# Long-Term Efficacy and Safety of Lumasiran in Patients With Primary Hyperoxaluria Type 1 in a Final Analysis of the ILLUMINATE-A Trial

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# Disclosures

**Jeffrey M. Saland:** Alnylam Pharmaceuticals–grants, personal fees, and nonfinancial support.

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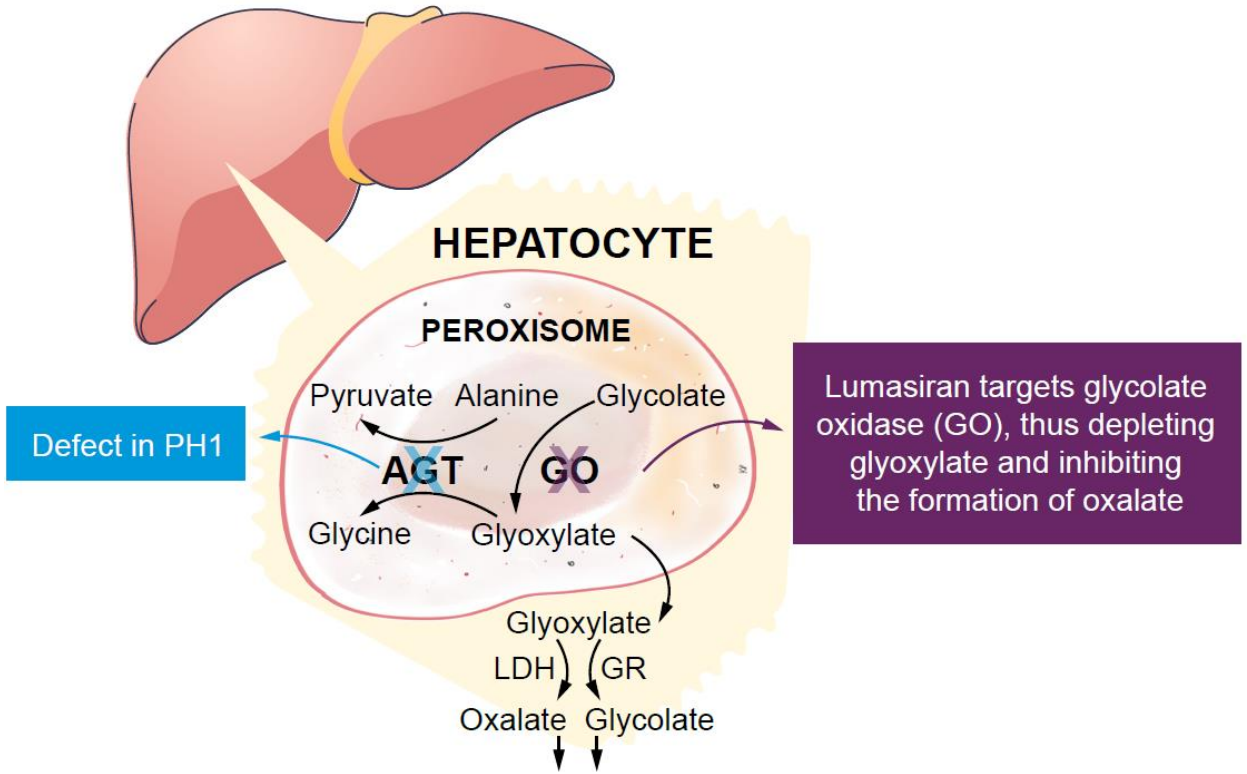
# Introduction

- Primary hyperoxaluria type 1 (PH1) is a rare disorder caused by disruption of the alanine-glyoxylate aminotransferase gene (AGT) and characterized by hepatic oxalate overproduction, increased kidney oxalate excretion, and calcium oxalate crystal formation in kidneys and urinary tract[1]
  - Patients may experience nephrolithiasis and/or nephrocalcinosis, which can ultimately progress to kidney failure and systemic oxalosis[1]
- Lumasiran, an RNAi therapeutic, targets and promotes degradation of the mRNA encoding glycolate oxidase, reducing hepatic oxalate production[2]




[a]ClinicalTrials.gov: NCT03681184; EudraCT: 2018-001981-40.

