Efficacy and Safety of Lumasiran for Infants and Young Children With Primary Hyperoxaluria Type 1: 12-Month Analysis of the Phase 3 ILLUMINATE-B Trial

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Disclosures

Dr. Mini Michael has disclosed the following financial relationships. Any real or apparent conflicts of interest related to the content of this presentation have been resolved.

Affiliation / Financial Interest	Organization
Principal investigator	Alnylam Pharmaceuticals

W Hayes: *travel and accommodation expenses from Alnylam Pharmaceuticals to attend an international investigators' meeting.*
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T Ngo, M Sweetser, JM Gansner: *employees of and shareholders in Alnylam Pharmaceuticals.*
Y Frishberg: *consultancy fees from Alnylam Pharmaceuticals and membership in the safety review committee.*

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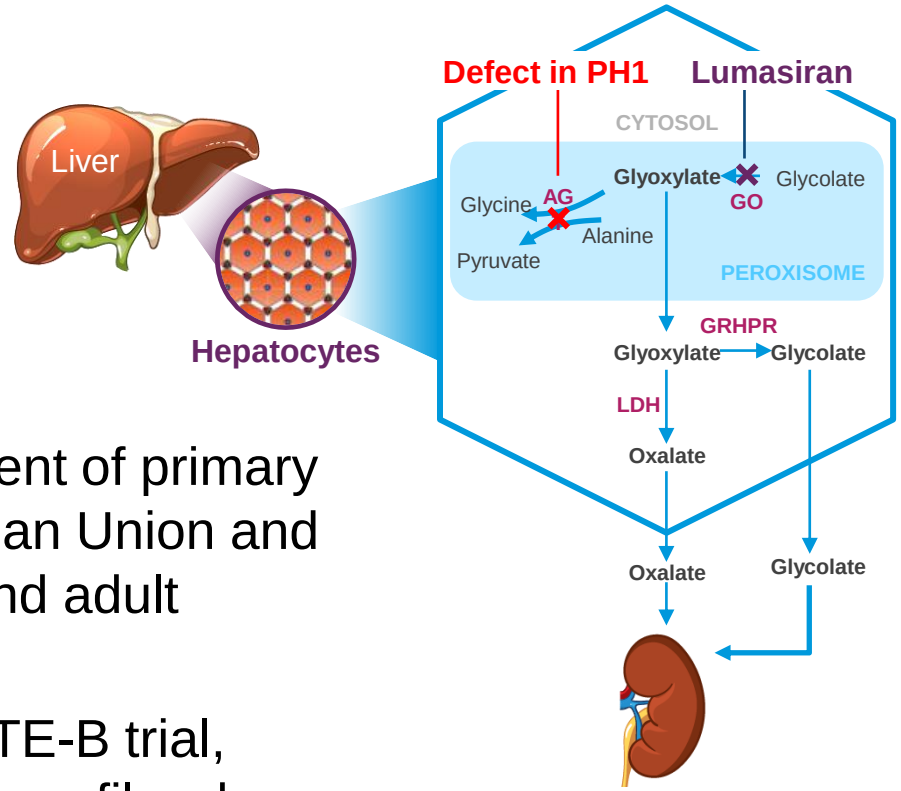
Primary Hyperoxaluria Type 1 and Lumasiran

- PH1 is characterized by excessive hepatic oxalate production due to a deficiency in the hepatic peroxisomal enzyme AGT[1,2]
- Excess oxalate results in recurrent kidney stones, nephrocalcinosis, progressive kidney disease, and multi-organ damage[1,2]
- Lumasiran is an RNAi therapeutic approved for the treatment of primary hyperoxaluria type 1 (PH1) in all age groups in the European Union and for the treatment of PH1 to lower UOx levels in pediatric and adult patients in the United States[3,4]
- In the 6-month primary analysis of the Phase 3 ILLUMINATE-B trial, lumasiran demonstrated efficacy and an acceptable safety profile when given to infants and children age <6 years with PH1[5]



AGT, alanine-glyoxylate aminotransferase; RNAi, ribonucleic acid interference; UOx, urinary oxalate.

