety review committee

Wesley Hayes: Principal investigator for Alnylam Pharmaceuticals; consultancy fees, travel and accommodation

Efrat Ben-Shalom: Principal investigator for Alnylam Pharmaceuticals

Hadas Shasha-Lavsky: Principal investigator for Alnylam Pharmaceuticals; travel and accommodation expenses to attend international investigators' meetings

David J. Sas: Grants and other from Alnylam Pharmaceuticals, and personal fees from Advicenne

Mini Michael: Principal investigator for Alnylam Pharmaceuticals; advisory board member for Novo Nordisk Inc.

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

Julien Hogan: Consultancy fees from Alnylam Pharmaceuticals

Richard Willey and **John M. Gansner:** Alnylam Pharmaceuticals – employee and shareholder

Cristin Kaspar: Alnylam Pharmaceuticals – employee

Daniella Magen: Research funding, consultancy fees, and non-financial support from Alnylam Pharmaceuticals

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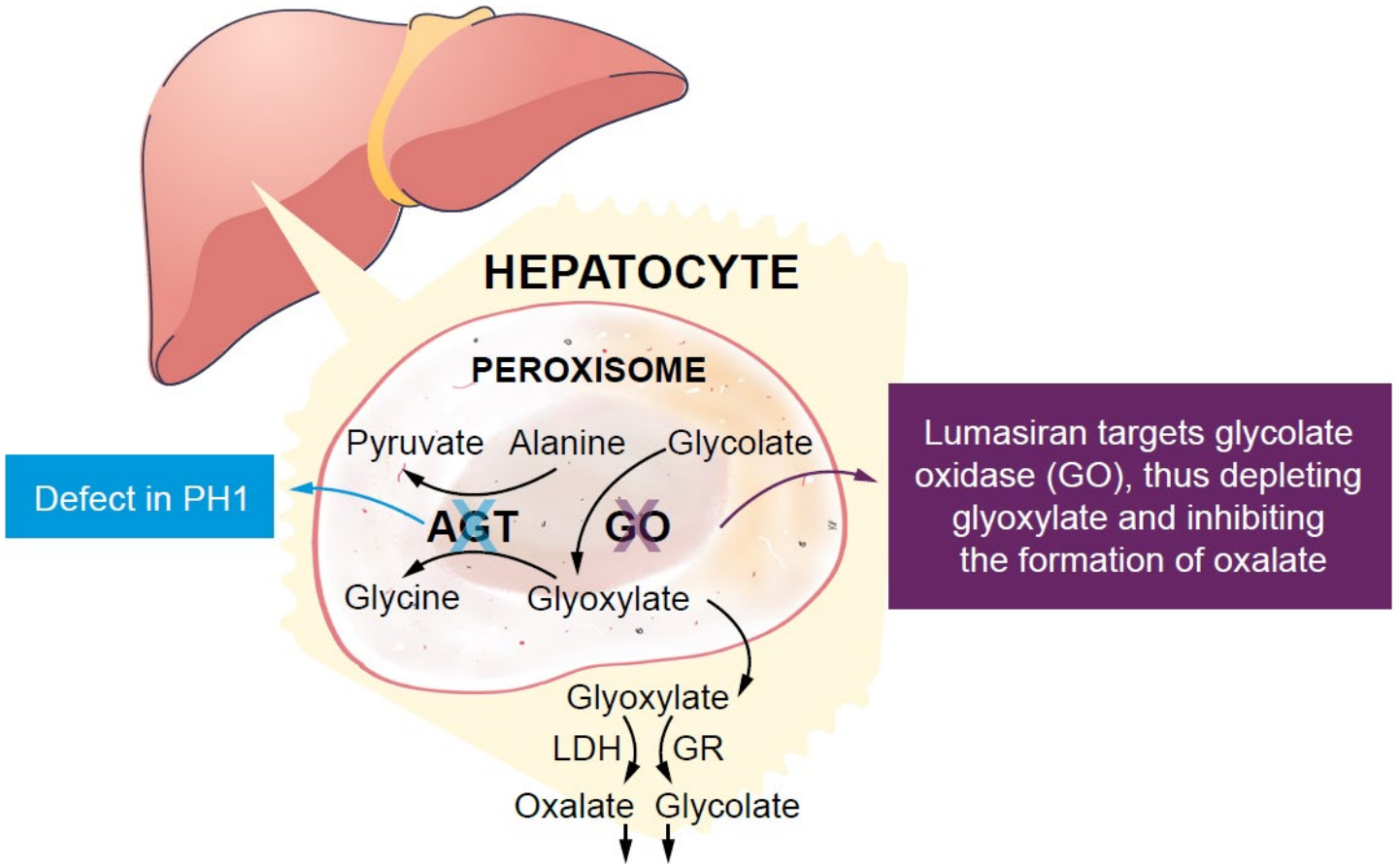
Introduction