**1.** Cochat P, Rumsby G. *N Engl J Med*. 2013;369:649-658. **2.** Liebow A, et al. *J Am Soc Nephrol*. 2017;28:494-503.

# Introduction, *continued*

- Lumasiran is approved in the US and EU for the treatment of PH1 in adult and pediatric patients[1,2]
- Lumasiran is the first approved RNAi treatment for PH1, with the largest and longest dataset for an RNAi therapy to treat PH1[3]

## Objective

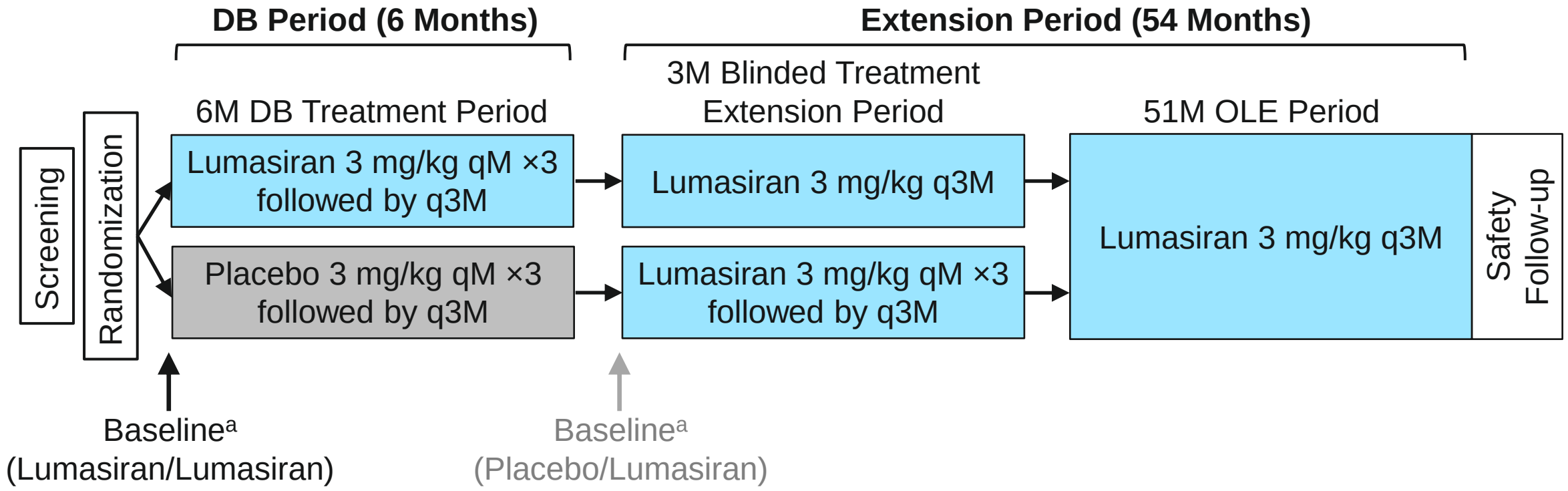
- To report data from the final, 60-month analysis of ILLUMINATE-A, the first Phase 3 pivotal study[a] of lumasiran in PH1

[a]ClinicalTrials.gov: NCT03681184; EudraCT: 2018-001981-40.

**1.** Oxlumo [package insert]. Cambridge, MA: Alnylam Pharmaceuticals; 2022. **2.** Oxlumo [summary of product characteristics]. Amsterdam, Netherlands: Alnylam Netherlands; 2022. **3.** U.S. Food and Drug Administration. FDA Approves First Drug to Treat Rare Metabolic Disorder [press release]. 2020; https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-treat-rare-metabolic-disorder. Accessed January 12, 2022.

# Methods

- ILLUMINATE-A was a multinational (Europe, Middle East, and North America) Phase 3 trial (November 2018 to January 2024)
- Eligible patients were ≥6 years old with confirmed PH1 and an eGFR ≥30 mL/min/1.73m$^2$
- Measures included 24-hour UOx excretion corrected for BSA, POx, plasma glycolate, eGFR, KSE rate, and NC




[a]Baseline is defined as the period prior to the first lumasiran dose; hence, the lumasiran/lumasiran sequence has 6 more months of on-lumasiran follow-up than the placebo/lumasiran sequence.