1. Cochat P, Rumsby G. *N Engl J Med*. 2013;369:649-58. 2. Danpure CJ. *The Online Metabolic and Molecular Bases of Inherited Disease*. New York, NY: The McGraw-Hill Companies, Inc.; 2019. 3. Oxlumo [package insert]. Cambridge, MA: Alnylam Pharmaceuticals; 2020. 4. Oxlumo [summary of product characteristics]. Amsterdam, Netherlands: Alnylam Netherlands; 2020. 5. Sas DJ, et al. *Genet Med*. 2022:24:654-662.

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ILLUMINATE-B Study Design

- Open-label Phase 3 study (NCT03905694) with up to 60 months of treatment with lumasiran (6-month primary analysis period followed by 54-month extension period)
- **Patient population (N=18)**
  - Infants and children <6 years old with genetically confirmed diagnosis of PH1
  - eGFR >45 mL/min/1.73m^2 if ≥12 months old or normal serum creatinine for age if <12 months old

Lumasiran Weight-Based Dosing		
Patient Weight	**Loading Dose**	**Maintenance Dose**
<10 kg	6 mg/kg once monthly for 3 doses	3 mg/kg once monthly, beginning 1 month after last loading dose
10 to <20 kg	6 mg/kg once monthly for 3 doses	6 mg/kg once every 3 months (quarterly), beginning 1 month after last loading dose
≥20 kg	3 mg/kg once monthly for 3 doses	3 mg/kg once every 3 months (quarterly), beginning 1 month after last loading dose

eGFR, estimated glomerular filtration rate.

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ILLUMINATE-B Key Endpoints

- **Primary endpoint**
  - Percent change in spot UOx:Cr from baseline to Month 6; previously described[1]
- **Secondary endpoints**
  - Absolute and percent change from baseline in UOx excretion
  - Absolute and percent change from baseline in plasma oxalate
  - Proportion of patients with UOx excretion ≤ULN and ≤1.5 × ULN for age
  - Change from baseline in eGFR
- **Exploratory endpoints**
  - Change in frequency of kidney stone events
  - Change in nephrocalcinosis grade

ULN, upper limit of normal; UOx:Cr, urinary oxalate:creatinine ratio.

1. Sas DJ, et al. *Genet Med*. 2022:24:654-662.

Baseline Demographic and Clinical Characteristics

	<10 kg (N=3)	10 to <20 kg (N=12)	≥20 kg (N=3)	All Treated (N=18)
Age at consent, median (range), months	10.1 (3–14)	50.1 (23–72)	62.2 (54–72)	50.1 (3–72)
Age at diagnosis, median, months	0.8	22.7	27.0	16.3
Time from diagnosis to first dose date, median, months	11.6	28.6	46.4	23.5
Genotype,[a] n (%)				
PR/*	0	3 (25)	0	3 (17)
M/M or M/N	1 (33)	8 (67)	1 (33)	10 (56)
N/N	2 (67)	1 (8)	2 (67)	5 (28)
Pyridoxine use, n (%)	2 (67)	7 (58)	2 (67)	11 (61)
Spot UOx:Cr, median (range), mmol/mmol[b]	1.253 (1.126–1.708)	0.453 (0.166–1.205)	0.350 (0.255–0.693)	0.469 (0.166–1.708)
Plasma oxalate, median (range), µmol/L[c]	22.3 (17.2–30.6)	9.6 (6.6–19.9)	11.7 (7.2–18.7)	11.5 (6.6–30.6)
eGFR, median (range), mL/min/1.73m^2 [d]	135 (135–135)	111 (76–174)	90 (65–135)	111 (65–174)

[a]M=missense; N=nonsense; PR=pyridoxine-responsive; *=any genotype of PR, M, or N. PR was defined as NM_000030.3(AGXT):c.508G>A (p.Gly170Arg) or NM_000030.3(AGXT):c.454T>A (p.Phe152Ile). M and N were defined based on a publication by Mandrile et al.[1] [b]1 mmol/mmol=0.796 mg/mg. [c]ULN=12.11 µmol/L for plasma oxalate, as determined based on data from 75 healthy adults. [d]eGFR (mL/min/1.73m^2) was calculated based on the Schwartz Bedside formula[2] for patients ≥12 months; N=16; eGFR was not calculated for 2 patients because their age at baseline was <12 months.

