Long-Term Efficacy, Safety, and Growth Outcomes in the Phase 3 ILLUMINATE-B Trial of Lumasiran for Primary Hyperoxaluria Type 1 in Infants and Young Children

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Disclosures

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

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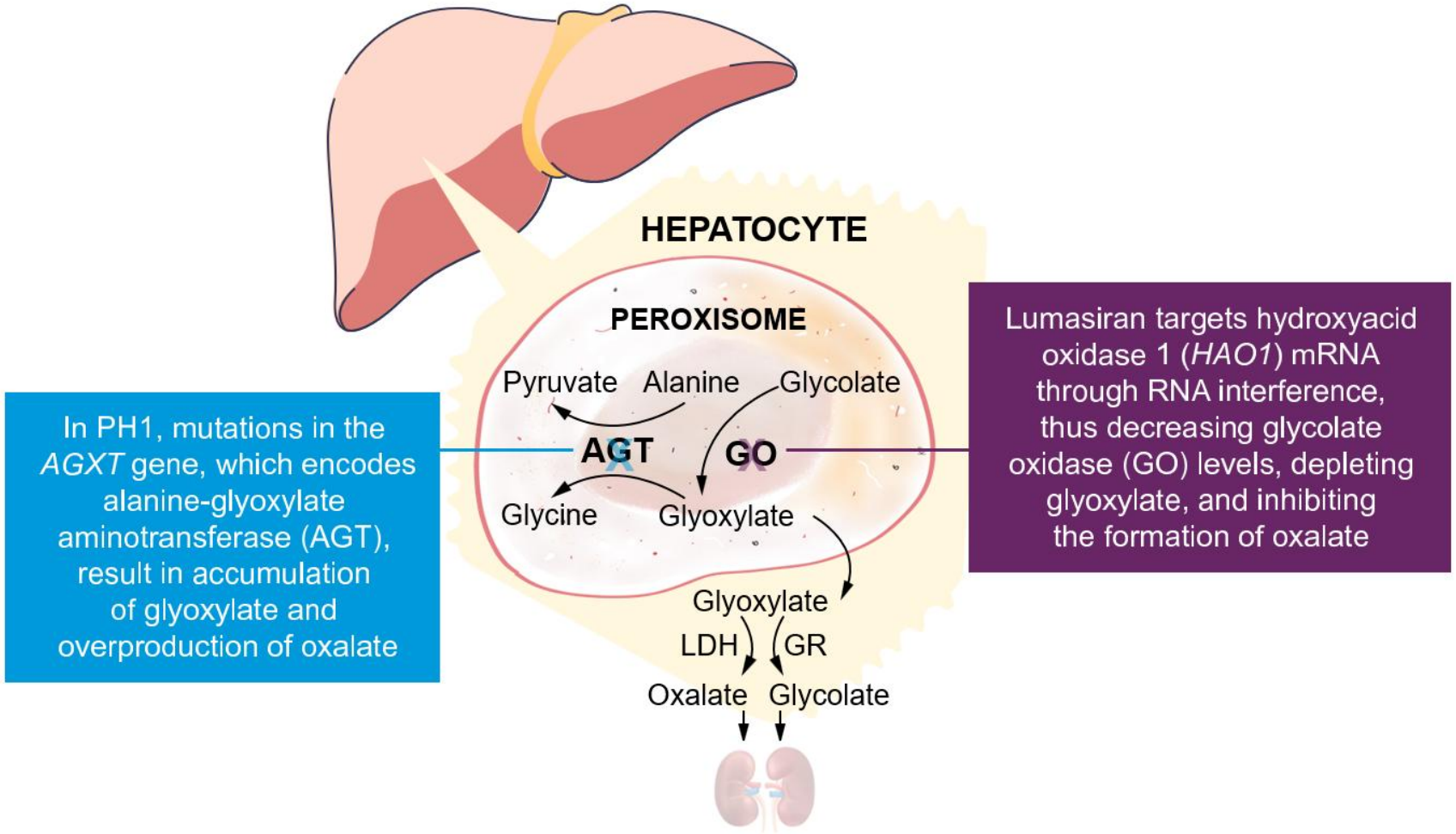
Introduction

