ILLUMINATE-A, a Phase 3 Study of Lumasiran, an Investigational RNAi Therapeutic, in Children and Adults with Primary Hyperoxaluria Type 1 (PH1)

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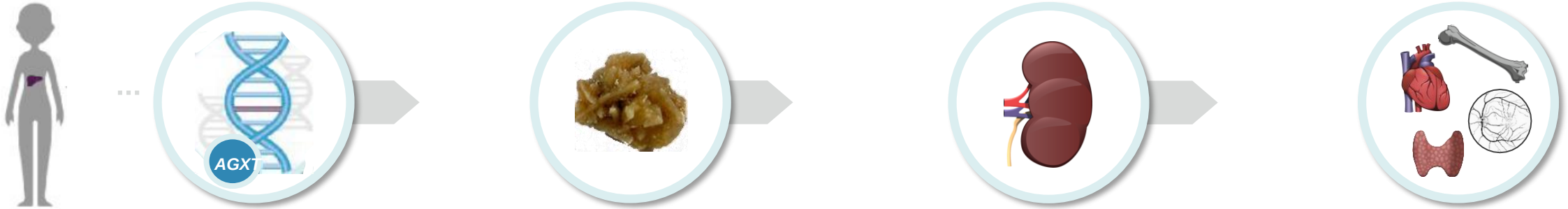
ILLUMINATE-A

Primary Hyperoxaluria Type 1

Progressive disease mediated by hepatic overproduction of oxalate



Homozygous or compound heterozygous *AGXT* mutations lead to hepatic AGT deficiency and overproduction of oxalate[1,2]

Excess oxalate results in insoluble calcium oxalate crystals, leading to recurrent kidney stones, nephrocalcinosis, and kidney injury[1,2]

As renal function declines due to progressive disease, oxalate elimination is further compromised and plasma oxalate increases[1,2]

In advanced disease, patients manifest systemic oxalosis, which can be life-threatening[1,2]

- Diagnosed prevalence: ~1 to 3 cases per 1 million population[1]
- >40% of patients with PH1 present with ESKD at diagnosis[3]
- Without effective treatment, PH1 often leads to death from renal failure or complications of oxalosis[1,2]
- Management options include hyperhydration, crystallization inhibitors, symptomatic care for kidney stones, and pyridoxine (vitamin B6) in some patients[1,2]
- Dual liver–kidney transplantation is frequently necessary to normalize hepatic oxalate production and restore renal function[1,2]
- No approved pharmacologic therapies

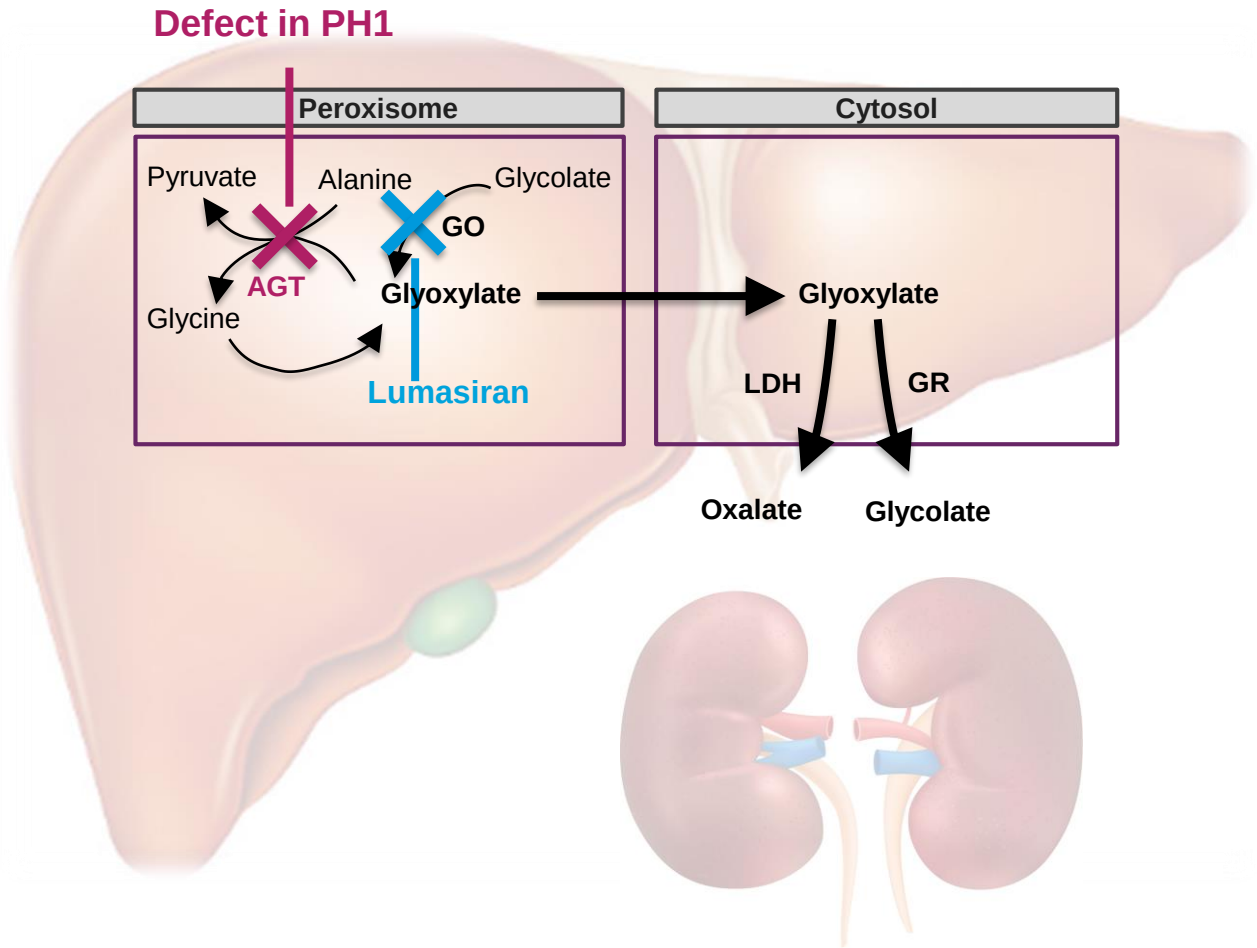
AGT, alanine-glyoxylate aminotransferase; AGXT, alanine-glyoxylate aminotransferase gene; ESKD, end-stage kidney disease; PH1, primary hyperoxaluria type 1

1. Cochat & Rumsby. N Engl J Med 2013;369:649–58; 2. Milliner et al. GeneReviews® [updated November 30, 2017]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1283 (accessed May 12, 2020);
3. Mandrile et al. Kidney Int 2014:86:1197–204

Lumasiran

Investigational RNAi therapeutic for PH1

- RNAi is a natural pathway involved in regulation of gene expression by targeting mRNA[1]
- Lumasiran targets the mRNA for *HAO1*, which encodes GO in the liver[1]
- Decreased production of GO reduces hepatic oxalate production, lowering oxalate levels[1]
- Early phase studies of lumasiran demonstrated an encouraging safety profile and a substantial reduction in urinary oxalate which is expected to confer clinical benefit in patients with PH1[2–4]
- ILLUMINATE-A is a randomized, double-blind, placebo-controlled Phase 3 study, designed to evaluate efficacy and safety of lumasiran in children and adults with PH1



AGT, alanine-glyoxylate aminotransferase; GO, glycolate oxidase; GR, glyoxylate reductase/hydroxypyruvate reductase; *HAO1*, hydroxyacid oxidase gene 1; LDH, lactate dehydrogenase; mRNA, messenger RNA; PH1, primary hyperoxaluria type 1; RNAi, RNA interference

1. Liebow et al. *J Am Soc Nephrol* 2017;28:494–503; 2. Frishberg et al. *Oxalosis & Hyperoxaluria International Workshop* 2019. Poster; 3. Hulton et al. *ASN Annual Meeting* 2019. Poster; 4. Milliner et al. *Clin J Am Soc Nephrol* 2020; doi:10.2215/CJN.13821119

ILLUMINATE-A

Lumasiran Clinical Development

Clinical pharmacology study → **Efficacy and safety studies in patients with PH1**