1. Mandrile G, et al. *Kidney Int*. 2014;84:1197-1204. 2. Schwartz GJ, et al. *J Am Soc Nephrol*. 2009;20:629-637.

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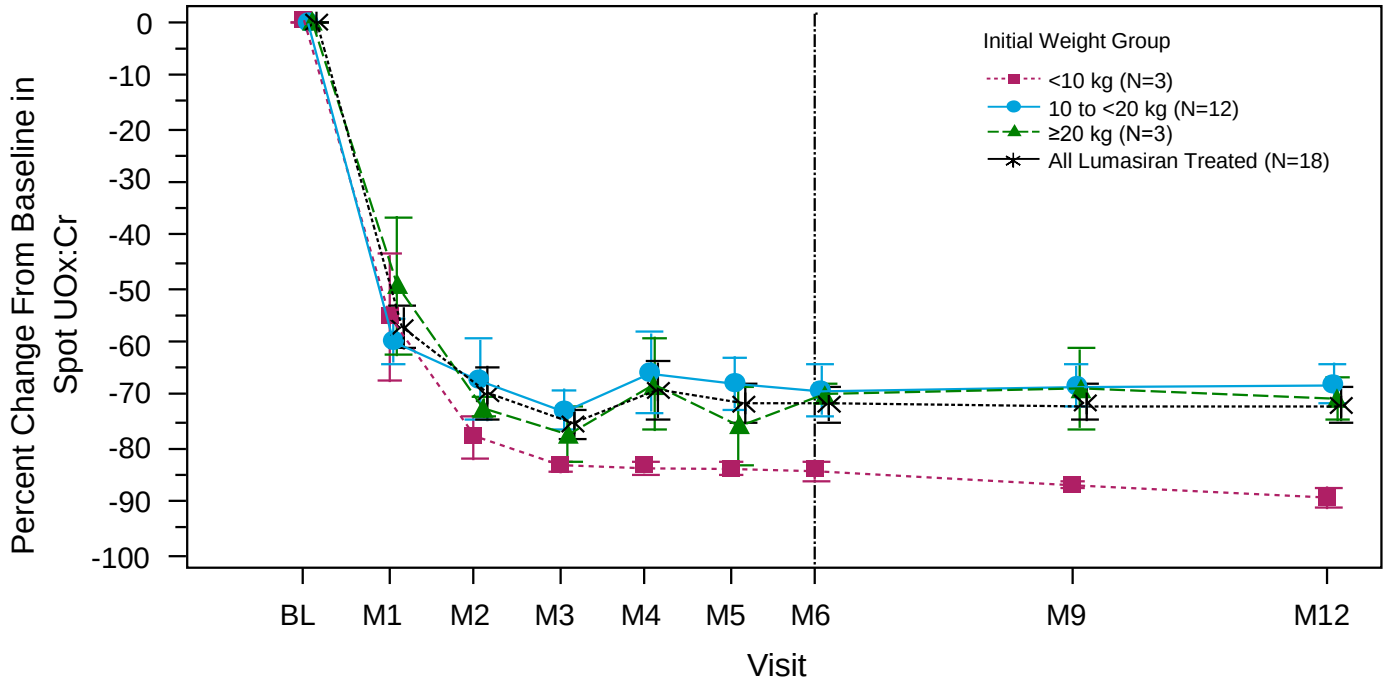
Sustained Reduction in UOx Excretion With Lumasiran Treatment

Lumasiran treatment resulted in sustained reductions in UOx excretion, as measured by spot UOx:Cr

- Mean (SEM) reduction from baseline:
  - 72% (3%) at Month 6
  - 72% (3%) at Month 12
- Mean Month 12 reduction in spot UOx:Cr:
  - 89% in patients <10 kg
  - 68% in patients 10 to <20 kg
  - 71% in patients ≥20 kg