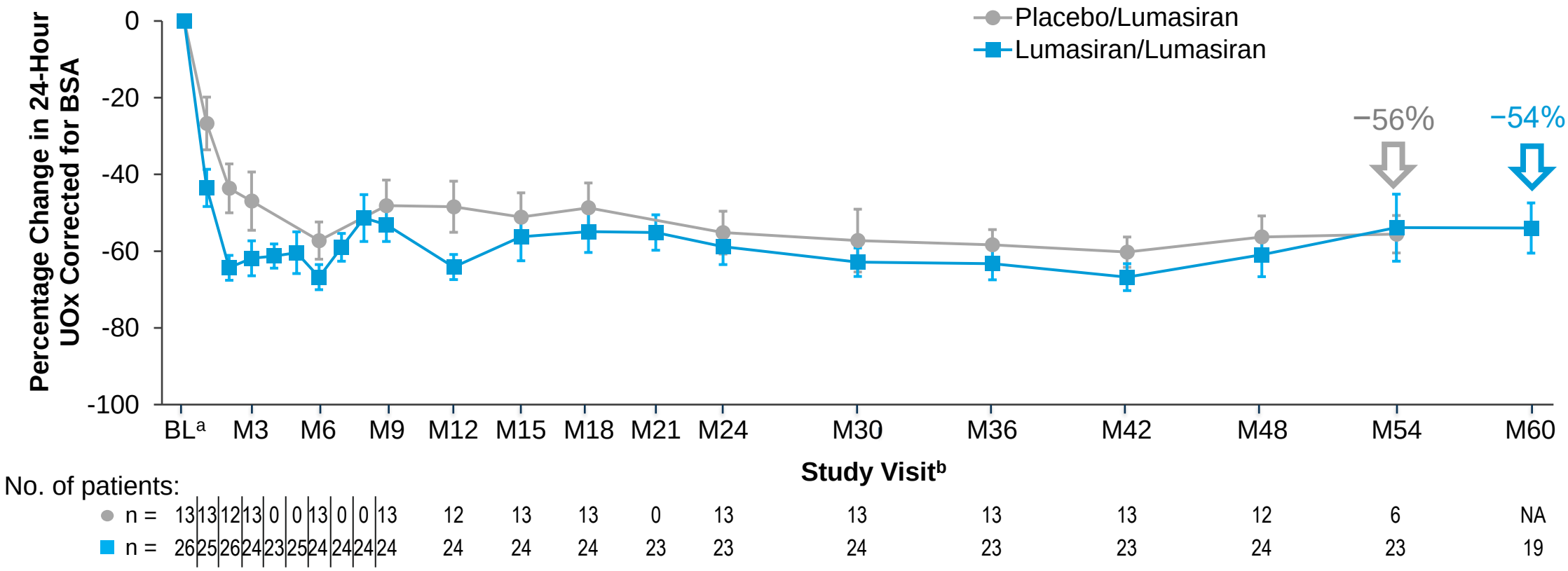
# Baseline Characteristics and Patient Disposition

| Characteristic | Placebo/Lumasiran (n=13) | Lumasiran/Lumasiran (n=26) |
|---|---|---|
| **Age at informed consent, mean (range), years** | 17.0 (6-60) | 18.7 (6-47) |
| **<18 years, n (%)** | 8 (62) | 14 (54) |
| **18 to <65 years, n (%)** | 5 (38) | 12 (46) |
| **Male, n (%)** | 8 (62) | 18 (69) |
| **Race, n (%)** | | |
| **Asian** | 3 (23) | 3 (12) |
| **White** | 9 (69) | 21 (81) |
| **Other, or >1 race** | 1 (8) | 2 (8) |
| **24-hour UOx excretion corrected for BSA, mean (SD), mmol/24h/1.73m$^2$[a,b]** | 1.6 (0.7) | 1.8 (0.6) |
| **POx, mean (SD), µmol/L[c,d]** | 19.3 (9.5) | 14.8 (7.6) |
| **eGFR, mean (SD), mL/min/1.73m$^2$[c]** | 78.8 (30.0) | 83.0 (25.5) |
| **Patients reporting history of kidney stone events, n (%)** | | |
| **Lifetime** | 10 (77) | 23 (88) |
| **12 months prior to consent** | 4 (31) | 11 (42) |