Phase 1/2

STUDY 001

Healthy volunteers

Part A: single ascending dose, n=32

Primary endpoint
- Safety

COMPLETED

PH1 patients

Part B: multiple ascending doses, n=20
- 6–64 years old
- eGFR >45 mL/min/1.73 m^2
- Up to 3 doses

Primary endpoint
- Safety

COMPLETED

→

STUDY 002
OLE
n=20
Up to 54 months' dosing

Phase 3

ILLUMINATE-A

PH1 patients

Double-blind, placebo-controlled, n=39
- ≥6 years old
- eGFR ≥30 mL/min/1.73 m^2
- 6-month dosing

Primary endpoint
- Percent change in 24 hr urinary oxalate excretion from baseline through month 6

COMPLETED

EXTENSION PERIOD
Up to 54 months' dosing

ILLUMINATE-B

PH1 patients

Single-arm, open-label n=18
- <6 years old
- eGFR[a] >45 mL/min/1.73 m^2 if ≥12 months old
- 6-month dosing

Primary endpoint
- Percent change from baseline in urinary oxalate excretion through month 6

COMPLETED ENROLLMENT

EXTENSION PERIOD
Up to 54 months' dosing

ILLUMINATE-C

PH1 patients

Single-arm, open-label n=16
- All ages
- eGFR[b] ≤45 mL/min/1.73 m^2
- 6-month dosing

Primary endpoint
- Percent change in plasma oxalate from baseline to month 6

ENROLLING

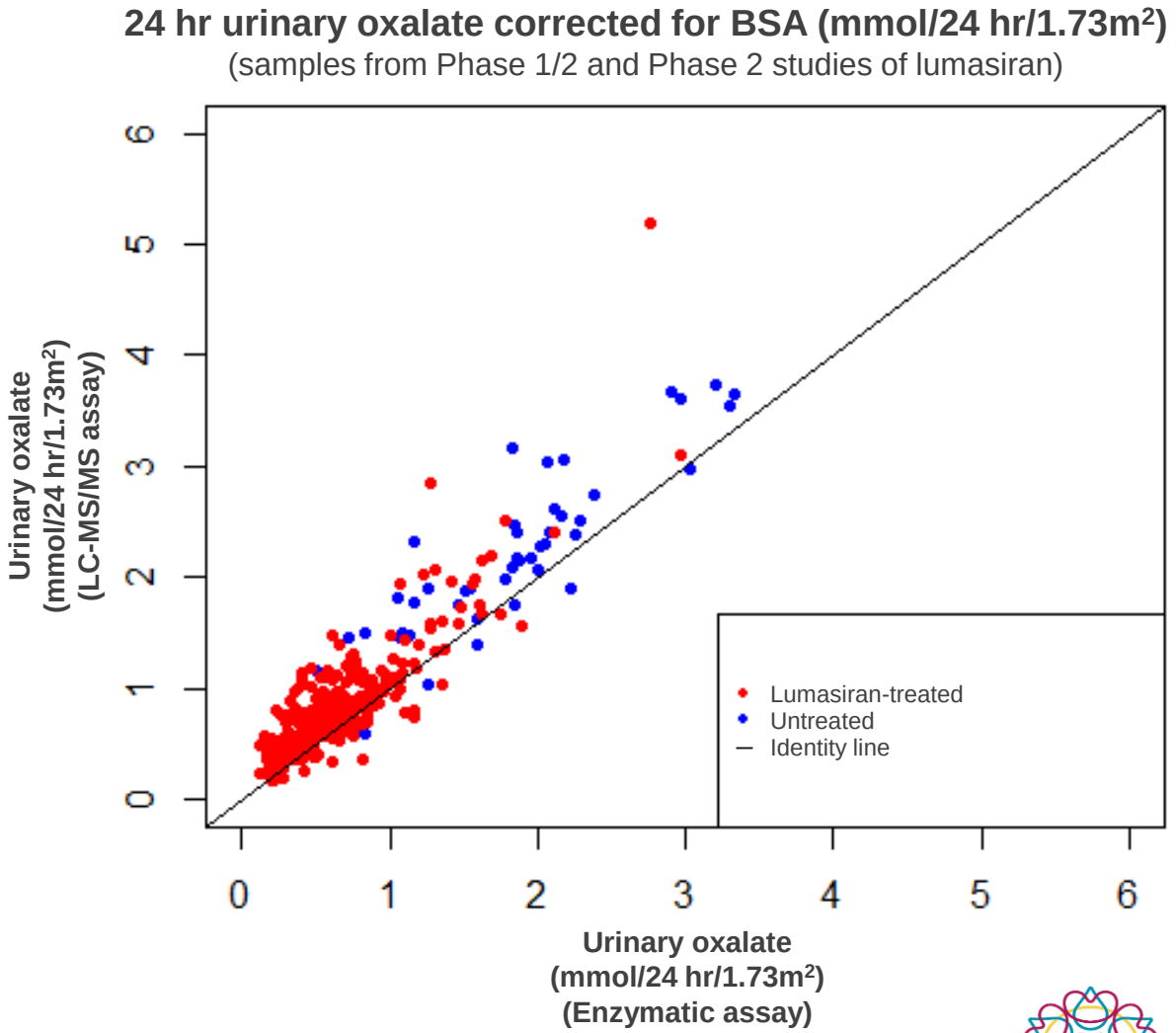
EXTENSION PERIOD
Up to 54 months' dosing

[a]Normal serum creatinine if <12 months old. [b]Elevated serum creatinine if <12 months old
eGFR, estimated glomerular filtration rate; hr, hour; min, minute; OLE, open-label extension; PH1, primary hyperoxaluria type 1

ILLUMINATE•A

Urinary Oxalate Assays Used in Clinical Trials of Lumasiran

- Enzymatic assay used in the Phase 1/2 study
  - Used clinically for diagnosis and clinical management
  - Available at multiple clinical labs
- Validated LC-MS/MS assay used in all Phase 3 studies
  - Developed by Alnylam to meet FDA and EMA regulatory requirements
  - Assay range: 5.00–250 µg/mL (0.0555–2.78 mmol/L)
- Pearson correlation between the two methods is 0.925
- LC-MS/MS assay values are higher than those of enzymatic assay; however, Phase 2 OLE 24 hr urinary oxalate percent reduction is consistent between the two



BSA, body surface area; EMA, European Medicines Agency; FDA, US Food and Drug Administration; hr, hour; LC-MS, liquid chromatography-mass spectrometry; MS, mass spectrometry

ILLUMINATE-A Phase 3 Study Design

PATIENT POPULATION (N=39)

- Adults and children ≥6 years
- Urinary oxalate excretion ≥0.7 mmol/24 hr/1.73 m^2
- Confirmed *AGXT* mutations
- eGFR ≥30 mL/min/1.73 m^2

2:1 RANDOMIZATION

6-MONTH DOUBLE-BLIND TREATMENT PERIOD

Lumasiran
qM × 3 loading dose, then q3M[a]
3.0 mg/kg subcutaneously

Placebo
qM × 3 loading dose, then q3M subcutaneously

54-MONTH EXTENSION PERIOD

Lumasiran
q3M
3.0 mg/kg subcutaneously[b]