Percent Change in UOx:Cr at Each Visit



No. of Patients:

	BL	M1	M2	M3	M4	M5	M6	M9	M12
■ N=	3	3	3	3	3	3	3	3	3
● N=	12	12	12	12	12	12	12	12	12
▲ N=	3	3	3	3	3	3	3	3	3
✳ N=	18	18	18	18	18	18	18	18	18

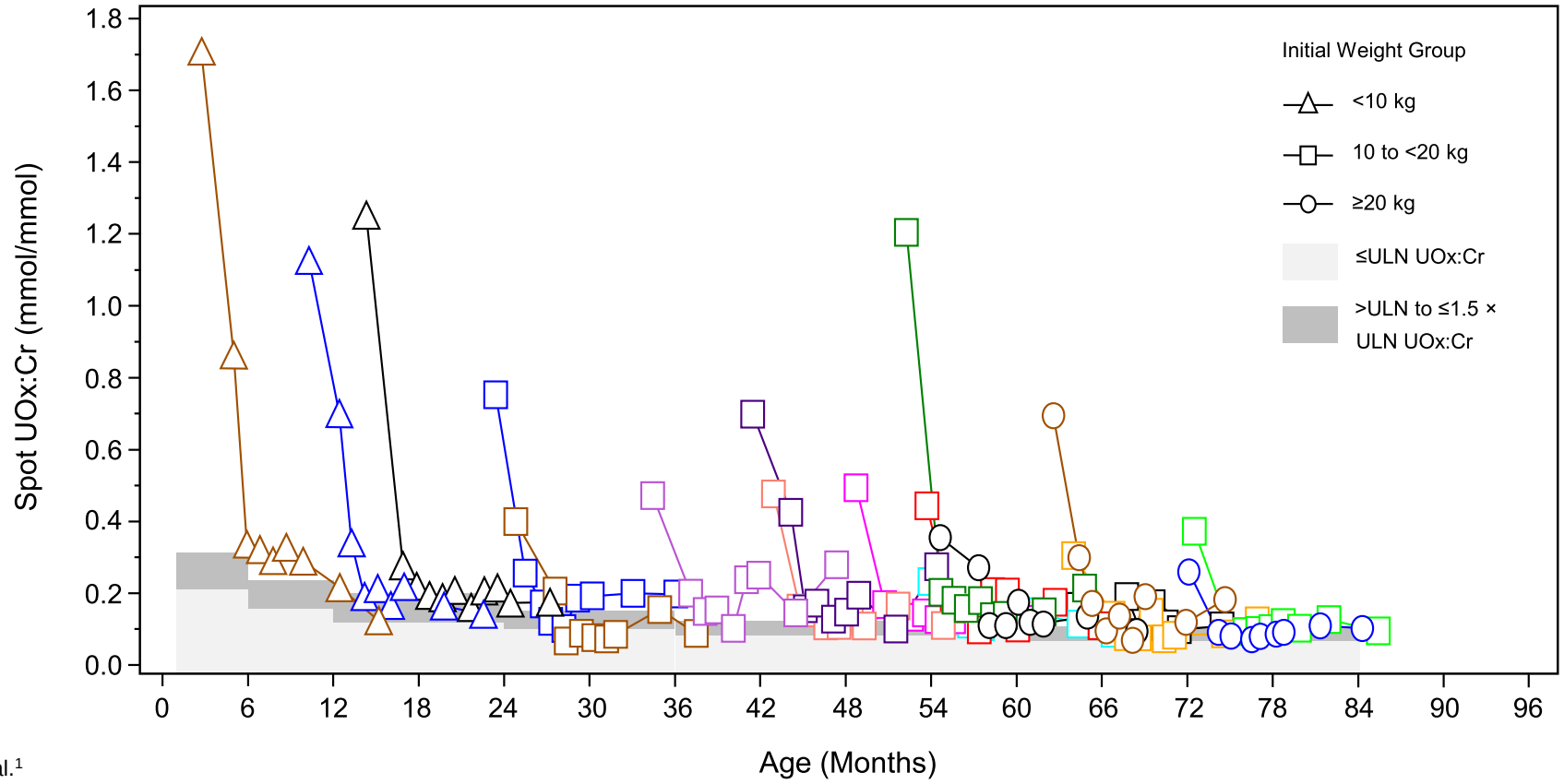
Baseline value was the mean of all assessments collected prior to the first dose of lumasiran.
The vertical line denotes the end of the primary analysis period.
BL, baseline; M, month; SEM, standard error of the mean.