Primary hyperoxaluria type 1 (PH1) is a genetic disorder resulting in excess hepatic oxalate production, which can lead to urolithiasis, nephrocalcinosis, and ultimately chronic kidney disease, kidney failure, and systemic oxalosis



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Methods

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- ILLUMINATE-B is a Phase 3, multinational, open-label, single-arm study that enrolled young children with PH1

PATIENT POPULATION (N=18)

- Children age <6 years
- Confirmed PH1 diagnosis
- Urinary oxalate:Creatinine (UOx:Cr) >upper limit of normal (ULN) for age for ≥2 of 3 samples
- eGFR >45 mL/min/1.73m^2 if age ≥12 months or normal serum Cr if age <12 months without extrarenal systemic oxalosis
- If taking vitamin B6 (pyridoxine), stable regimen for ≥90 days pre-screening and maintained through at least Month 6

6-MONTH PRIMARY ANALYSIS PERIOD FOLLOWED BY 54-MONTH EXTENSION PERIOD

Loading Dose

<10 kg: 6 mg/kg once monthly for 3 doses

10 to <20 kg: 6 mg/kg once monthly for 3 doses

≥20 kg: 3 mg/kg once monthly for 3 doses

Maintenance Dose[a]

<10 kg: 3 mg/kg once monthly

10 to <20 kg: 6 mg/kg once quarterly

≥20 kg: 3 mg/kg once quarterly

[a]Beginning 1 month after last loading dose(s).

Baseline Characteristics

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- All 18 patients enrolled in ILLUMINATE-B completed the 60-month study

Characteristic	All Treated (N=18)
Age at consent, median (range), months	50 (3-72)
Age at diagnosis of PH1, median (range), months	16 (0-44)
Time from diagnosis to first dose date, median (range), months	24 (4-56)
Genotype,[a] n (%)	
PR/*	3 (17)
M/M or M/N	10 (56)
N/N	5 (28)
Pyridoxine (vitamin B6) use, n (%)	11 (61)
Spot UOx:Cr, median (range), mmol/mmol	0.469 (0.166-1.708)
POx, median (range), µmol/L	11.5 (6.6-30.6)
eGFR, median (range), mL/min/1.73m^2	111 (65-174)
At least 1 kidney stone event in the 12 months prior to informed consent, n (%)	3 (16.7)
Presence of medullary nephrocalcinosis, n (%)	14 (77.8)

[a]M=missense; N=nonsense; PR=pyridoxine-responsive; *=any genotype of PR, M, or N.

Spot Urinary Oxalate:Creatinine (UOx:Cr)

