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Lumasiran Demonstrated Comparable Oxalate Reduction and Safety in Children and Adults with Primary Hyperoxaluria Type 1

Hadas Shasha-Lavsky[1], Sander F. Garrelfs[2], David J. Sas[3], John C. Lieske[4], Taylor Ngo[5], Nune Makarova[5], John M. Gansner[5], Tracy L. McGregor[5], Yaacov Frishberg[6]

[1]Pediatric Nephrology Unit, Galilee Medical Center, Nahariya, Israel; [2]Department of Pediatric Nephrology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; [3]Division of Pediatric Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA; [4]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA; [5]Alnylam Pharmaceuticals, Cambridge, MA, USA; [6]Division of Pediatric Nephrology, Shaare Zedek Medical Center, Jerusalem, Israel

Disclosures

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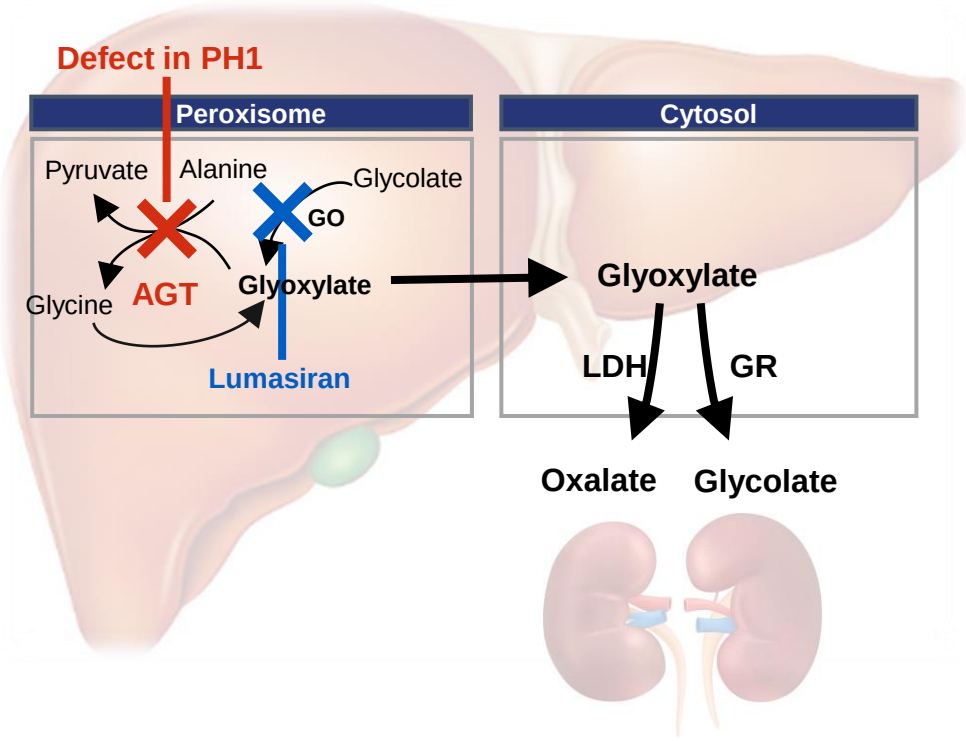
Primary Hyperoxaluria Type 1 and Lumasiran

- PH1 is a rare, progressive, genetic disorder characterized by hepatic overproduction of oxalate due to a deficiency in the liver peroxisomal enzyme AGT[1,2]
- Excess oxalate excreted via the kidneys leads to recurrent kidney stones, nephrocalcinosis, progressive kidney failure, and multiorgan damage from systemic oxalosis[1,2]
- Lumasiran is a subcutaneously administered RNAi therapeutic approved for the treatment of PH1 in all age groups[3,4]
  - Lumasiran decreases hepatic oxalate production by inhibiting the production of GO[5]
- In the Phase 3 ILLUMINATE-A (NCT03681184) and ILLUMINATE-B (NCT03905694) studies, lumasiran resulted in substantial reductions in urinary oxalate with an acceptable safety profile in patients with PH1 from infants to adults[6,7]