Of the 39 patients enrolled in the Phase 3 study,13/13 (placebo/lumasiran) and 24/26 (lumasiran/lumasiran) completed treatment in the open-label extension

[a]For the lumasiran/lumasiran group, baseline is the median of all valid 24-hour urine assessments collected prior to the first dose date/time of lumasiran without any non-protocol-related sample issues. For the placebo/lumasiran group, baseline is the median of all valid 24-hour urine assessments at Month 6 without any non-protocol-related sample issues (or, if the patient did not have 2 valid 24-hour urine pharmacodynamic assessments at Month 6, then the baseline was calculated using the latest 3 valid 24-hour urine pharmacodynamic collections prior to the first dose date/time of lumasiran). [b]ULN is 0.514 mmol/24h/1.73m$^2$ = 45 mg/24h/1.73m$^2$ (1 mmol/24h/1.73m$^2$ = 90 mg/24h/1.73m$^2$). [c]Baseline is defined as the last non-missing value prior to the first dose of lumasiran (all-lumasiran-treated set). [d]ULN is 12.11µmol/L.

# 24-Hour Urinary Oxalate Reductions



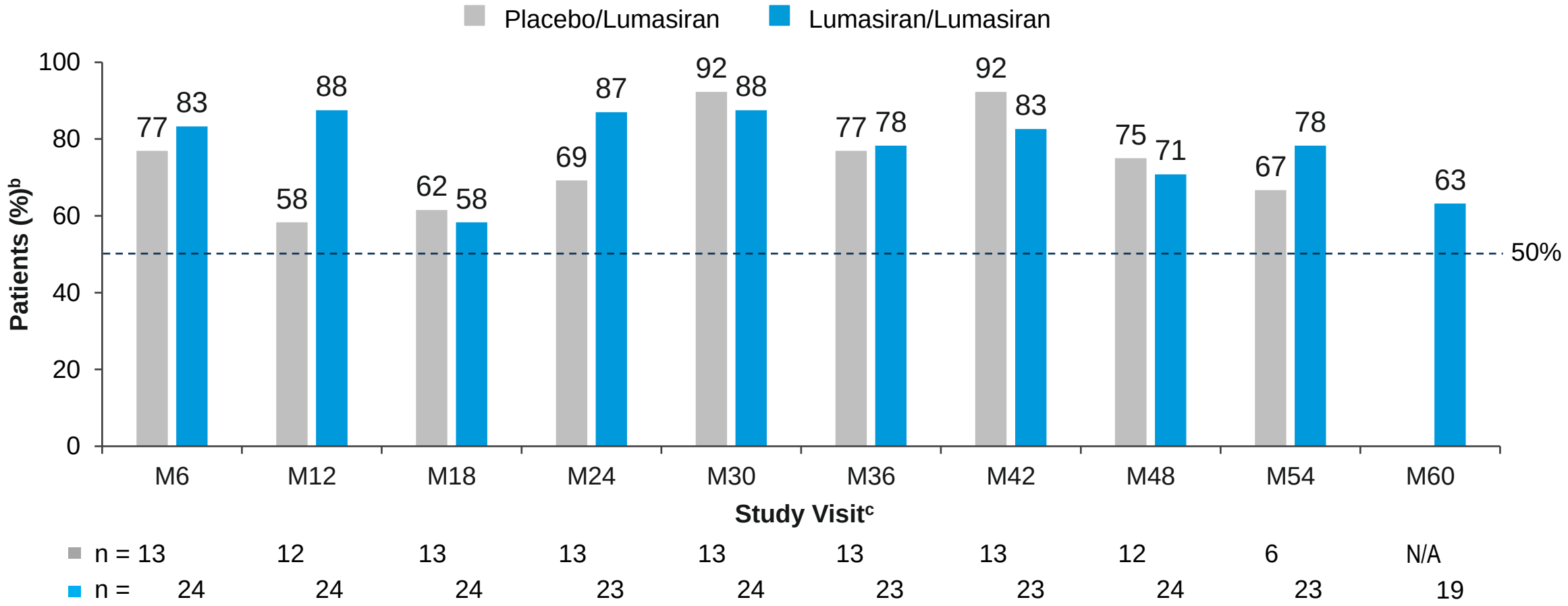

Values are mean (SEM).