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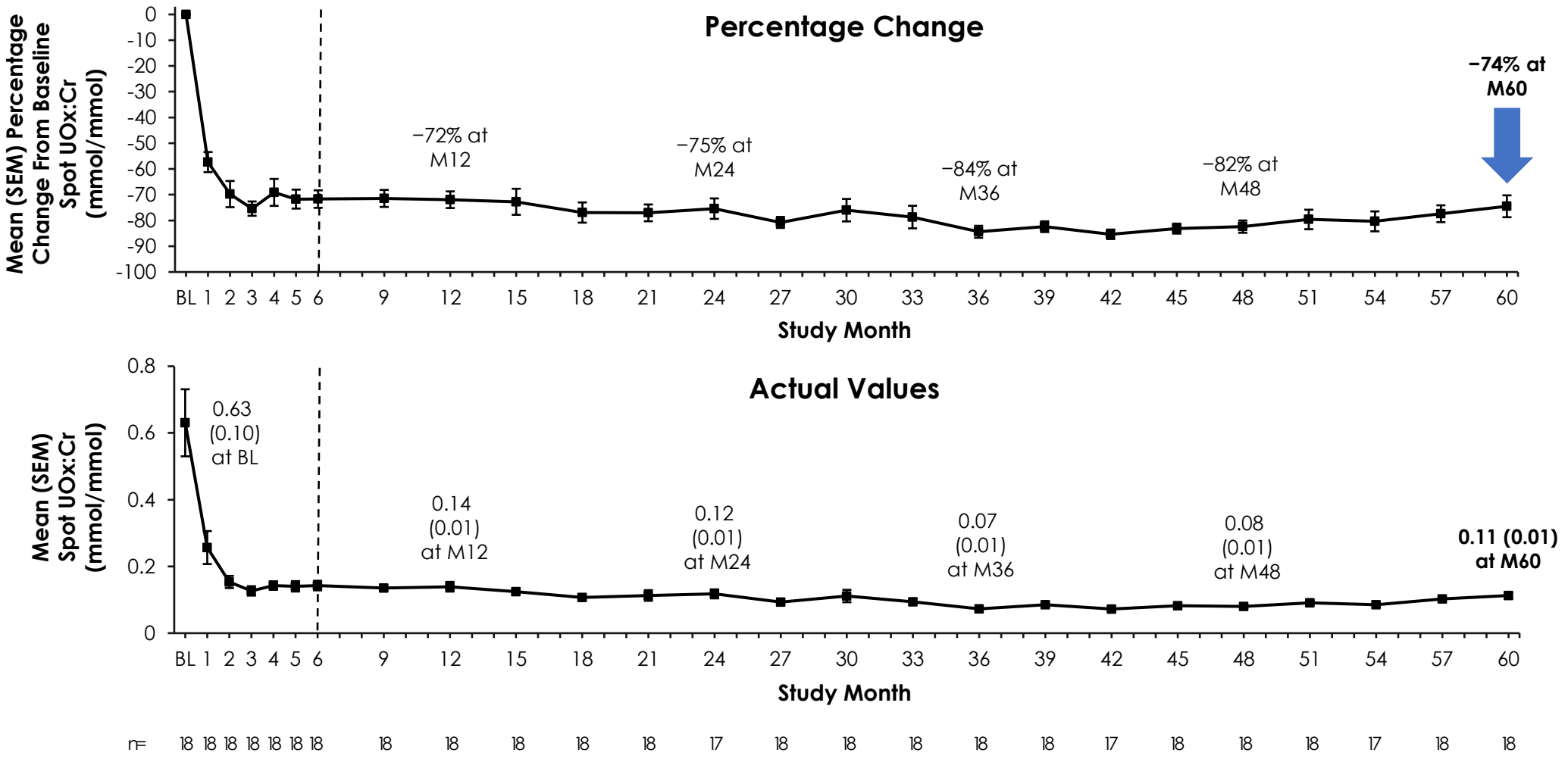
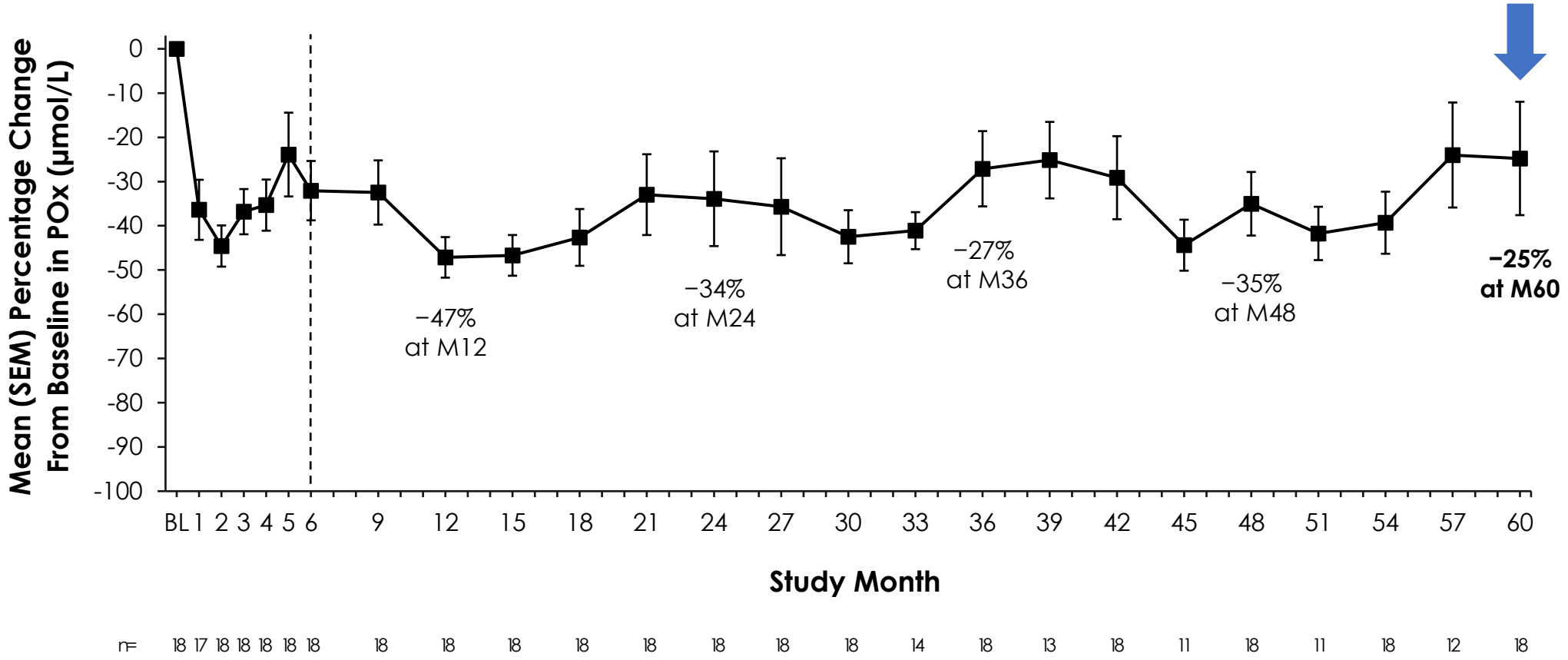
- Mean spot UOx:Cr decreased by 74%, from 0.63 at baseline to 0.11 at Month 60