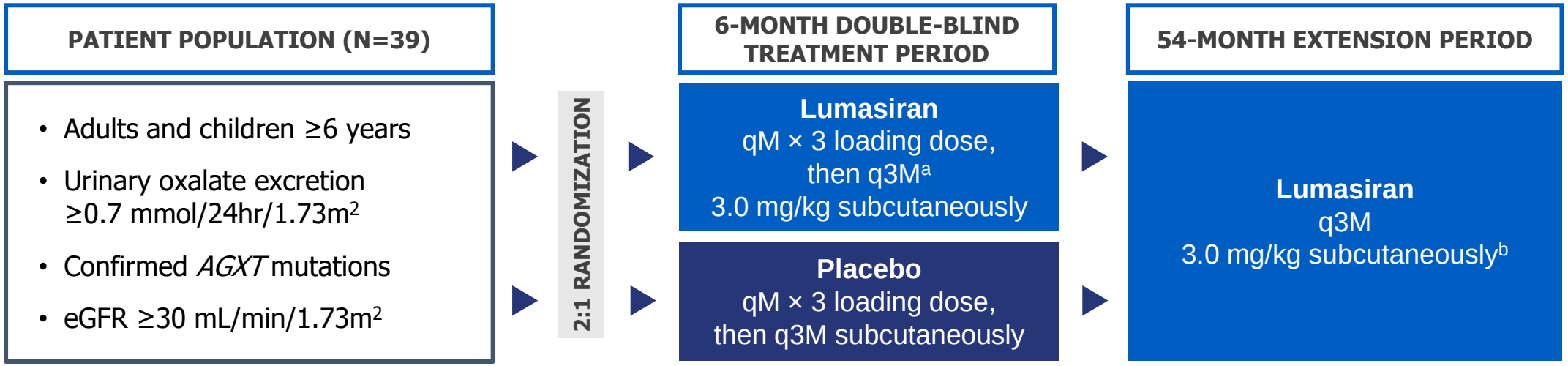
Here we present a comparison of the efficacy and safety of lumasiran in children versus adults with PH1 using pooled data from ILLUMINATE-A and ILLUMINATE-B

1. Cochat P, Rumsby G. *N Engl J Med.* 2013;369:649-58. **2.** Milliner DS, et al. *GeneReviews®*. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1283. **3.** OXLUMO (lumasiran) [prescribing information]. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; 2020. **4.** OXLUMO (lumasiran) [summary of product characteristics]. Alnylam Netherlands B.V.; 2020. **5.** Liebow A, et al. *J Am Soc Nephrol.* 2017;28:494-503. **6.** Garrelfs S, et al. *N Engl J Med.* 2021;384:1216-26. **7.** Deschênes G, et al. Presented at: American Society Nephrology Annual Meeting; October 2020; virtual.

AGT, alanine-glyoxylate aminotransferase; GO, glycolate oxidase; GR, glyoxylate reductase/hydroxypyruvate reductase; LDH, lactate dehydrogenase; PH1, primary hyperoxaluria type 1; RNAi, ribonucleic acid interference.

ILLUMINATE-A Study Design

Randomized, Double-blind, Placebo-controlled, Phase 3 Trial in Adults and Children ≥6 Years



- Treatment arms were stratified at randomization based upon mean 24-hour urinary oxalate[c] from the first 2 valid samples collected during screening (≤1.70 mmol/24hr/1.73m² vs >1.70 mmol/24hr/1.73m²)
- Oxalate was measured with a validated liquid chromatography-tandem mass spectrometry assay

- **Primary endpoint met: Lumasiran reduced 24-hour urinary oxalate from baseline to Month 6[d] by 53.5% relative to placebo ($P=1.7\times10^{-14}$), with a LS mean reduction of 65.4% in the lumasiran group and 11.8% in the placebo group[1]**

ILLUMINATE-A: NCT03681184; EudraCT Number: 2018-001981-40. [a]Maintenance dose of 3.0 mg/kg (q3M) started 1 month after last loading dose. [b]Patients randomized to placebo received loading doses of 3.0 mg/kg lumasiran at Months 6, 7, and 8; patients randomized to lumasiran received a maintenance dose of 3.0 mg/kg lumasiran at Month 6, and placebo at Months 7 and 8. [c]1.70 mmol/24hr/1.73m² = 153 mg/24hr/1.73m² (1 mmol/24hr/1.73m² = 90 mg/24hr/1.73m²). [d]Averaged over Months 3 through 6.