- 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



Methods

- ILLUMINATE-B (NCT03905694) 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

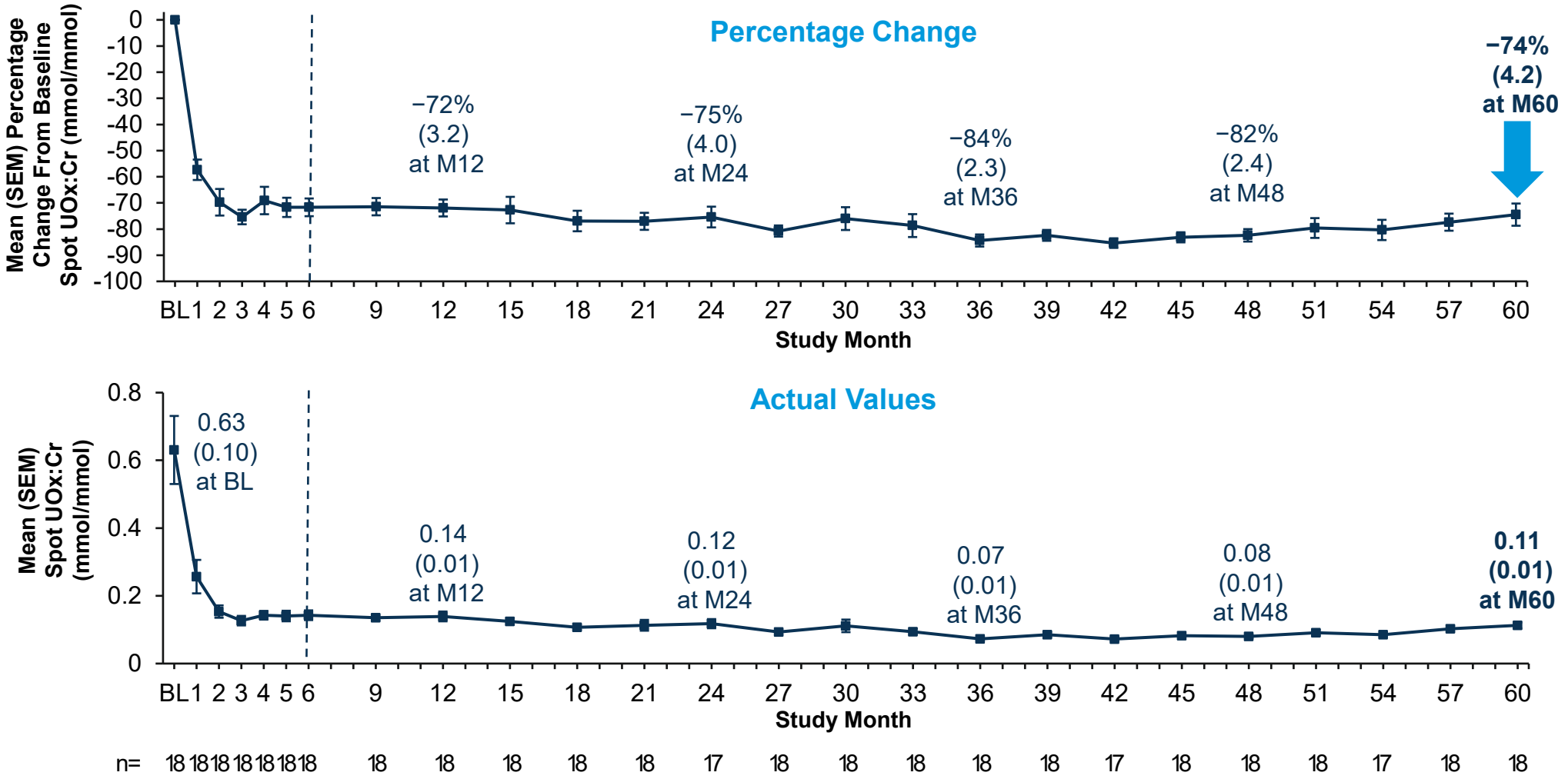
- All 18 patients enrolled in ILLUMINATE-B completed the 60-month study