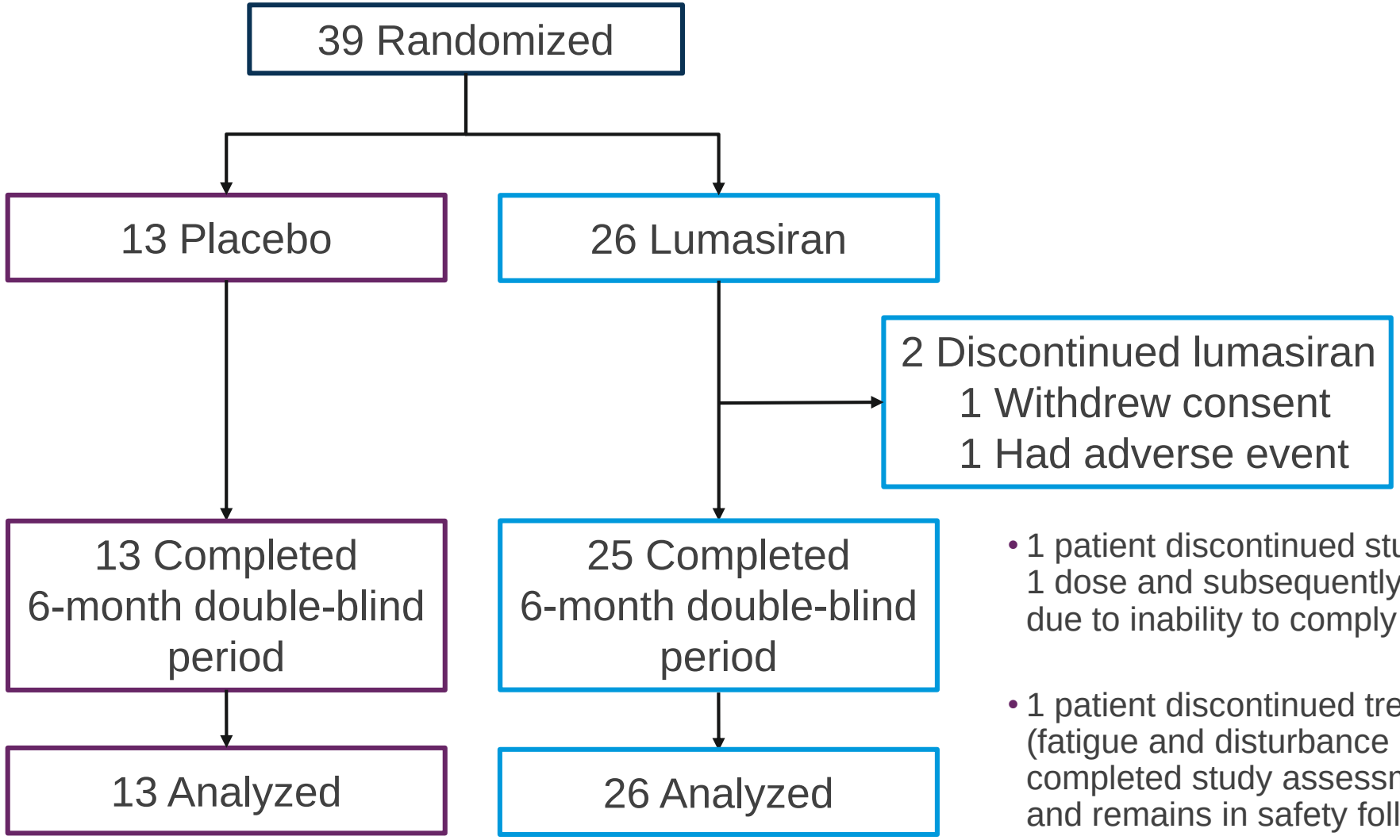
- Treatment arms were stratified at randomization based upon mean 24 hr urinary oxalate from the first 2 valid samples collected during screening (≤1.70 mmol/24 hr/1.73 m^2 vs >1.70 mmol/24 hr/1.73 m^2)
- Oxalate was measured with a validated liquid chromatography-tandem mass spectrometry assay

NCT03681184; EudraCT Number: 2018-001981-40

[a]Maintenance dose of 3.0 mg/kg (q3M) starts 1 month after last loading dose. [b]Patients randomized to placebo receive loading doses of 3.0 mg/kg lumasiran at months 6, 7, and 8; patients randomized to lumasiran receive a maintenance dose of 3.0 mg/kg lumasiran at month 6, and placebo at months 7 and 8

AGXT, alanine-glyoxylate aminotransferase gene; eGFR, estimated glomerular filtration rate; hr, hour; min, minute; q3M, once every 3 months; qM, once monthly; qM × 3, once monthly for 3 consecutive months

Patient Disposition



- 1 patient discontinued study drug after receiving 1 dose and subsequently withdrew from study due to inability to comply with protocol
- 1 patient discontinued treatment due to AE (fatigue and disturbance in attention), but completed study assessments through month 6 and remains in safety follow-up

AE, adverse event

ILLUMINATE-A: Baseline Demographic Characteristics

Balanced between placebo and lumasiran groups

Demographic characteristic	Placebo (N=13)	Lumasiran (N=26)	Overall (N=39)
Mean age at informed consent, years (range)	17.0 (6–60)	18.7 (6–47)	18.1 (6–60)
Pediatric (0–18 years), n (%)	8 (61.5)	14 (53.8)	22 (56.4)
Sex, male, n (%)	8 (61.5)	18 (69.2)	26 (66.7)
Race, n (%)			
White	9 (69.2)	21 (80.8)	30 (76.9)
Asian	3 (23.1)	3 (11.5)	6 (15.4)
Other or >1 race	1 (7.7)	2 (7.7)	3 (7.7)
Region, n (%)			
Europe	8 (61.5)	10 (38.5)	18 (46.2)
North America	2 (15.4)	11 (42.3)	13 (33.3)
Middle East	3 (23.1)	5 (19.2)	8 (20.5)

ILLUMINATE-A: Baseline Clinical Characteristics

Balanced between placebo and lumasiran groups

Clinical characteristic	Placebo (N=13)	Lumasiran (N=26)	Overall (N=39)
Mean 24 hr urinary oxalate excretion corrected for BSA[a] (SD), mmol/24 hr/1.73 m²	1.79 ± 0.68	1.84 ± 0.60	1.82 ± 0.62
Mean 24 hr urinary oxalate:creatinine ratio[b] (SD), mmol/mmol	0.237 ± 0.110	0.209 ± 0.101	0.218 ± 0.104
Mean plasma oxalate[c] (SD), µmol/liter	15.5 ± 7.3	14.8 ± 7.6	15.0 ± 7.4
eGFR, mL/min/1.73 m²			
Overall, mean (SD)	78.9 ± 26.8	83.0 ± 25.5	81.6 ± 25.7
≥90 (CKD stage 1), n (%)	4 (30.8)	9 (34.6)	13 (33.3)
60–<90 (CKD stage 2), n (%)	6 (46.2)	13 (50.0)	19 (48.7)
45–<60 (CKD stage 3a), n (%)	1 (7.7)	2 (7.7)	3 (7.7)
30–<45 (CKD stage 3b), n (%)	2 (15.4)	2 (7.7)	4 (10.3)
Pyridoxine (vitamin B6) use, n (%)	9 (69.2)	13 (50.0)	22 (56.4)
Nephrocalcinosis grade ≥1, n (%)[d]	12 (92.3)	17 (70.8)	29 (78.4)
Number of patients with reported history of symptomatic renal stone events[e], n (%)			
Lifetime	10 (76.9)	23 (88.5)	33 (84.6)
12 months prior to consent	4 (30.8)	11 (42.3)	15 (38.5)

[a]ULN is 0.514 mmol/24 hr/1.73 m². [b]ULN is 0.0799 mmol/mmol. [c]ULN is 12.11 µmol/liter. [d]Denominator includes all patients who had a graded renal ultrasound at baseline. [e]A renal stone event is defined as an event that includes at least one of the following: visit to healthcare provider because of a renal stone, medication for renal colic, stone passage, or macroscopic hematuria due to a renal stone

BSA, body surface area; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; hr, hour; SD, standard deviation; ULN, upper limit of normal