[a]For the lumasiran/lumasiran treatment sequence, baseline is the median of all valid 24-hour urine assessments collected prior to the first dose date/time of lumasiran without any non-protocol-related sample issues. For the placebo/lumasiran treatment sequence, baseline is the median of all valid 24-hour urine assessments at Month 6 without any non-protocol-related sample issues (or, if the patient did not have 2 valid 24-hour urine pharmacodynamic assessments at Month 6, then the baseline was calculated using the latest 3 valid 24-hour urine pharmacodynamic collections prior to the first dose date/time of lumasiran).

[b]Visit is relative to the first dose of lumasiran.

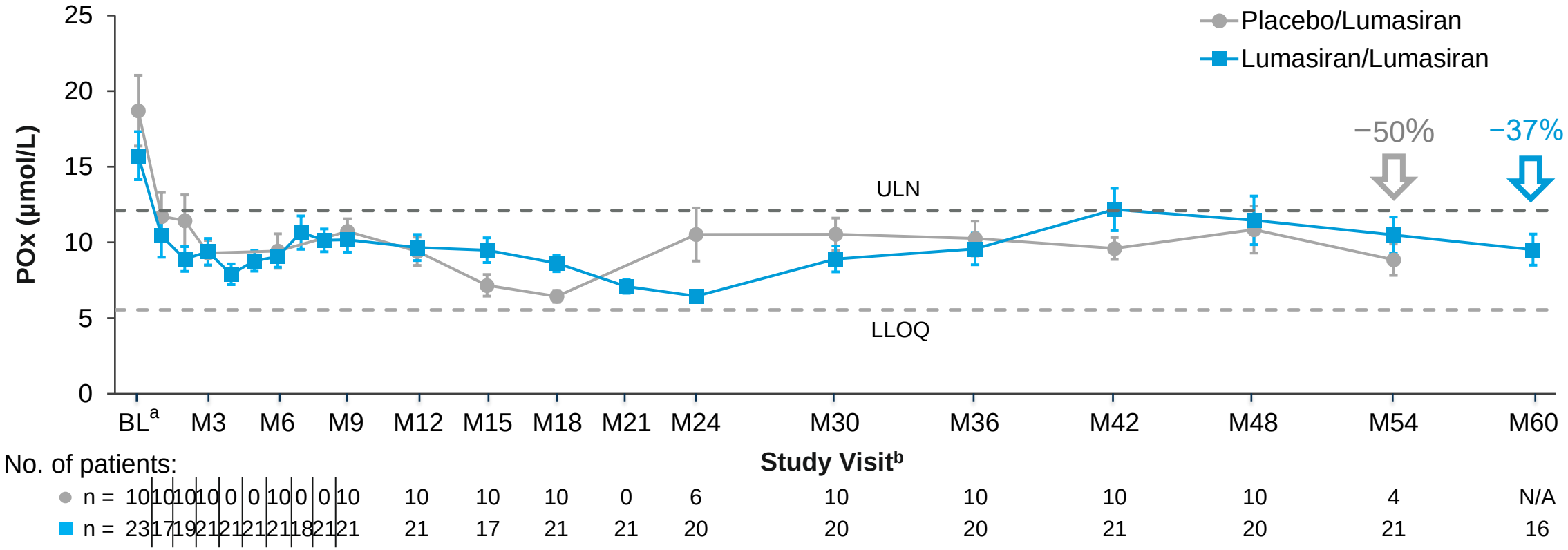
# Patients With 24-Hour UOx Corrected for BSA ≤1.5 × ULN

- Beginning 2 months after lumasiran treatment initiation, ≥50% of patients in each group achieved 24-hour UOx excretion ≤1.5 × ULN[a] at each time point




[a]ULN is 0.514 mmol/24h/1.73m$^2$=45 mg/24h/1.73m$^2$ (1 mmol/24h/1.73m$^2$=90 mg/24h/1.73m$^2$).
[b]Percentages are based upon the number of patients having 24-hour UOx corrected for BSA data at the visit.
[c]Visit is relative to the first dose of lumasiran.