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[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 (KSE) in the 12 months prior to informed consent[e], 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)

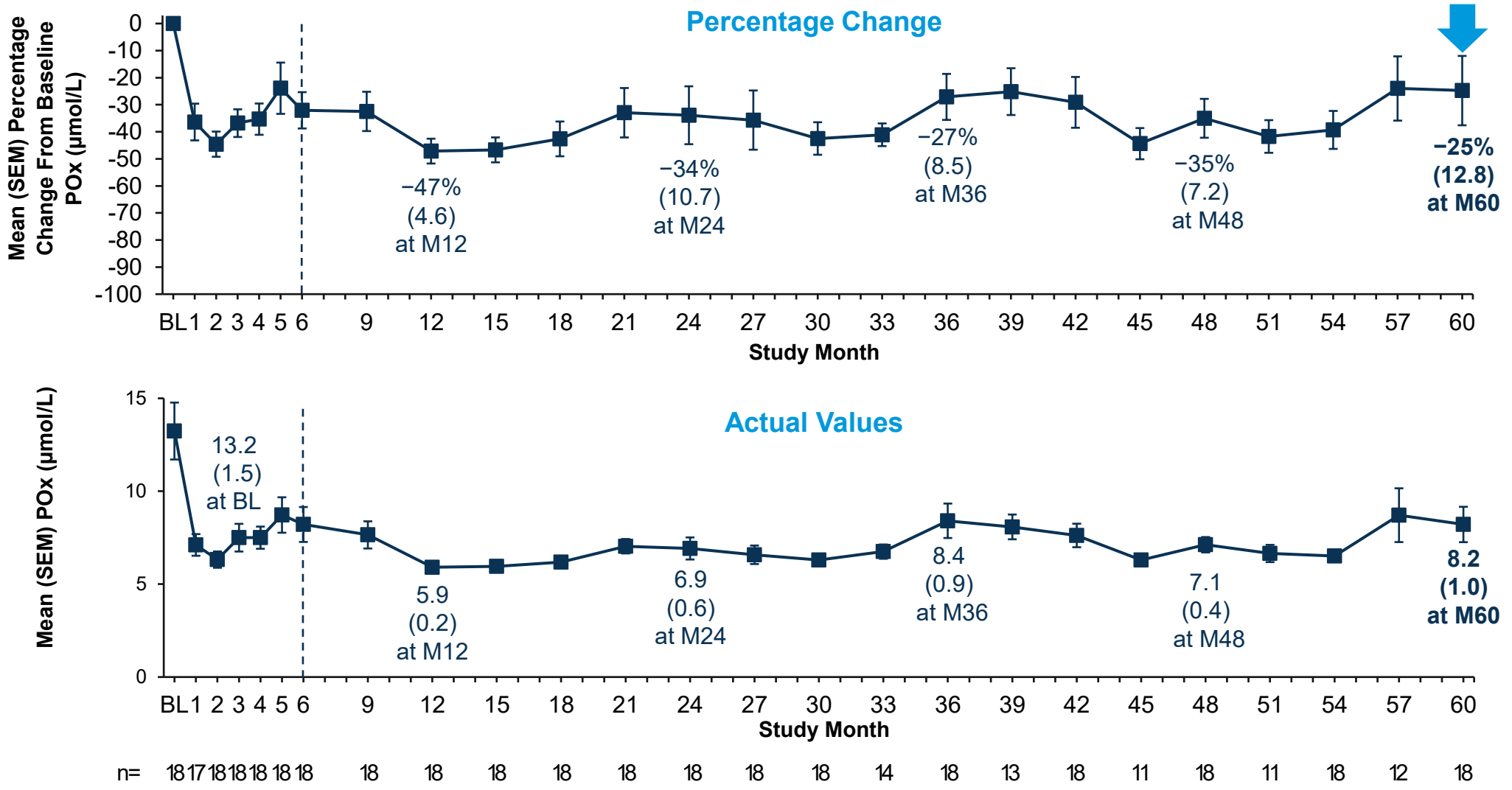
- Mean spot UOx:Cr decreased by 74%, from 0.63 mmol/mmol at baseline to 0.11 mmol/mmol at Month 60