ILLUMINATE-A

Primary and Secondary Endpoints

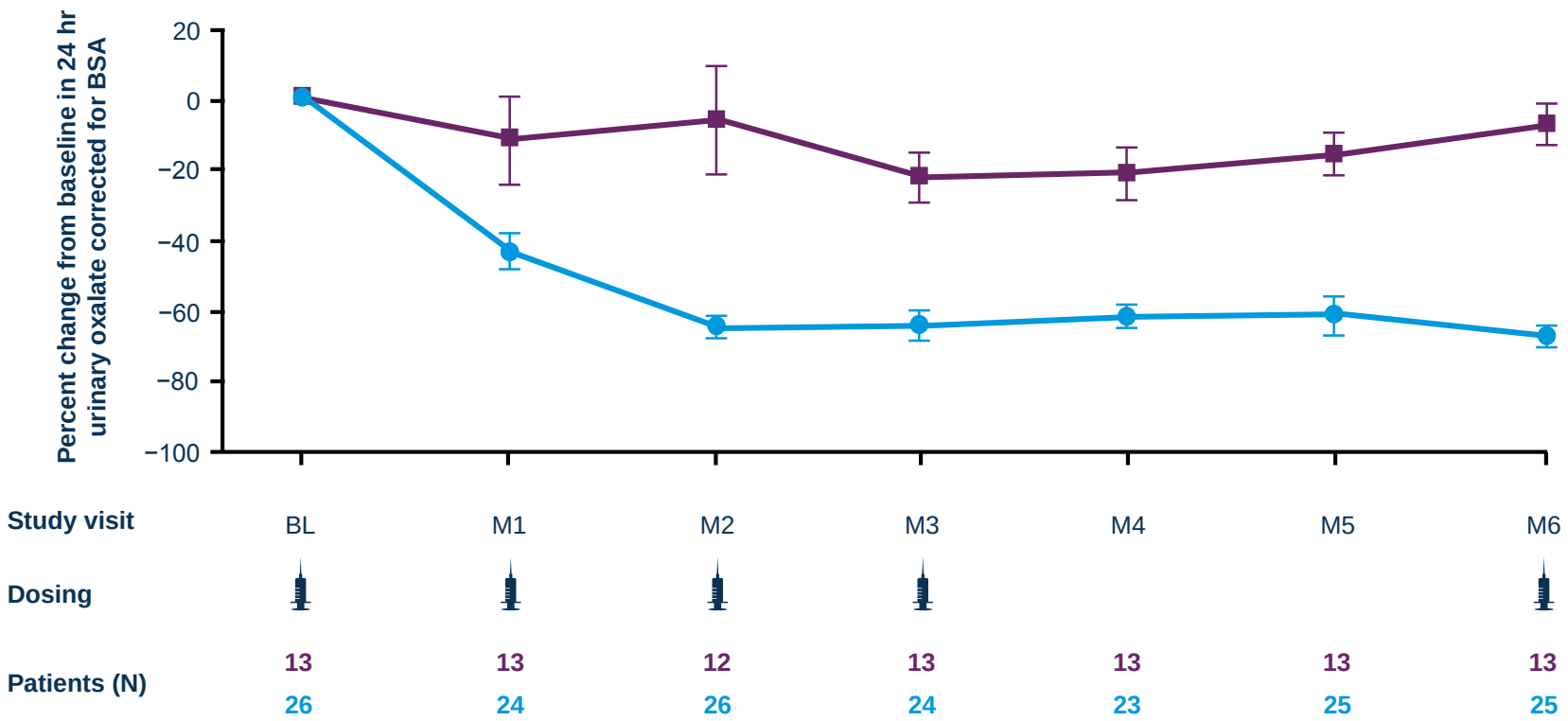
ILLUMINATE-A met its primary endpoint and all tested secondary endpoints

Endpoint	Placebo (N=13)	Lumasiran (N=26)	Difference, Lumasiran−Placebo	p-value
Primary endpoint				
Percent change in 24 hr urinary oxalate excretion corrected for BSA from baseline to month 6 (average of months 3 to 6)[a] (95% CI)	**–11.8** (–19.5 to –4.1)	**–65.4** (–71.3 to –59.5)	**–53.5** (–62.3 to –44.8)	**1.7×10^{-14}**
Secondary endpoints				
Absolute change in 24 hr urinary oxalate corrected for BSA from baseline to month 6[a] (95% CI), mmol/24 hr/1.73 m^2	–0.27 (–0.44 to –0.10)	–1.24 (–1.37 to –1.12)	–0.98 (–1.18 to –0.77)	**1.2×10^{-11}**
Percent change in 24 hr urinary oxalate:creatinine ratio from baseline to month 6[a] (95% CI)	–10.8 (–21.6 to 0.0)	–62.5 (–70.7 to –54.4)	–51.8 (–64.3 to –39.3)	**5.0×10^{-10}**
Percent change in plasma oxalate from baseline to month 6[a,b] (95% CI)	–0.3 (–9.1 to 8.5)	–39.8 (–45.8 to –33.8)	–39.5 (–50.1 to –28.9)	**2.9×10^{-8}**
Proportion of patients with 24 hr urinary oxalate level at or below 1.5 × ULN at month 6[c] (95% CI)	0.00 (0.00 to 0.25)	0.84 (0.64 to 0.95)	0.84 (0.55 to 0.94)[d]	**8.3×10^{-7}**
Proportion of patients with 24 hr urinary oxalate level at or below ULN at month 6[c] (95% CI)	0.00 (0.00 to 0.25)	0.52 (0.31 to 0.72)	0.52 (0.23 to 0.70)[d]	**0.0010**
Absolute change in plasma oxalate from baseline to month 6[a,b] (95% CI), µmol/liter	1.3 (–1.0 to 3.5)	–7.5 (–9.0 to –5.9)	–8.7 (–11.5 to–6.0)	**3.9×10^{-7}**
Change in eGFR from baseline to month 6 (SD), mL/min/1.73 m^2	–0.1 (6.5)	–2.6 (10.6)	Not applicable[d]	Not applicable[d]

[a]Estimated by MMRM. [b]Based on the plasma oxalate analysis set, including patients who had a baseline plasma oxalate level ≥1.5 × LLOQ. [c]Analyzed using a Cochran–Mantel–Haenszel test.
[d]As prespecified, no statistical testing was performed
BSA, body surface area; CI, confidence interval; eGFR, estimated glomerular filtration rate; hr, hour; LLOQ, lower limit of quantification; MMRM, mixed-effect model repeated measures; SD, standard deviation; ULN, upper limit of normal

Primary Endpoint: Percent Change in 24 hr Urinary Oxalate from Baseline to Month 6

Rapid and sustained reduction in 24 hr urinary oxalate levels



LS mean average of M3–M6	
−11.8%	Placebo (N=13)
−65.4%	Lumasiran (N=26)

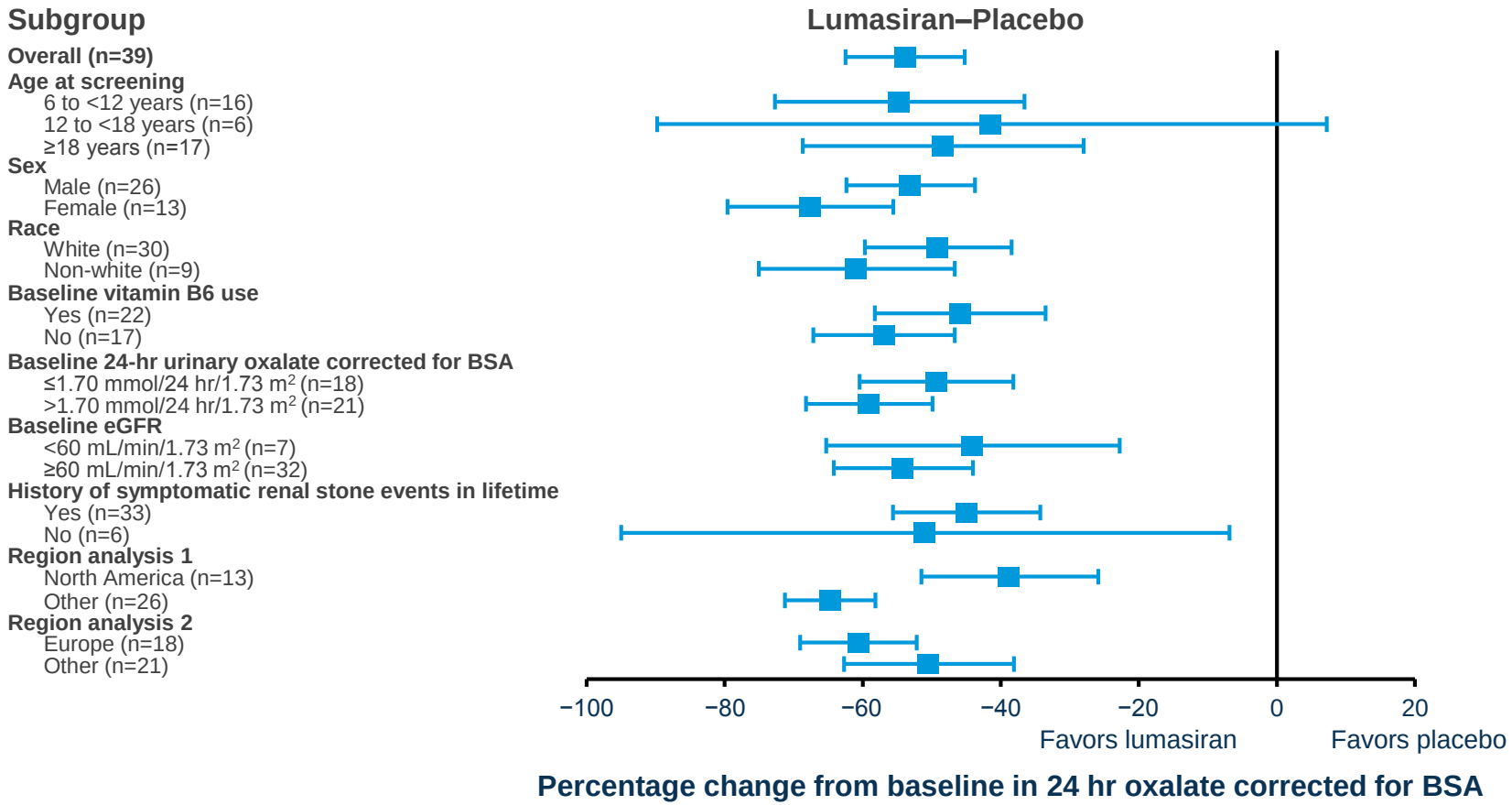
Difference in LS mean average M3–M6 (Lumasiran−Placebo): −53.5%; p-value: 1.7×10^{-14}