1. Garrelfs SF, et al. *N Engl J Med.* 2021;384:1216-26.

eGFR, estimated glomerular filtration rate; LS, least-squares; q3M, once every 3 months; qM, once monthly; qM × 3, once monthly for 3 consecutive months.

ILLUMINATE-B Study Design

Single-arm, Open-label, Phase 3 Trial in Infants and Children <6 Years

PATIENT POPULATION (N=18)

- Infants and children <6 years
- Elevated urinary oxalate: creatinine ratio
- Confirmed AGXT mutations
- eGFR >45 mL/min/1.73m^2 if ≥12 months old; normal serum creatinine if <12 months old

OPEN LABEL

6-MONTH TREATMENT PERIOD

Lumasiran
qM × 3 loading dose, then qM or q3M maintenance dosing dependent on weight[a]

54-MONTH EXTENSION PERIOD

Lumasiran
qM or q3M maintenance dosing dependent on weight[a]

- Oxalate was measured with a validated liquid chromatography-tandem mass spectrometry assay
- **Positive results demonstrated for the primary endpoint: Lumasiran led to a LS mean reduction of 72.0% in spot urinary oxalate: creatinine ratio from baseline to Month 6[b,1]**

ILLUMINATE-B: NCT03905694; EudraCT Number: 2018-004014-17.

[a]Patients <10 kg received loading doses 6.0 mg/kg qM for 3 months and then maintenance doses 3.0 mg/kg qM; patients ≥10 to <20 kg received loading doses 6.0 mg/kg qM for 3 months and then maintenance doses 6.0 mg/kg q3M; patients ≥20 kg received loading doses 3.0 mg/kg qM for 3 months and then maintenance doses 3.0 mg/kg q3M. Maintenance dose was started 1 month after last loading dose. [b]Averaged over Months 3 through 6.

1. Deschênes G, et al. Presented at: American Society Nephrology Annual Meeting; October 2020; virtual.

eGFR, estimated glomerular filtration rate; LS, least-squares; q3M, once every 3 months; qM, once monthly; qM × 3, once monthly for 3 consecutive months.

Pooled Analysis

- Efficacy and safety data from ILLUMINATE-A and ILLUMINATE-B, including urinary oxalate, plasma oxalate, eGFR, and AEs were pooled and assessed according to age <18 (N=40) or ≥18 years (N=17)
  - Percent reduction from baseline to Month 6 in urinary oxalate was evaluated by 24-hour urinary oxalate corrected for BSA and urinary oxalate:creatinine ratio from spot urine samples
  - Percent reduction from baseline to Month 6 in plasma oxalate was evaluated in all patients with a baseline plasma oxalate ≥1.5 x LLOQ (5.55 µmol/L)[a]
  - eGFR was calculated over time based on the Modification of Diet in Renal Disease formula for patients ≥18 years of age and the Schwartz Bedside Formula for patients ≥12 months to <18 years of age[1,2]
- Descriptive statistics were used to summarize all available data from 57 patients with PH1, ages 4 months to 60 years, during the initial 6 months of treatment with lumasiran
  - ILLUMINATE-A: Data available for 26 patients randomized to lumasiran and 13 patients initially randomized to placebo who crossed over to lumasiran and completed the first 6 months of lumasiran during the extension period
  - ILLUMINATE-B: Data available for 18 patients treated with lumasiran during the 6-month primary analysis period

[a]Values below LLOQ were assigned a value of 5.55 µmol/L.
AEs, adverse events; BSA, body surface area; eGFR, estimated glomerular filtration rate; LLOQ, lower limit of quantitation; PH1, primary hyperoxaluria type 1.