Substantial Reduction in Spot UOx:Cr With Lumasiran Treatment

All patients showed a substantial reduction in spot UOx:Cr regardless of age

- Patients who achieved near normalization (≤1.5 × ULN) of spot UOx:Cr
  - 9 patients at Month 6
  - 10 patients at Month 12
- Patients who achieved normalization (≤ULN) of spot UOx:Cr
  - 1 patient at Month 6
  - 2 patients at Month 12

Actual Spot UOx:Cr Values by Age



1 mmol/mmol=0.796 mg/mg.

Age-dependent ULN values are based on a publication by Matos et al.[1]

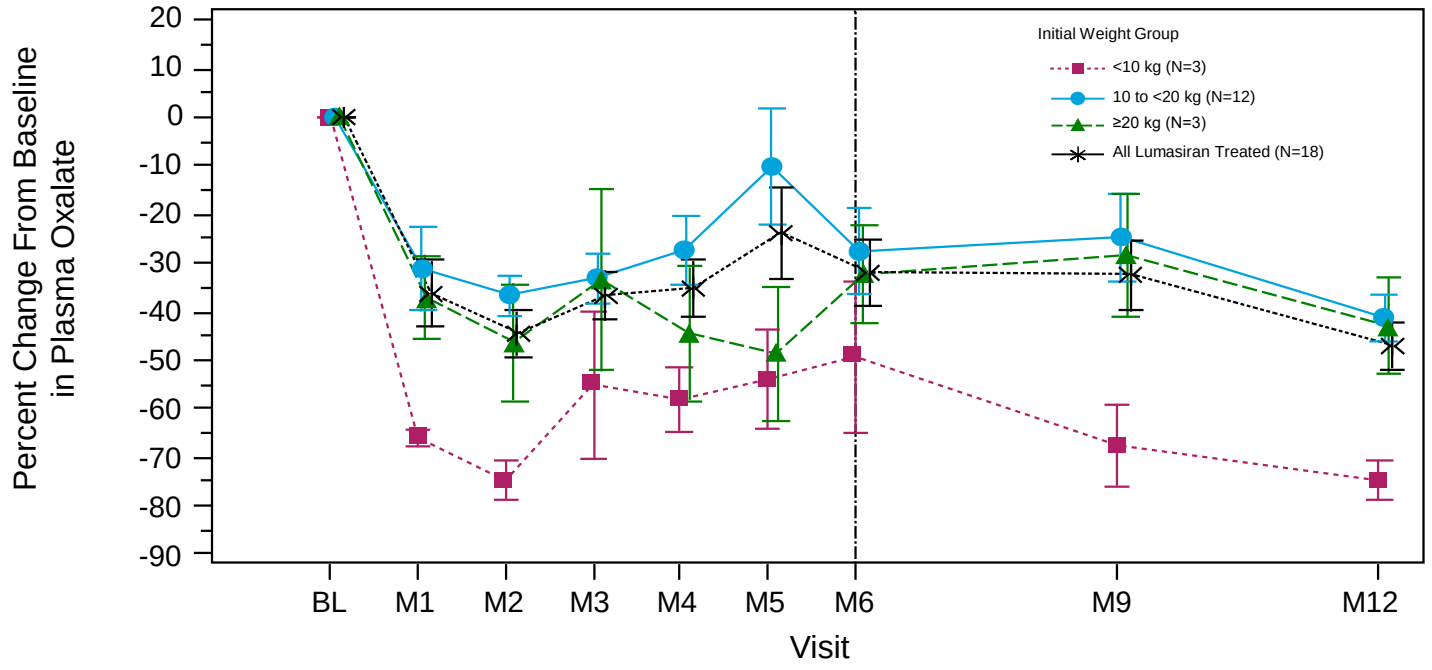
1. Matos V, et al. *Am J Kidney Dis*. 1999;34:e1.