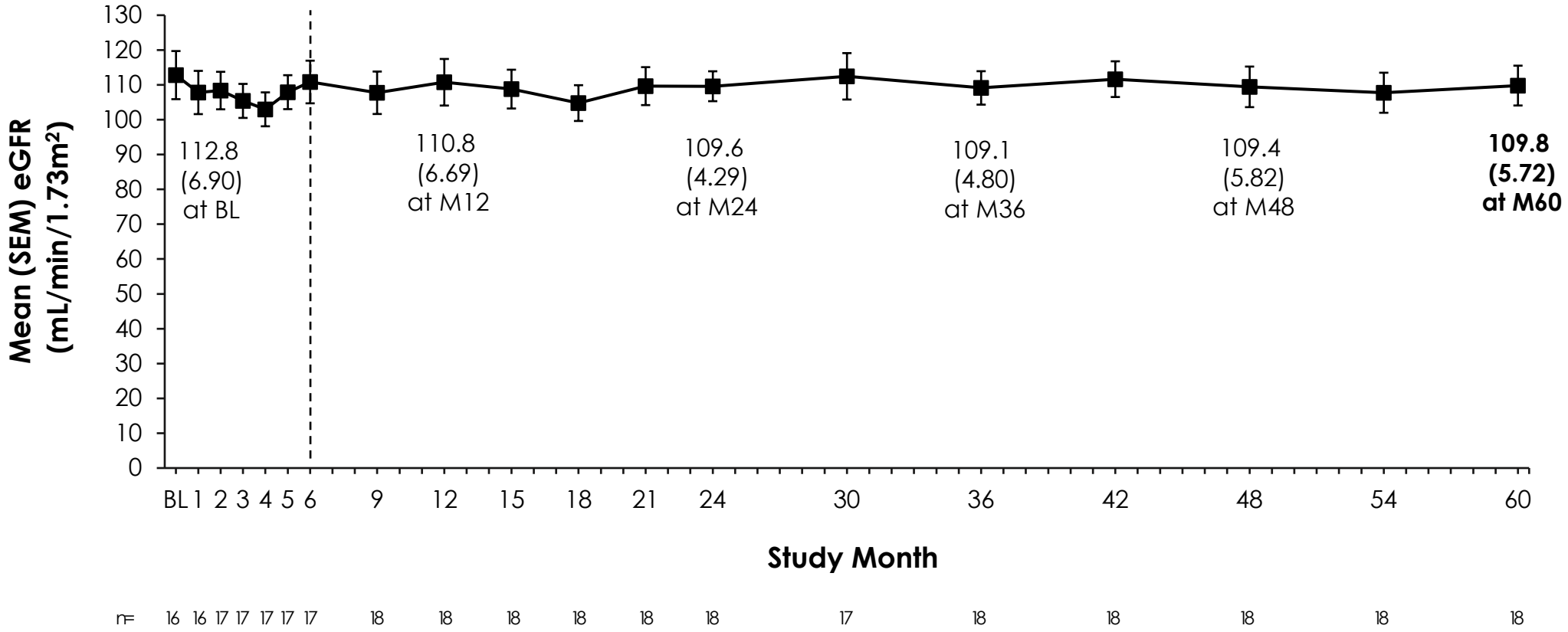
Plasma Oxalate (POx)