1. Levey AS, et al. *Ann Intern Med.* 2009;150:604-12. **2.** Schwartz GJ, et al. *J Am Soc Nephrol.* 2009;20:629-37.

Baseline Urinary and Plasma Oxalate Levels

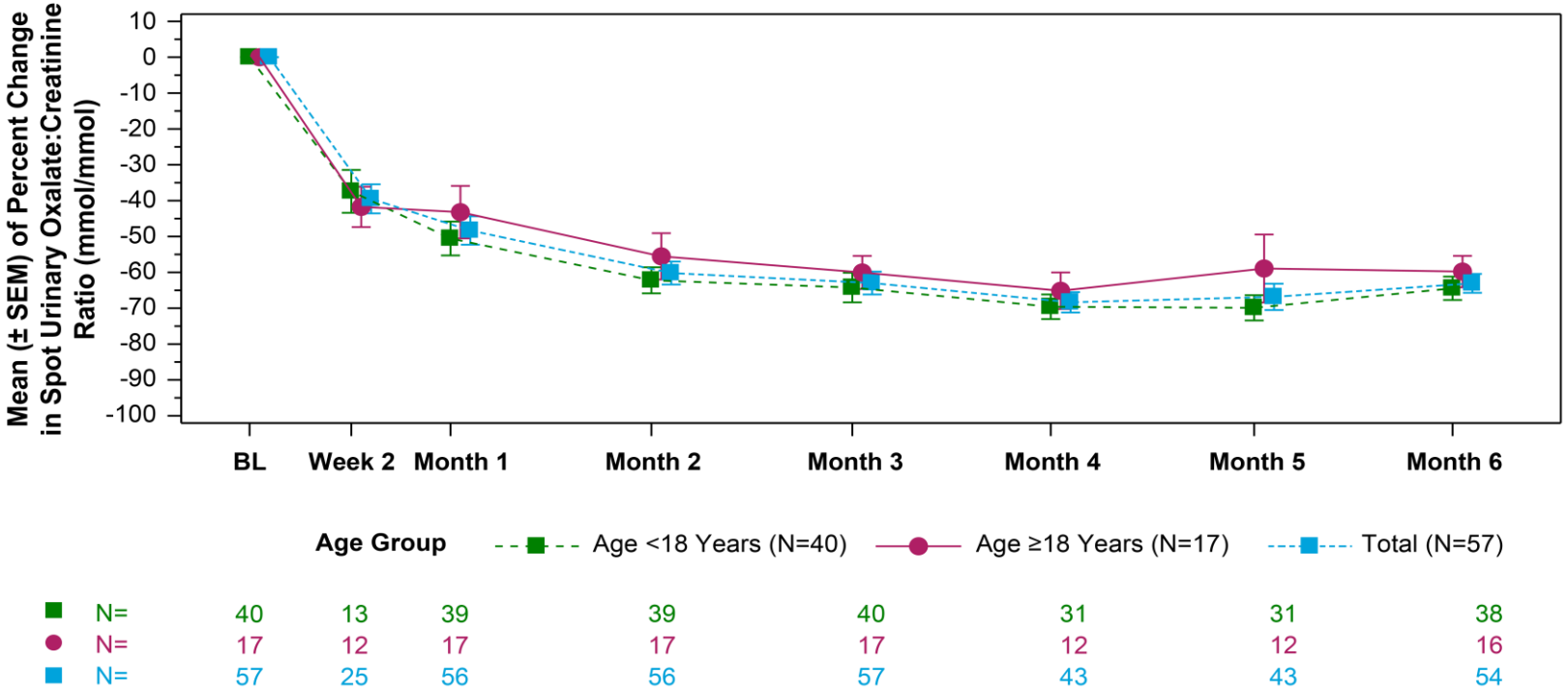
Measurement	Patients		
	<18 Years N=40	≥18 Years N=17	Total N=57
Spot Urinary Oxalate:Creatinine Ratio, mean (SD), mmol/mmol	N=40	N=17	N=57
	0.423 (0.351)	0.175 (0.078)	0.349 (0.317)
24-hour Urinary Oxalate, mean (SD), mmol/24hr/1.73m^2	N=27	N=17	N=44
	1.85 (0.72)	1.73 (0.48)	1.80 (0.63)
Plasma Oxalate,[a] mean (SD), µmol/L	N=31	N=15	N=46
	16.5 (7.5)	15.9 (6.6)	16.3 (7.2)
eGFR, mean (SD), mL/min/1.73m^2	N=38	N=17	N=55
	97.9 (29.5)	74.5 (26.4)	90.7 (30.4)