End of the primary analysis period is represented by the vertical dashed line. BL, baseline; M, month; SEM, standard error of the mean.

Plasma Oxalate (POx)

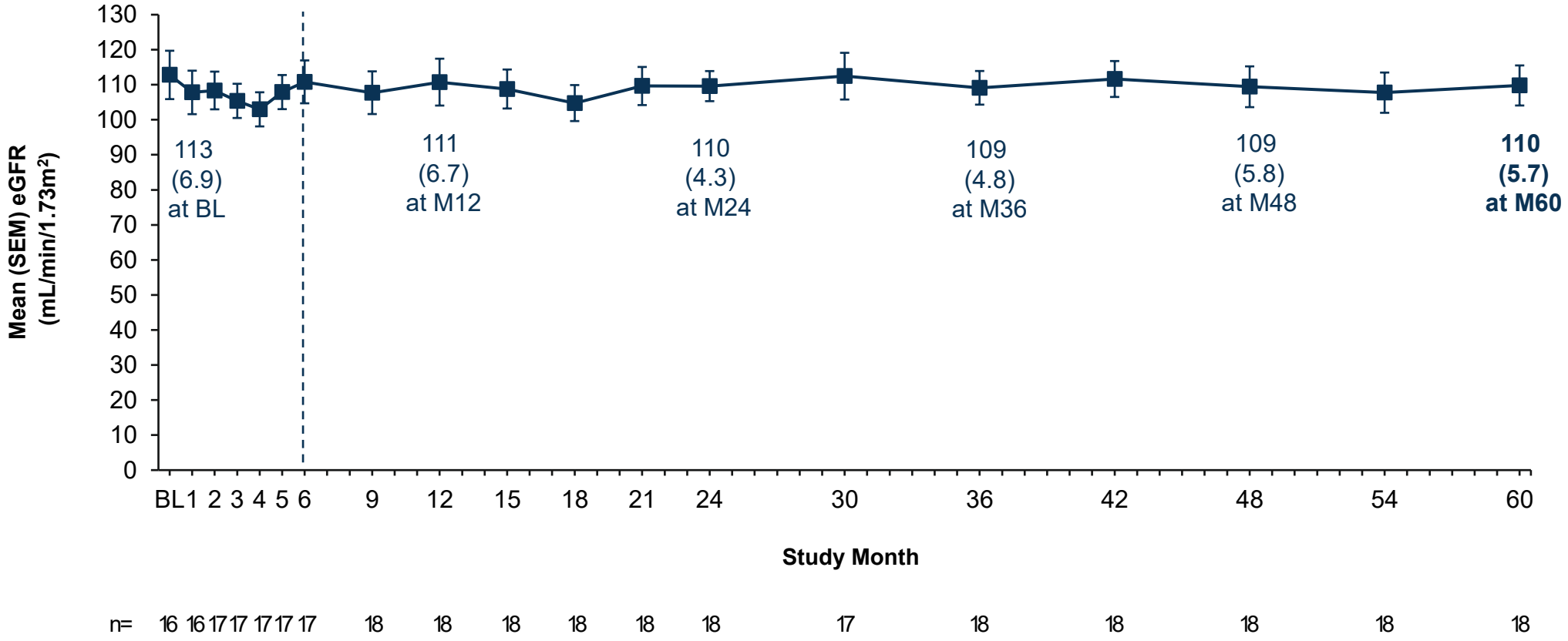
- Mean POx decreased by 25%, from 13.2 µmol/L at baseline (ULN = 12.11 µmol/L) to 8.2 µmol/L at Month 60



End of the primary analysis period is represented by the vertical dashed line. BL, baseline; M, month; SEM, standard error of the mean.