Mean maximal reduction: 76.0%

Data in graph are mean ± SEM of observed values
BL, baseline; BSA, body surface area; hr, hour; LS, least squares; M, month; SEM, standard error of the mean

Subgroup Analysis: Percent Change in 24 hr Urinary Oxalate from Baseline to Month 6

Consistent treatment effect across all subgroups, including baseline 24 hr urinary oxalate excretion, pyridoxine use, and eGFR

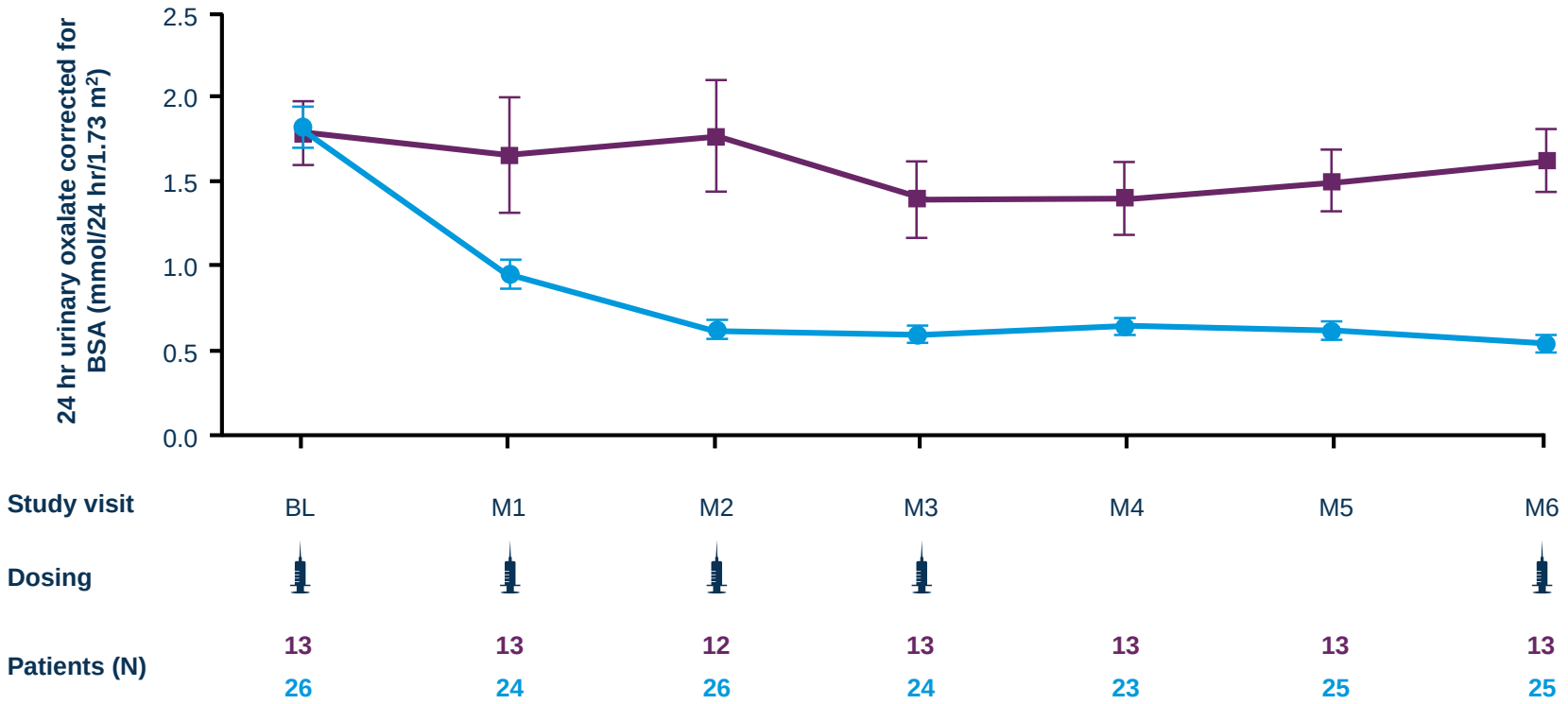


Subgroup analysis was performed with a restricted maximum likelihood-based MMRM model and a forest plot was generated, showing the associated 95% CI of the treatment effect in urinary oxalate corrected for BSA

BSA, body surface area; CI, confidence interval; eGFR, estimated glomerular filtration rate; hr, hour; MMRM, mixed-effect model repeated measures

Secondary Endpoint: Absolute Change in 24 hr Urinary Oxalate Levels from Baseline to Month 6

Rapid and sustained reduction in 24 hr urinary oxalate levels



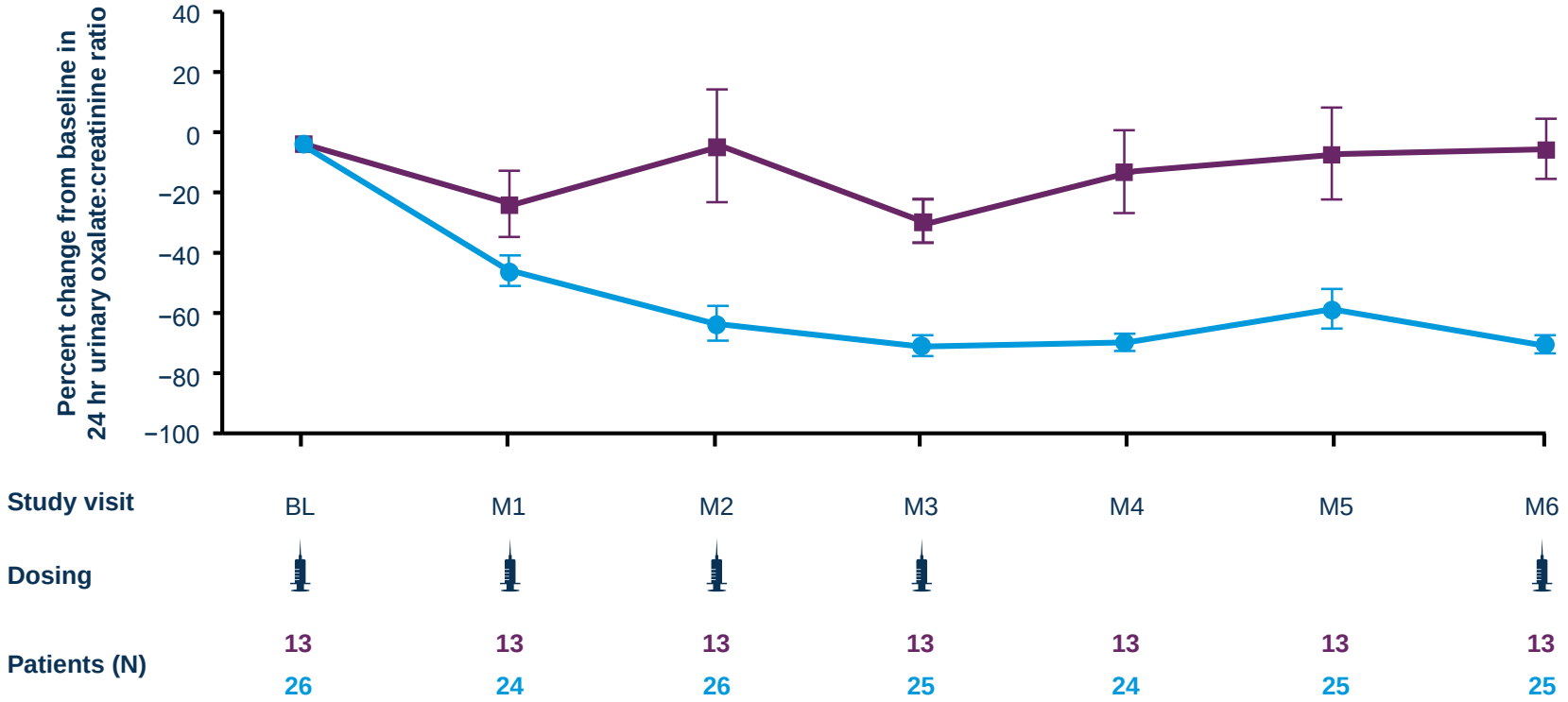
LS mean average of M3–M6 (mmol/24 hr/1.73 m²)	
−0.27	Placebo (N=13)
−1.24	Lumasiran (N=26)