[a]The plasma oxalate analysis set included all patients with a baseline plasma oxalate level ≥1.5× LLOQ (5.55 µmol/L). Values below LLOQ were assigned a value of 5.55 µmol/L.
eGFR, estimated glomerular filtration rate; LLOQ, lower limit of quantitation; SD, standard deviation.

Percent Change in Spot Urinary Oxalate: Creatinine Ratio

Rapid and Sustained Decrease in Urinary Oxalate in Both Age Groups

- A similar time course and magnitude of reduction was seen in patients <18 years and ≥18 years



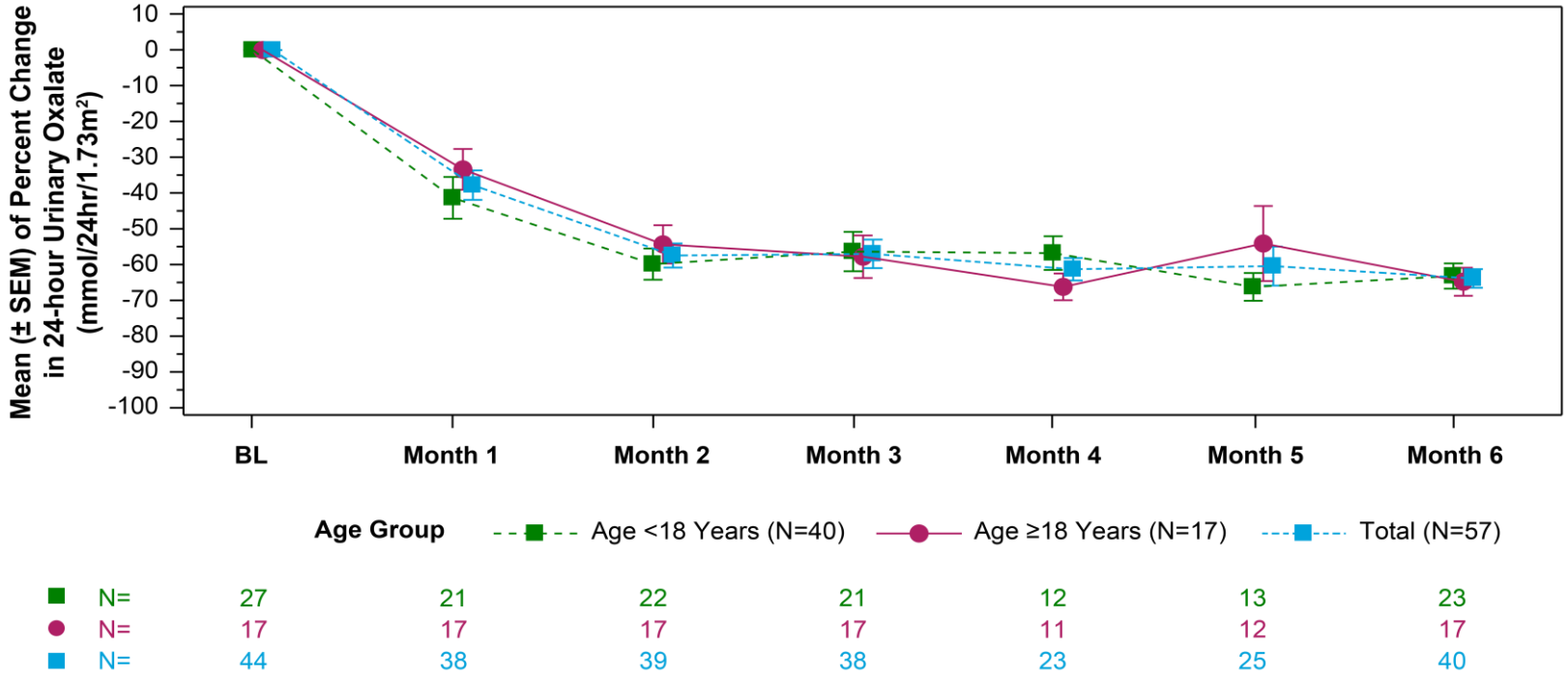
Mean (SEM) percent reduction from baseline to Month 6		
<18 Years N=38	**≥18 Years N=16**	**Total N=54**
64.5% (3.3)	59.8% (4.4)	63.1% (2.6)