Stable eGFR

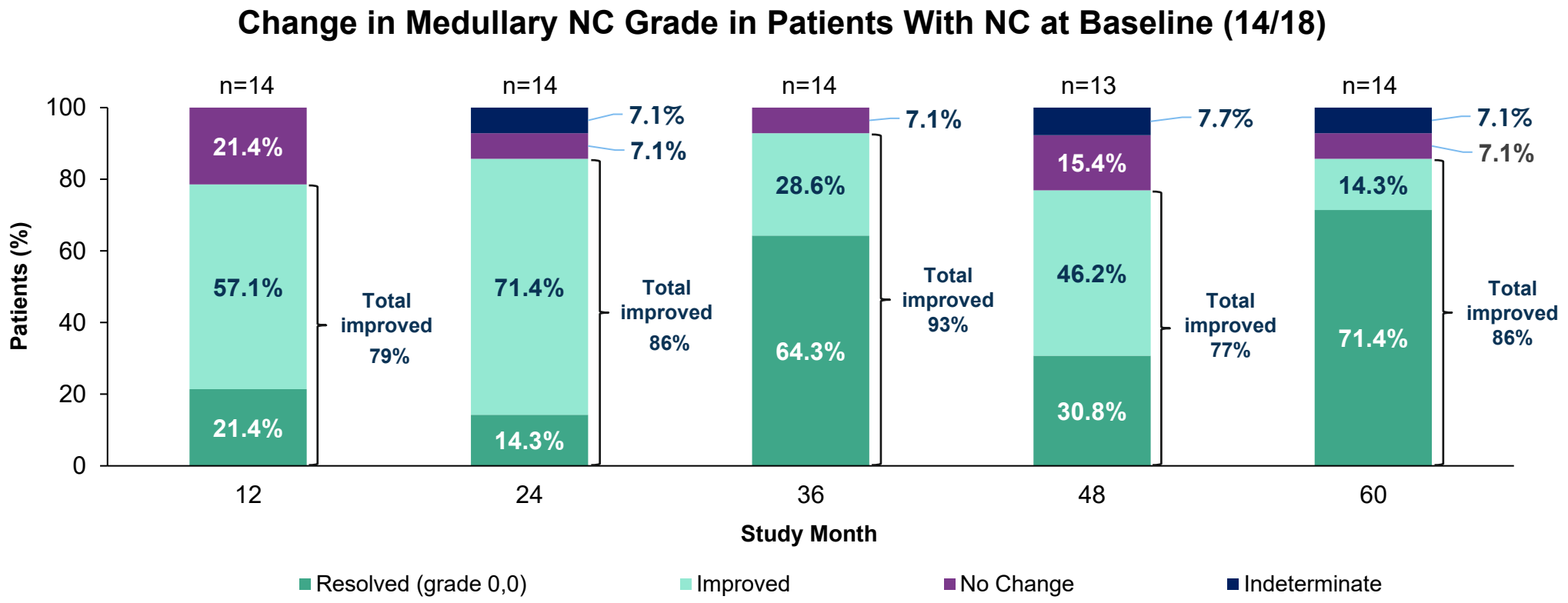
- Annual change in mean eGFR (slope) was +0.26 (SEM 0.8) mL/min/1.73m²/y over 60 months



eGFR is calculated based on the Schwartz Bedside formula in patients aged ≥12 months at the time of the assessment. At baseline, eGFR was assessed in 16 patients who were aged ≥12 months; 2 patients were aged <12 months. End of the primary analysis period is represented by the vertical dashed line. BL, baseline; M, month; SEM, standard error of the mean.