- Mean POx decreased by 25%, from 13.2 µmol/L at baseline (ULN = 12.11 µmol/L) to 8.2 µmol/L at Month 60



Stable eGFR

- Annual change in mean eGFR (slope) was +0.26 (SEM 0.8) mL/min/1.73m²/y over 60 months



Medullary Nephrocalcinosis (NC)

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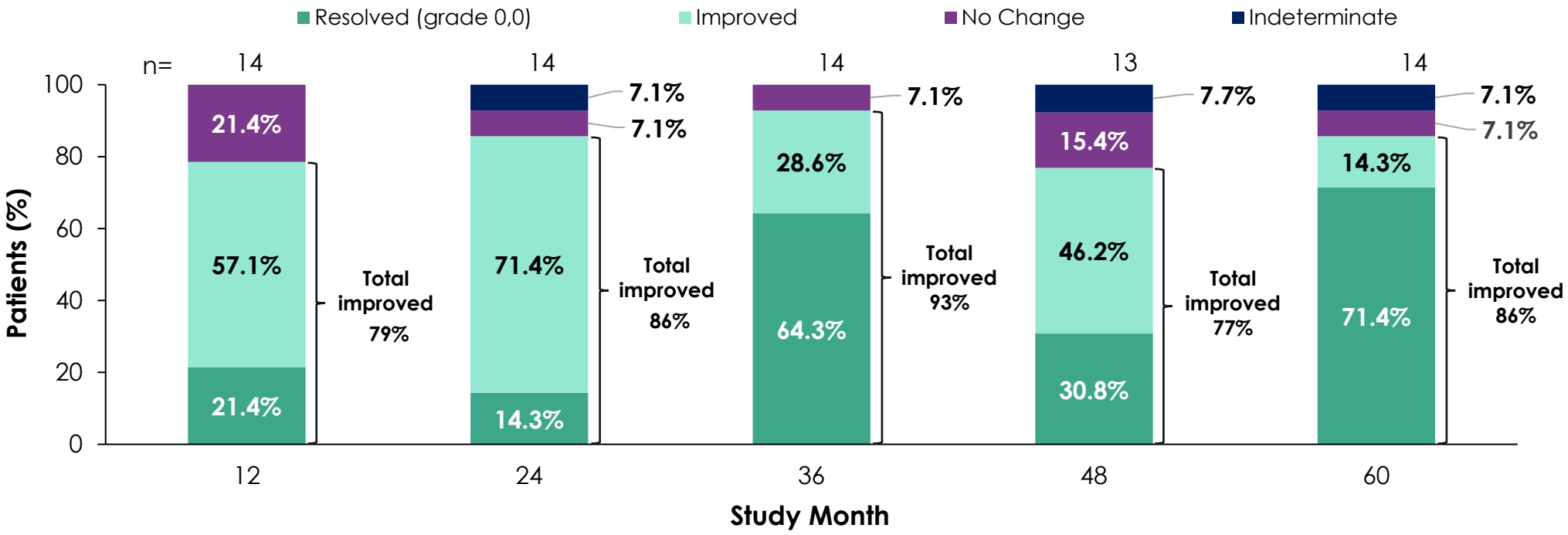
- In 14 patients with medullary NC at baseline, 12 patients had improved NC grade at Month 60; NC resolved (grade 0,0) in 10 patients