Sustained Reduction in POx With Lumasiran Treatment

Plasma oxalate levels were reduced after 6 months of lumasiran treatment, and the reductions were sustained at Month 12 across all weight subgroups

- Mean (SEM) reduction in POx from baseline:
  - 32% (7%) at Month 6
  - 47% (5%) at Month 12
- Mean (SEM) POx level:
  - 13.24 (1.53) µmol/L at baseline
  - 8.21 (0.94) µmol/L at Month 6
  - 5.91 (0.19) µmol/L at Month 12

Percent Change in POx at Each Visit



No. of Patients:

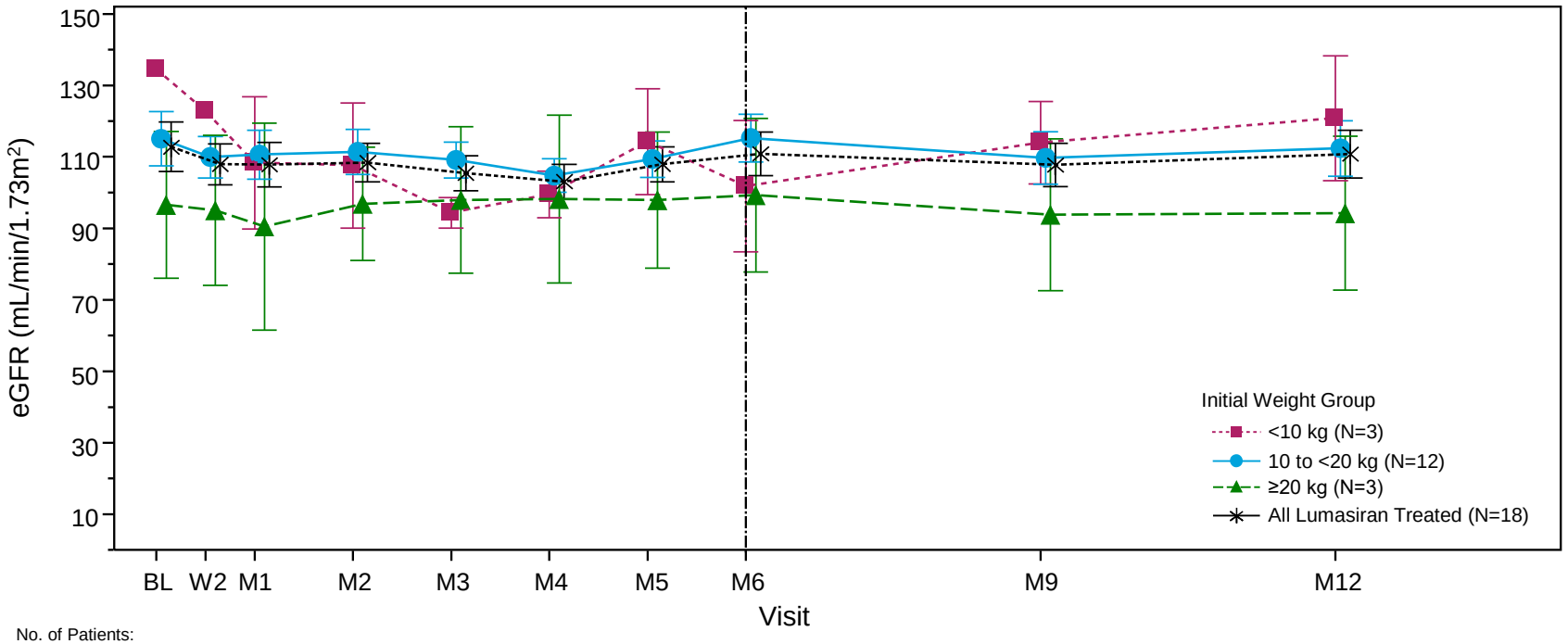
	BL	M1	M2	M3	M4	M5	M6	M9	M12
N=	3	2	3	3	3	3	3	3	3
N=	12	12	12	12	12	12	12	12	12
N=	3	3	3	3	3	3	3	3	3
N=	18	17	18	18	18	18	18	18	18