Difference in LS mean average M3–M6 (Lumasiran−Placebo): −0.98 mmol/24 hr/1.73 m²; p-value: 1.2×10^{-11}

Data in graph are mean ± SEM of observed values. ULN is 0.514 mmol/24 hr/1.73 m²
BL, baseline; BSA, body surface area; hr, hour; LS, least squares; M, month; SEM, standard error of the mean; ULN, upper limit of normal

Secondary Endpoint: Percent Change in 24 hr Urinary Oxalate:Creatinine Ratio from Baseline to Month 6

Rapid and sustained reduction in 24 hr urinary oxalate:creatinine ratio



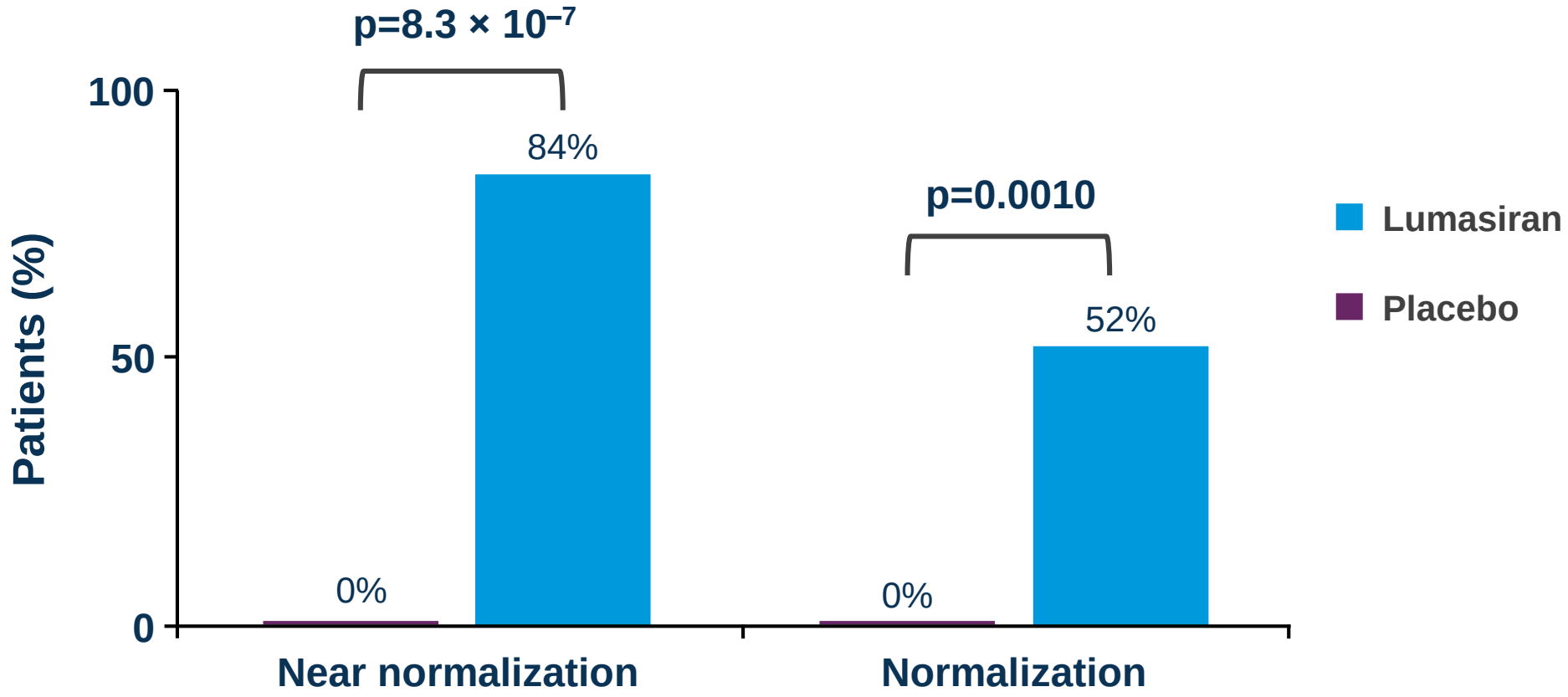
LS mean average of M3–M6	
−10.8%	Placebo (N=13)
−62.5%	Lumasiran (N=26)

Difference in LS mean average M3–M6 (Lumasiran−Placebo): −51.8%; p-value: 5.0×10^{-10}

Data in graph are mean ± SEM of observed values
BL, baseline; hr, hour; LS, least squares; M, month; SEM, standard error of the mean

Secondary Endpoints: Proportion of Patients with 24 hr Urinary Oxalate Level ≤1.5 × ULN or ≤ULN at Month 6

Majority of patients achieved near normalization (≤1.5 × ULN) or normalization (≤ULN) in 24 hr urinary oxalate levels at month 6