BL, baseline; SEM, standard error of the mean.

Percent Change in 24-hour Urinary Oxalate

Rapid and Sustained Decrease in Urinary Oxalate in Both Age Groups

- A similar time course and magnitude of reduction was seen in patients <18 years and ≥18 years



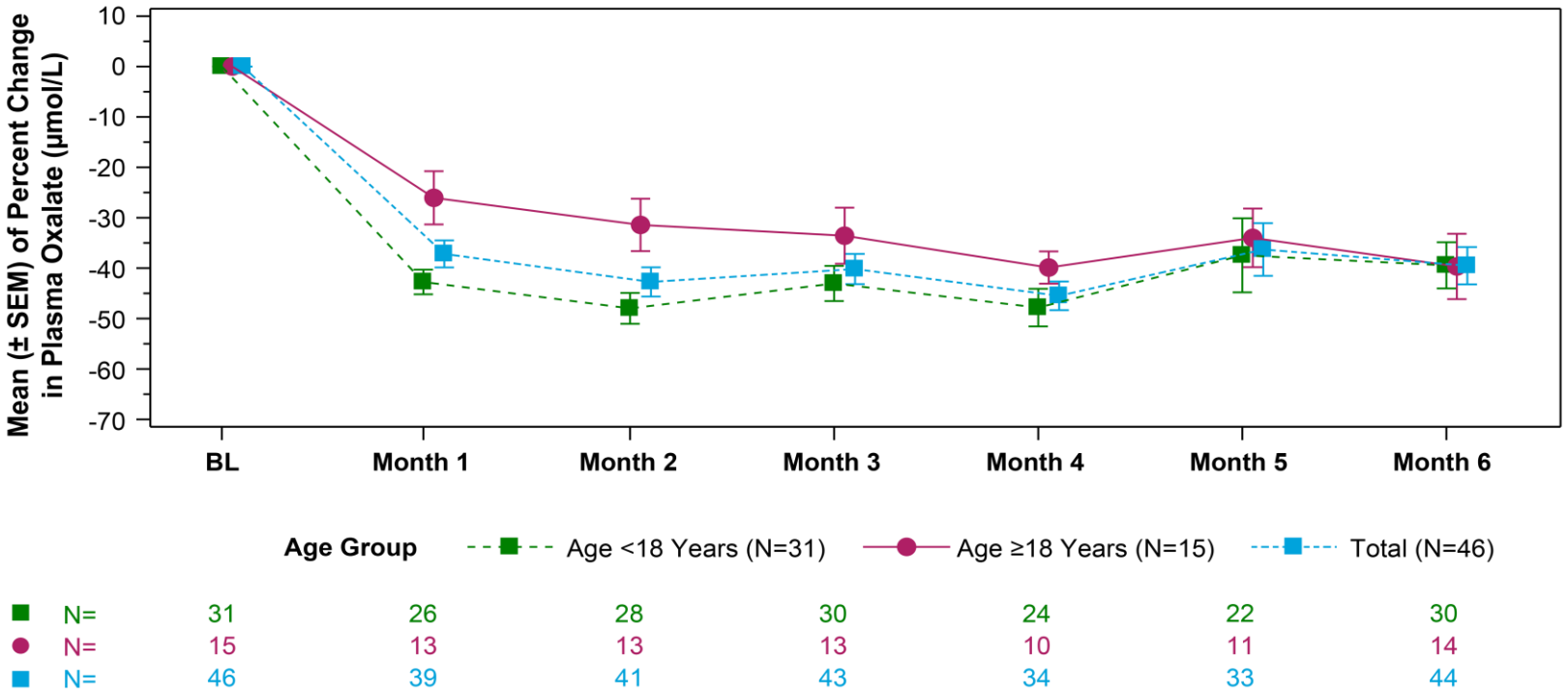
Mean (SEM) percent reduction from baseline to Month 6		
<18 Years N=23	**≥18 Years N=17**	**Total N=40**
63.2% (3.5)	64.8% (3.9)	63.8% (2.6)