Medullary Nephrocalcinosis (NC)

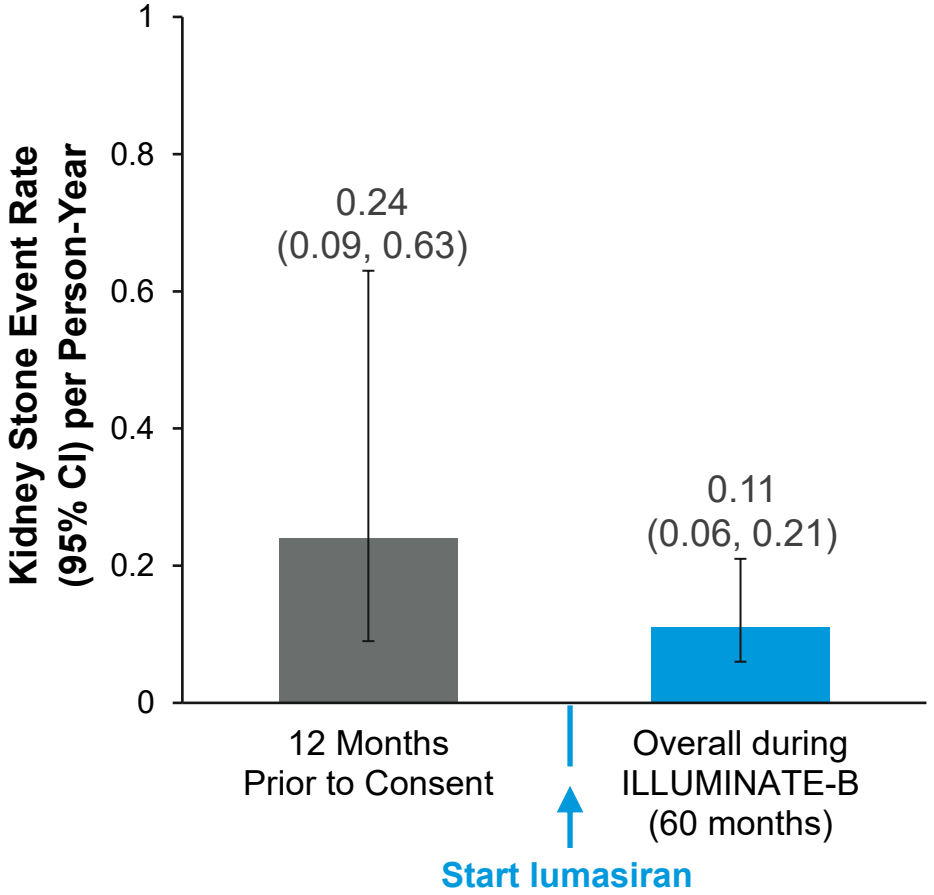
- At Month 60, NC grade improved in 12/14 (86%) patients who had NC at baseline; 10 patients improved to grade 0 bilaterally
- In patients without NC at baseline, 4/4 (100%) had no change in NC grade at Month 60