Change in Medullary NC Grade in Patients With NC at Baseline (14/18)



Resolved (grade 0,0) denotes bilateral grade of '0,0' (both kidneys), **Improved** denotes grade lower than baseline (unilateral improvement if one side improved and other side did not change), **Indeterminate** denotes improvement on one side and worsening on the other. **Worsened** denotes grade higher than baseline (no patients worsened).

Kidney Stone Events (KSEs)

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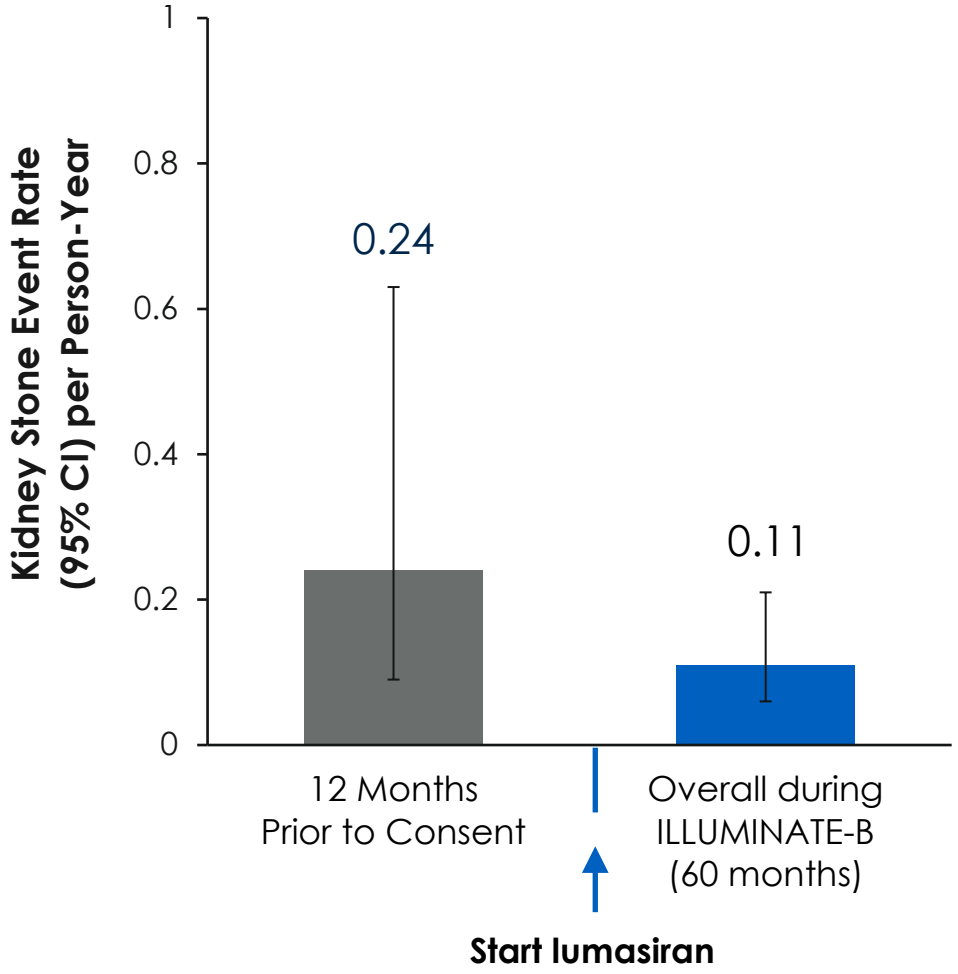
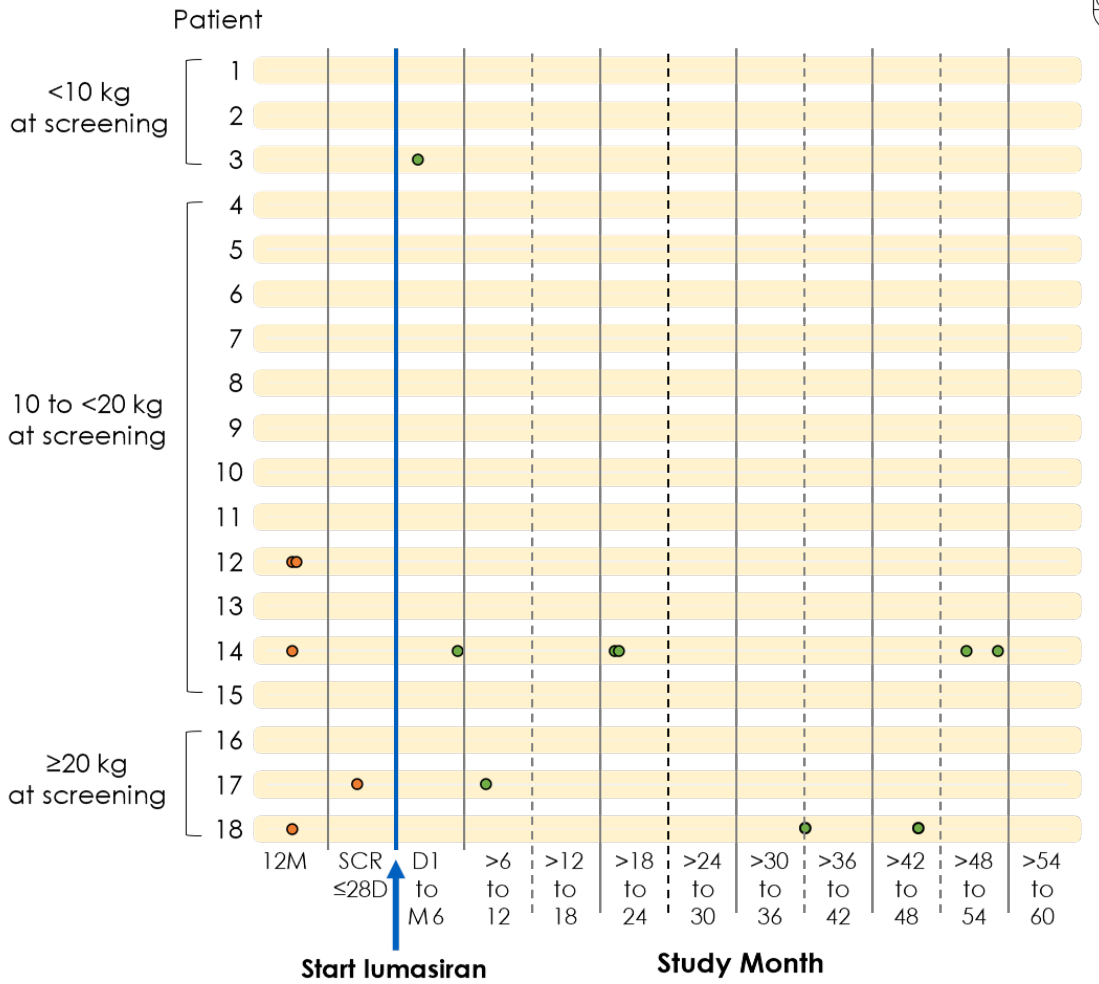
- Nine KSEs in 4 patients were reported during ILLUMINATE-B; 14 patients (77.8%) had no KSEs





Safety

- The most common lumasiran-related AEs were mild, transient injection site reactions (3 patients [17%])

Event, n (%)	All Treated (N=18)
AEs	18 (100)
Treatment-related AEs	5 (28)
Severe treatment-related AEs	0
AEs leading to treatment discontinuation	0
AEs leading to study withdrawal	0
Serious AEs	2 (11)
Death	0

Conclusions

In the ILLUMINATE-B Phase 3 60-month trial in infants and young children <6 years old with PH1:

- Long-term lumasiran treatment in children as young as 3 months old resulted in sustained reductions in UOx and POx
- There were no new safety concerns; the most common lumasiran-related AEs were mild, transient injection site reactions
- Infants and children with PH1 had stable eGFR
- Medullary nephrocalcinosis improved in the majority of patients
- Kidney stone event rates were low

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Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in ILLUMINATE-B

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