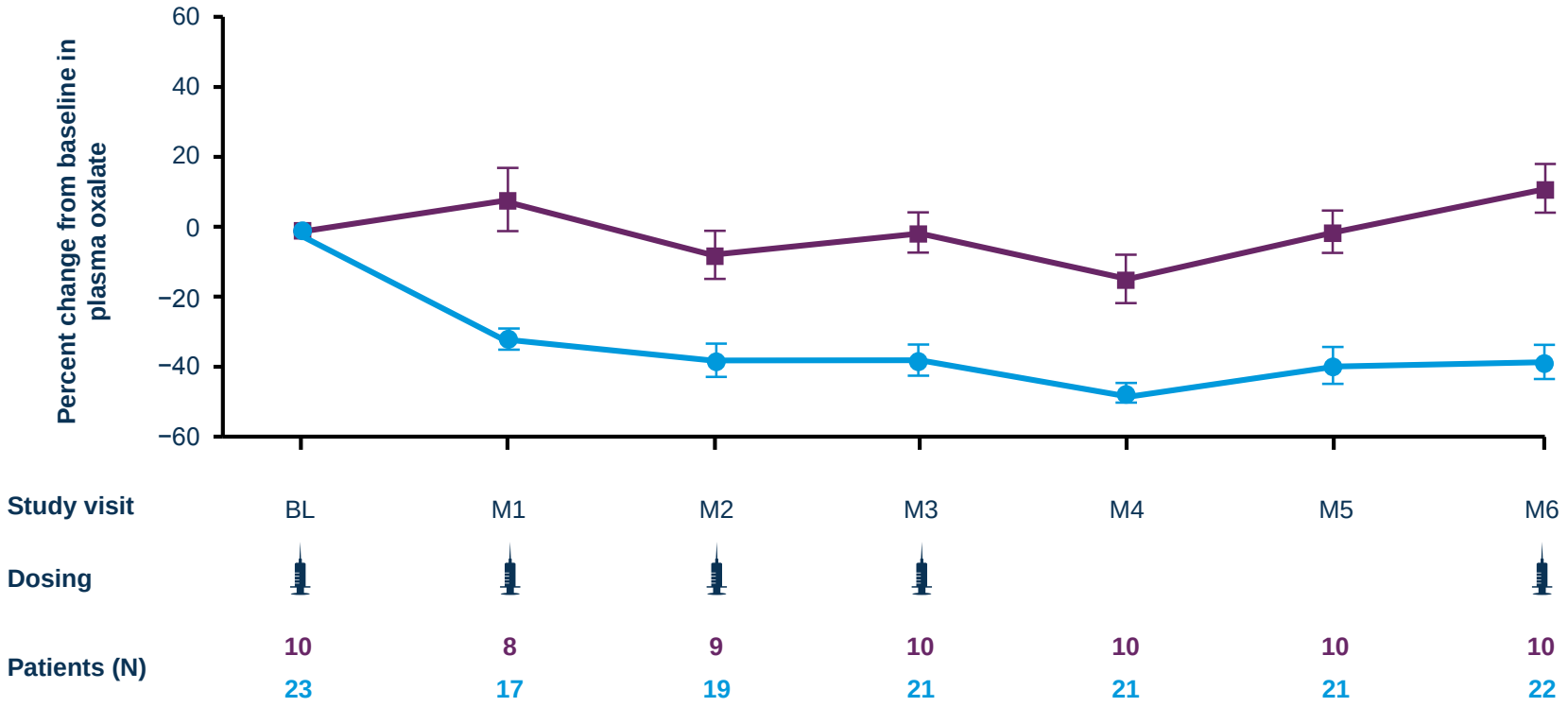


p-value is based on Cochran–Mantel–Haenszel test stratified by baseline 24 hr urinary oxalate corrected for BSA (≤1.70 vs >1.70 mmol/24 hr/1.73 m^2)

BSA, body surface area; hr, hour; ULN, upper limit of normal

Secondary Endpoint: Percent Change in Plasma Oxalate from Baseline to Month 6

Rapid and sustained reduction in plasma oxalate levels



LS mean average of M3–M6	
−0.3%	Placebo (N=10)
−39.8%	Lumasiran (N=23)

Difference in LS mean average M3–M6 (Lumasiran−Placebo): −39.5%; p-value: 2.9×10^{-8}

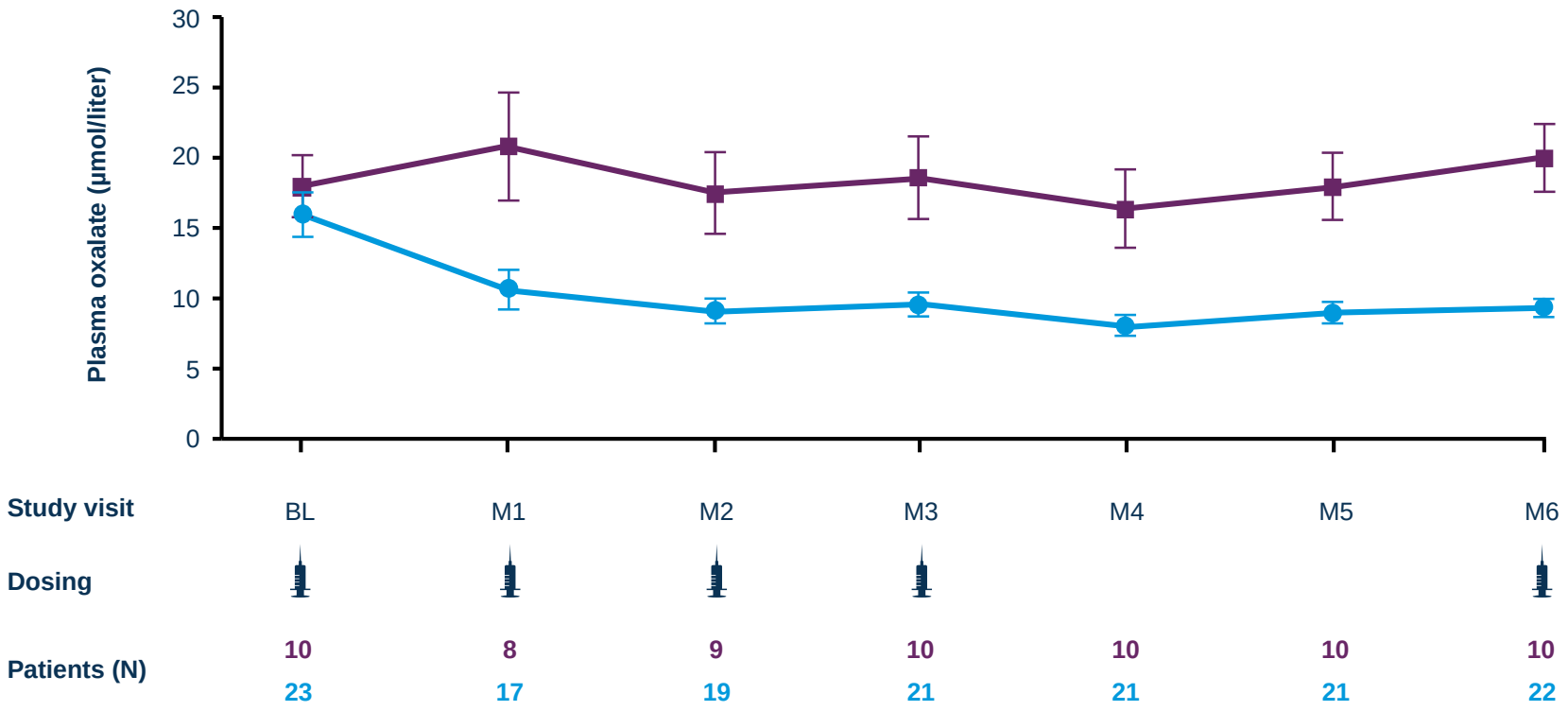
The plasma oxalate analysis set was defined as those patients who had a baseline plasma oxalate level ≥1.5 × LLOQ (LLOQ is 5.55 µmol/liter). Data in graph are mean ± SEM of observed values

BL, baseline; LLOQ, lower limit of quantification; LS, least squares; M, month; SEM, standard error of the mean

ILLUMINATE-A

Secondary Endpoint: Absolute Change in Plasma Oxalate from Baseline to Month 6

Rapid and sustained reduction in plasma oxalate levels



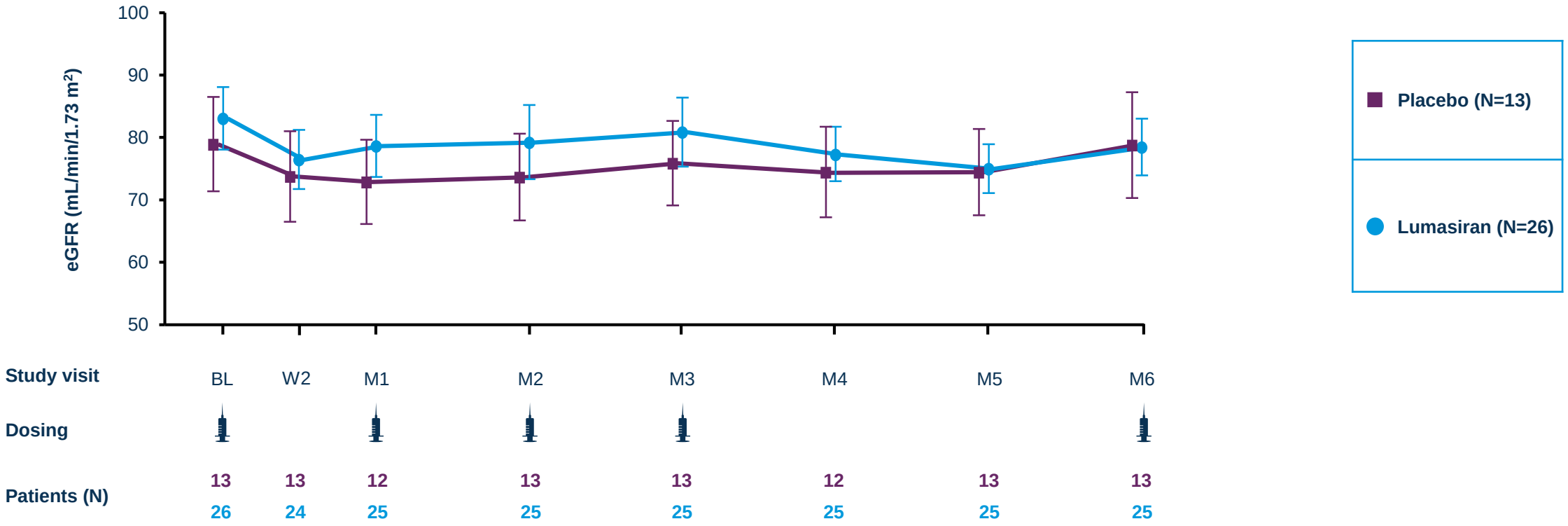
LS mean average of M3–M6 (µmol/liter)	
1.3	Placebo (N=10)
−7.5	Lumasiran (N=23)