BL, baseline; SEM, standard error of the mean.

Percent Change in Plasma Oxalate[a]

Reductions in Plasma Oxalate Observed in Both Age Groups

- The overall mean reduction from baseline to Month 6 was 39.5% across all ages, with similar reductions in patients <18 years and ≥18 years



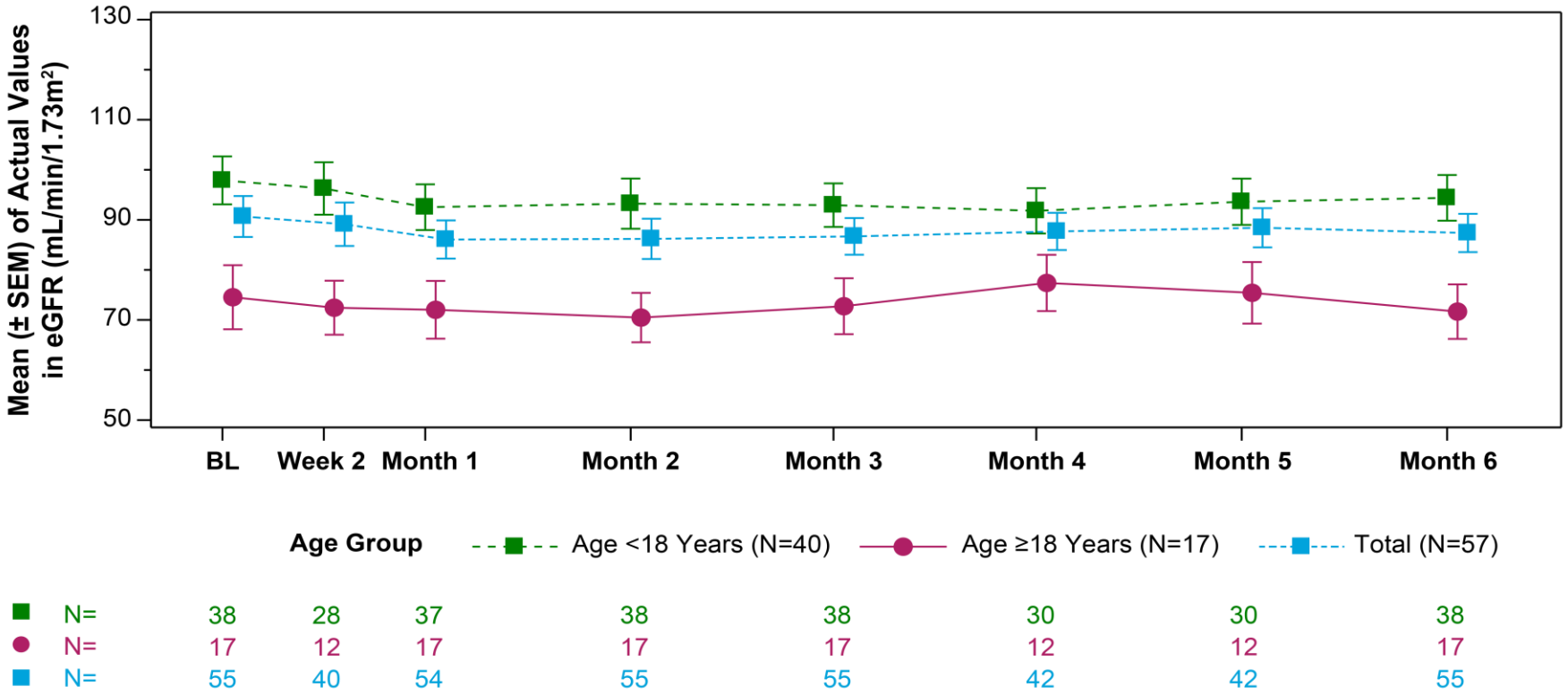
Mean (SEM) percent reduction from baseline to Month 6		
<18 Years N=30	**≥18 Years N=14**	**Total N=44**
39.4% (4.6)	39.7% (6.5)	39.5% (3.7)