Baseline value was the mean of all assessments collected prior to the first dose of lumasiran.
The vertical line denotes the end of the primary analysis period.
ULN=12.11 µmol/L for POx, as determined based on data from 75 healthy adults.

eGFR Remained Stable With Lumasiran Treatment

Mean (SEM) eGFR remained stable through Month 12

Actual eGFR Values at Each Visit



No. of Patients:

	BL	W2	M1	M2	M3	M4	M5	M6	M9	M12
N=	1	1	2	2	2	2	2	2	3	3
N=	12	12	12	12	12	12	12	12	12	12
N=	3	3	2	3	3	3	3	3	3	3
N=	16	16	16	17	17	17	17	17	18	18

Baseline value was the last non-missing value collected prior to the first dose of lumasiran.
The vertical line denotes the end of the primary analysis period.
eGFR was calculated in patients ≥12 months old at assessment. eGFR was not calculated for 2 patients because their age at baseline was <12 months, but their serum creatinine remained stable (not shown).

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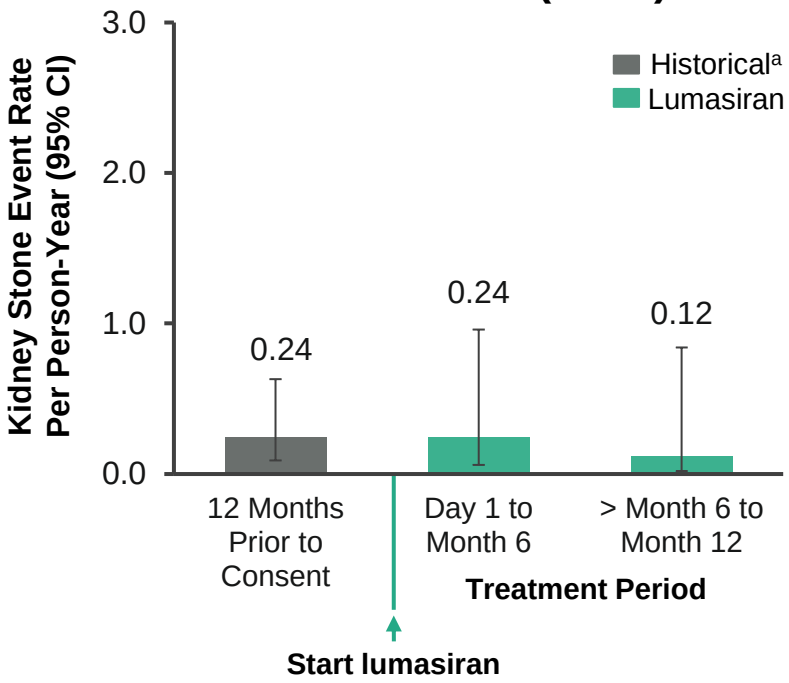
Low Rate of Kidney Stone Events and Improved Nephrocalcinosis Grade With Lumasiran