Difference in LS mean average M3–M6 (Lumasiran−Placebo): −8.7 µmol/liter; p-value: 3.9×10^{-7}

Data in graph are mean ± SEM of observed values. ULN is 12.11 µmol/liter. The plasma oxalate analysis set was defined as those patients who had a baseline plasma oxalate level ≥1.5 × LLOQ (LLOQ is 5.55 µmol/liter)
BL, baseline; LLOQ, lower limit of quantification; LS, least squares; M, month; SEM, standard error of the mean; ULN, upper limit of normal

Secondary Endpoint: Change in eGFR from Baseline to Month 6

eGFR remained stable from baseline to month 6



Data in graph are mean ± SEM of observed values

BL, baseline; eGFR, estimated glomerular filtration rate; M, month; SEM, standard error of the mean; W, week

Exploratory Endpoints: Renal Stone Events and Nephrocalcinosis

No apparent difference between treatment groups with regard to renal stone events; 3 patients with improvements in nephrocalcinosis

Renal stone events[a]

	Placebo (N=13)	Lumasiran (N=26)
BASELINE		
Number of patients with reported history of symptomatic renal stone events, n (%) Lifetime 12 months prior to consent	 10 (76.9) 4 (30.8)	 23 (88.5) 11 (42.3)
TREATMENT PERIOD		
Number of patients with post-baseline renal stone events, n (%)	2 (15.4)	5 (19.2)

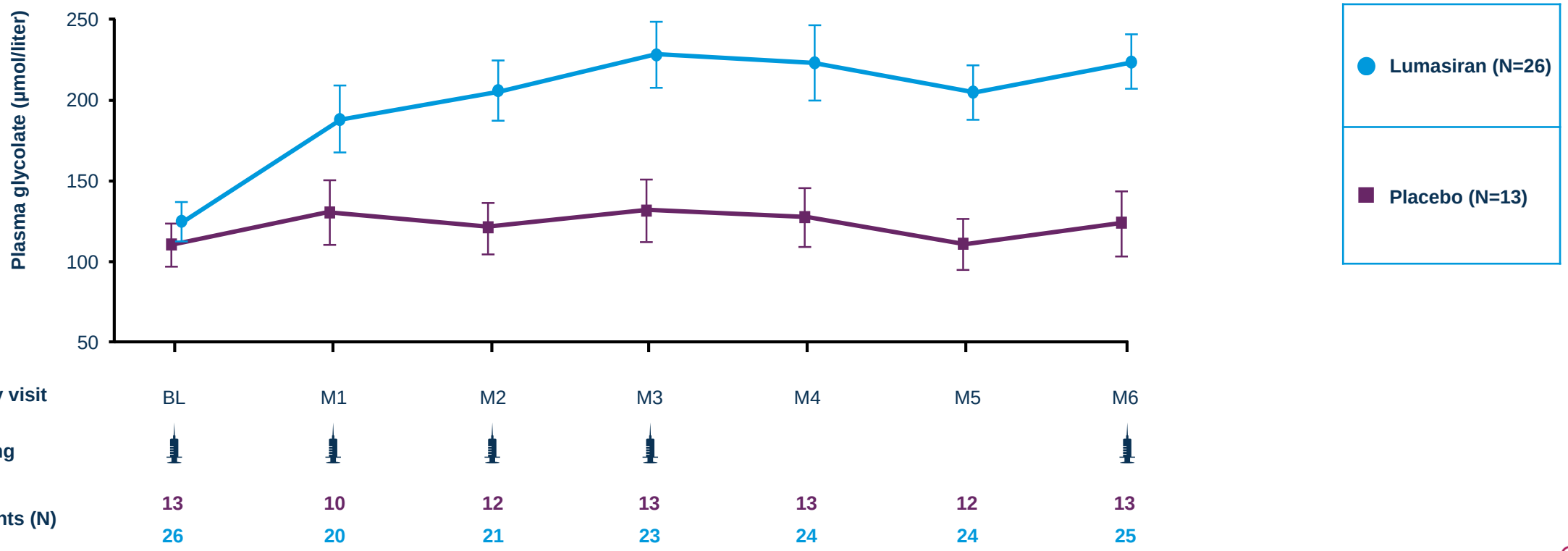
Nephrocalcinosis[b]

Change from baseline to month 6	Placebo (N=12)	Lumasiran (N=22)
Unilateral improvement (1 grade)	0	2
Bilateral improvement (≥1 grade)	0	1
Unilateral worsening (1 grade)	1	0
No change	11	19

[a]A renal stone event was defined as an event that includes at least one of the following: visit to healthcare provider because of a renal stone, medication for renal colic, stone passage, or macroscopic hematuria due to a renal stone. [b]In the subset of patients with renal ultrasounds at baseline and month 6

Exploratory Endpoint: Change in Plasma Glycolate from Baseline to Month 6

Plasma glycolate initially increased and then plateaued, consistent with reduction in hepatic GO activity



Data in graph are mean ± SEM of observed values

BL, baseline; GO, glycolate oxidase; M, month; SEM, standard error of the mean

Lumasiran Safety Profile

- There were no deaths, severe, or serious AEs
- All AEs were mild or moderate in severity
- Most common related AEs were injection-site reactions
  - All were transient and mild in severity, with no treatment interruption or discontinuation
  - Most common symptoms were erythema, pain, pruritus, or discomfort at the injection site
- No hepatic AEs reported in either group
- No clinically relevant changes in laboratory measures, vital signs, and electrocardiograms related to lumasiran were observed

Event, n (%)	Placebo (N=13)	Lumasiran (N=26)
AEs	9 (69)	22 (85)
AEs occurring in ≥10% of patients in either group		
Injection-site reactions[a]	0	9 (35)
Headache	3 (23)	3 (12)
Rhinitis	2 (15)	2 (8)
Upper respiratory infection	2 (15)	2 (8)
AE leading to discontinuation of study treatment[b]	0	1 (4)
AE leading to study withdrawal	0	0
Death	0	0
Serious AE	0	0
Severe AE	0	0

[a]Includes injection-site reactions, injection-site erythema, and injection-site pain. [b]Fatigue and disturbance in attention
AE, adverse event

Conclusions

- PH1 is a rare devastating disease, with high morbidity and mortality in all age groups
- Current management options for PH1 are limited and there is an urgent need for new therapies that can reduce hepatic oxalate production, the key toxic metabolite in PH1
- Substantial reduction in urinary oxalate is expected to confer clinical benefit in patients with PH1[1]
- ILLUMINATE-A is the first Phase 3, randomized, double-blind, placebo-controlled study, designed to evaluate safety and efficacy of lumasiran, an RNAi therapeutic, in the treatment of PH1
- Lumasiran reduced urinary oxalate, the cause of progressive renal failure in PH1, with the majority of patients achieving normal or near-normal levels within 6 months of treatment initiation; lumasiran also led to a substantial reduction in plasma oxalate
- Lumasiran had an encouraging safety profile
  - Most common drug-related AEs were injection-site reactions, all of which were mild and transient
  - No severe or serious AEs reported

AE, adverse event; PH1, primary hyperoxaluria type 1; RNAi, RNA interference

1. Milliner et al. *Clin J Am Soc Nephrol* 2020; doi:10.2215/CJN.13821119

ILLUMINATE-A

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