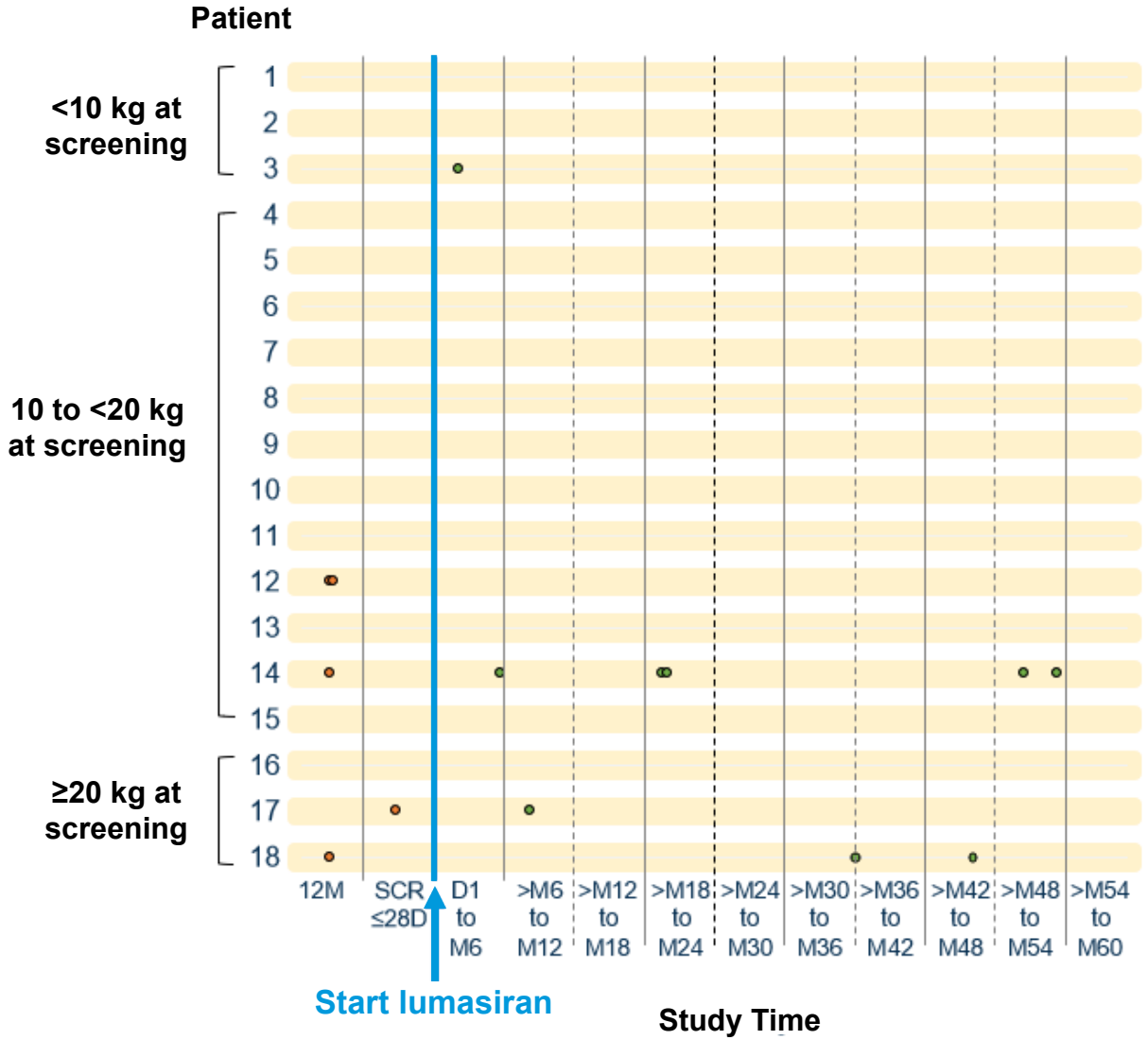
Improved denotes grade lower than baseline (unilateral improvement if one side improved and other side did not change, or bilateral improvement), **Resolved (grade 0,0)** denotes improvement to grade 0 in both kidneys, **Indeterminate** denotes improvement on one side and worsening on the other. **Worsened**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

Kidney Stone Events (KSEs)

- 4 patients experienced 9 KSEs
- 14/18 (78%) patients had no KSEs



Left: Gray bar represents the patient-reported historical rate of KSEs based on recall. Blue bar represents KSEs occurring during ILLUMINATE-B, defined as an event including ≥1 of the following: visit to healthcare provider due to kidney stone; medication for renal colic; stone passage; macroscopic hematuria due to a kidney renal stone.



Right: Each yellow line represents 1 patient. Each data point indicates 1 KSE. Weight is at time of screening (SCR). The timing for historical events (prior 12 months; 12M) was not documented. KSEs portrayed for prior 12M and SCR are not drawn based on when each event occurred. The 12M and SCR data points are centered; other data points are plotted according to when they occurred during the period.