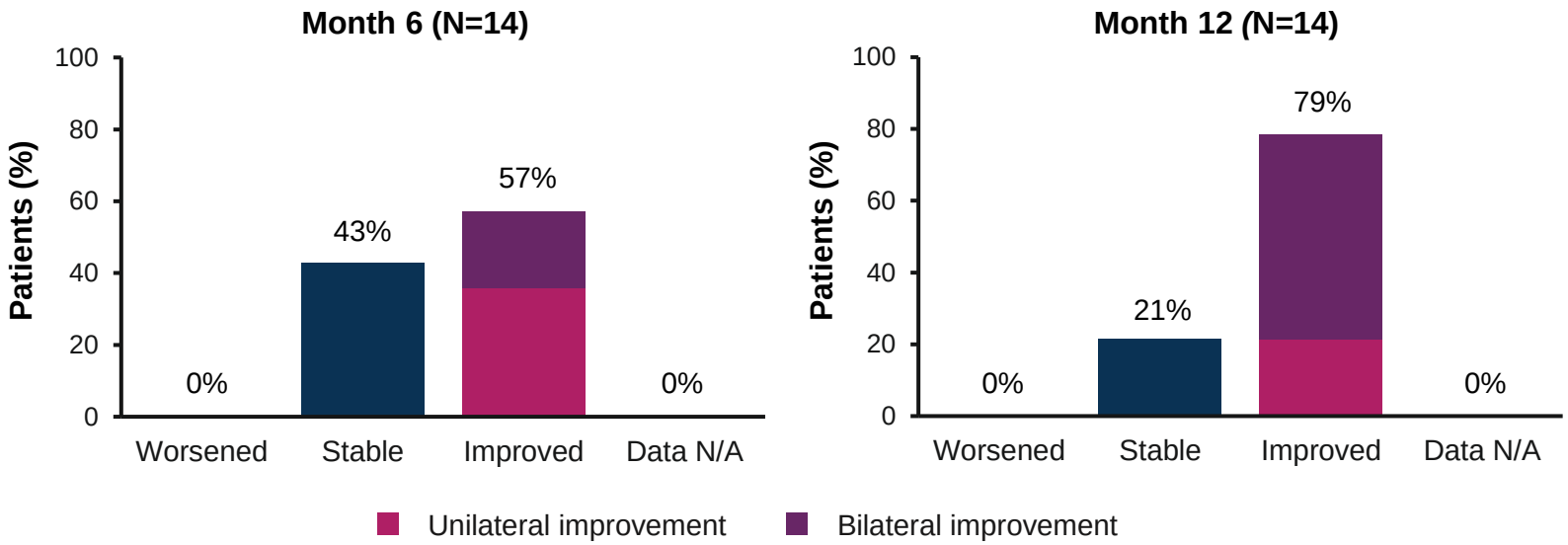
Kidney Stone Events

Lumasiran (N=18)



Change in Medullary Nephrocalcinosis Grade

Patients With Nephrocalcinosis at Baseline[b,c]



[a]Historical group: patient-reported history of kidney stone events; annualized rate was not calculated for patients <6 months old.
[b]Indeterminate (one side improves and the other side worsens) is not graphed because there were 0 cases.
[c]Of the 4 patients without nephrocalcinosis at baseline, 4 remained stable at Month 6; at Month 12, 3 remained stable and data were unavailable for 1 patient.
N/A, not available.

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Safety Profile of Lumasiran Remained Acceptable

Event, n (%)	Patients			
	<10 kg (N=3)	10 to <20 kg (N=12)	≥20 kg (N=3)	All Treated (N=18)
AEs	3 (100)	12 (100)	3 (100)	18 (100)
Treatment-related AEs	0	2 (17)	2 (67)	4 (22)
AEs leading to treatment discontinuation	0	0	0	0
AEs leading to study withdrawal	0	0	0	0
Serious AEs	0	0	1 (33)[a]	1 (6)[a]
Severe AEs	0	0	0	0
Death	0	0	0	0

- Median (range) exposure was 17.8 (12.7–20.5) months
- The most common lumasiran-related AEs were mild, transient injection-site reactions (3 patients [17%]); symptoms included erythema, discoloration, and pain at the injection site
- There were no clinically relevant changes in laboratory measures, vital signs, physical examinations, or electrocardiograms related to lumasiran

Safety data from first dose of lumasiran to data cutoff date of February 3, 2021.
[a]One 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 has been reported previously.[1]
AE, adverse event.
1. Sas DJ, et al. *Genet Med*. 2022:24:654-662.

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Conclusions

- Lumasiran treatment resulted in sustained reductions in urinary and plasma oxalate through Month 12
- Given the causal role of UOx in kidney damage, it is encouraging that patients maintained stable kidney function and low rates of kidney stone events and most patients had improvement in nephrocalcinosis grade
- Lumasiran demonstrated an acceptable safety profile in infants and young children with PH1
  - The most common lumasiran-related AEs were mild, transient injection-site reactions

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