[a]The plasma oxalate analysis set included all patients with a baseline plasma oxalate level ≥1.5× LLOQ (5.55 µmol/L). Values below LLOQ were assigned a value of 5.55 µmol/L.
BL, baseline; LLOQ, lower limit of quantitation; SEM, standard error of the mean.

Change in eGFR

eGFR Remained Stable in Both Age Groups

- While the baseline kidney function differed between age groups, eGFR remained stable in patients <18 years and ≥18 years during the 6 months of treatment with lumasiran



BL, baseline; eGFR, estimated glomerular filtration rate; SEM, standard error of the mean.

Safety of Lumasiran During Initial 6 Months of Treatment

Safety Profile in Pediatric and Adult Patients

- The 57 patients received 227 doses of lumasiran, with a cumulative exposure of 27.1 patient-years
- AEs were reported in 86% of all patients, 88% of patients <18 years, and 82% of patients ≥18 years; all were mild or moderate in severity
- One serious AE of viral infection, not related to lumasiran, was reported in one patient <18 years
- Mild, transient injection-site reactions were the most common AEs related to lumasiran, experienced by 30% of all patients, 23% of patients <18 years, and 47% of patients ≥18 years
  - Symptoms of injection-site reactions reported in ≥2 patients included: erythema, pain, pruritus, discomfort, and swelling
- There were no treatment interruptions or discontinuations related to lumasiran and no deaths

Patients with Event, N (%)	Lumasiran for 6 Months		
	<18 Years (N=40)	≥18 Years (N=17)	Total (N=57)
AEs	35 (88)	14 (82)	49 (86)
AEs occurring in ≥10% of patients in either group			
Injection-site reactions[a]	9 (23)	8 (47)	17 (30)
Rhinitis	8 (20)	0	8 (14)
Pyrexia	7 (17)	0	7 (12)
Abdominal pain[b]	6 (15)	1 (6)	7 (12)
Upper respiratory tract infection	5 (13)	1 (6)	6 (11)
Urinary tract infection	1 (3)	2 (12)	3 (5)
Headache	4 (10)	0	4 (7)
Serious AEs	1 (3)[c]	0	1 (2)[c]
Severe AEs	0	0	0
AEs leading to treatment interruption	1 (3)	2 (12)	3 (5)
AEs leading to treatment discontinuation	0	1 (6)[d]	1 (2)[d]
AEs leading to study discontinuation	0	0	0
Death	0	0	0

[a]Injection-site reactions include: injection-site erythema, injection-site pain, injection site pruritus, injection-site discomfort, injection site swelling, injection site discolouration, injection site exfoliation, injection site rash, and injection-site reaction. [b]Abdominal pain includes: abdominal discomfort, abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal tenderness. [c]This patient had a serious AE of viral infection; this event was not considered to be related to lumasiran. [d]This patient had AEs of fatigue and disturbance in attention that were not considered to be related to lumasiran.

AE, adverse event.

Conclusions

- Lumasiran led to substantial and clinically meaningful urinary and plasma oxalate reductions, which were similar in pediatric and adult patients with PH1 enrolled in the Phase 3 studies ILLUMINATE-A and ILLUMINATE-B
- Reductions in urinary oxalate were similar between spot urine samples and 24-hour urine collections
- Lumasiran demonstrated an acceptable safety profile in both pediatric and adult patients

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PH1, primary hyperoxaluria type 1.