Safety

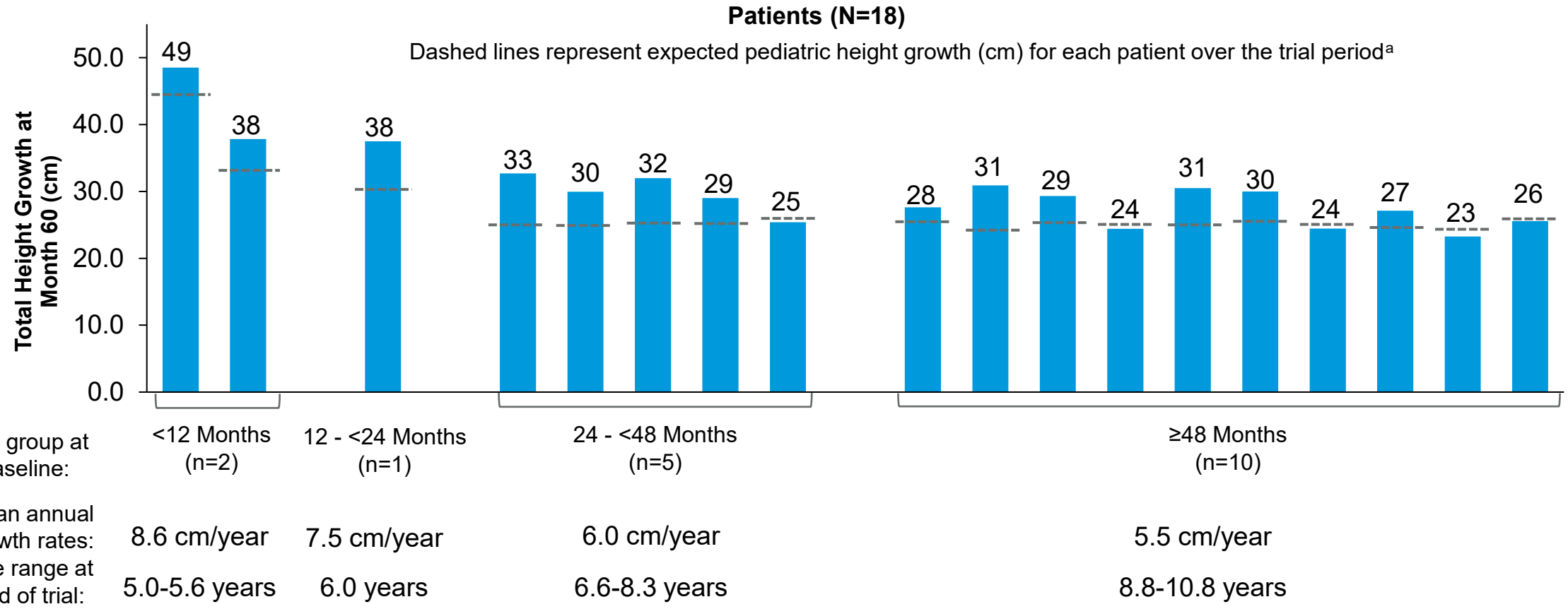
- The most common lumasiran-related adverse events (AEs) were mild, transient injection site reactions (3 patients [17%])

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

[a]Treatment-related AEs, affecting 5 patients, 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).
[b]Both serious AEs (n=2) were not related to lumasiran and dosing was not changed.

Height Growth Over 60 Months

- Overall, mean change in height z-score from baseline to Month 60 was −0.116 (SEM, 0.116)
- By Month 60, height growth over the 5-year study period exceeded age-based estimates[a] of expected typical pediatric growth in 13/18 (72%) patients



[a]Expected growth over the 60-month trial period was calculated for each patient based on patient ages and time on trial, derived from typical growth of 25 cm during the first year of life, 12 to 13 cm in the second year of life, then 5 to 6 cm/year from age 2 years through puberty. (Rogol AD, et al. *Am J Clin Nutr.* 2000;72(suppl):521S–8S.)

Conclusions

- In the ILLUMINATE-B 60-month Phase 3 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

Patients achieved a normal expected pediatric growth per year

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