# Plasma Oxalate Reductions




No. of patients:

| | BL[a] | M3 | M6 | M9 | M12 | M15 | M18 | M21 | M24 | M30 | M36 | M42 | M48 | M54 | M60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| n = | 10 | 10 | 10 | 10 | 0 | 0 | 10 | 0 | 0 | 10 | 10 | 10 | 10 | 10 | 4 | N/A |
| n = | 23 | 17 | 19 | 21 | 21 | 21 | 21 | 18 | 21 | 21 | 21 | 17 | 21 | 21 | 20 | 20 | 20 | 21 | 20 | 21 | 16 |

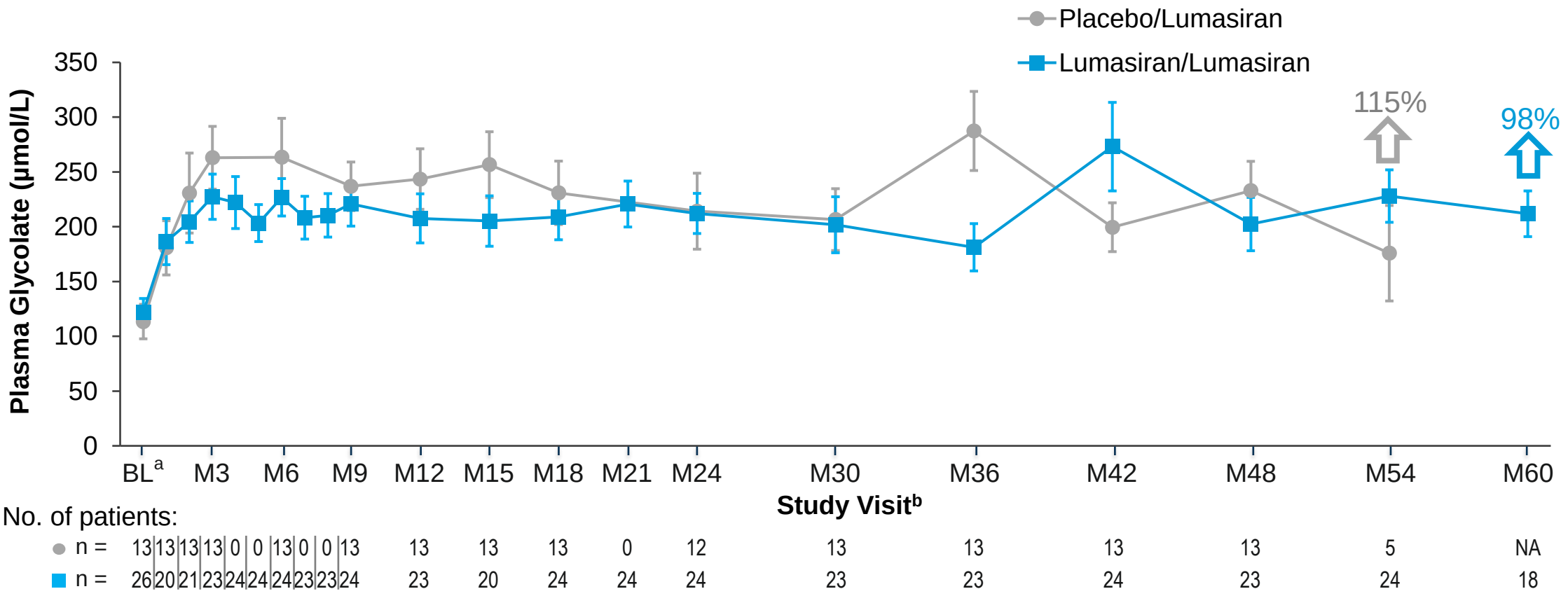
Values are mean (SEM).

Dark gray dotted line represents the ULN of 12.11 µmol/L for POx. Light gray dotted line represents the LLOQ of the POx assay at 5.55 µmol/L; values below the LLOQ were assigned a value of 5.55 µmol/L.

[a]For the lumasiran/lumasiran treatment sequence, baseline is defined as the mean of all measurements prior to the first dose date/time of lumasiran. For the placebo/lumasiran treatment sequence, baseline is the mean of the last 2 non-missing measurements prior to the first dose date/time of lumasiran.

[b]Visit is relative to the first dose of lumasiran.

# Plasma Glycolate Increases



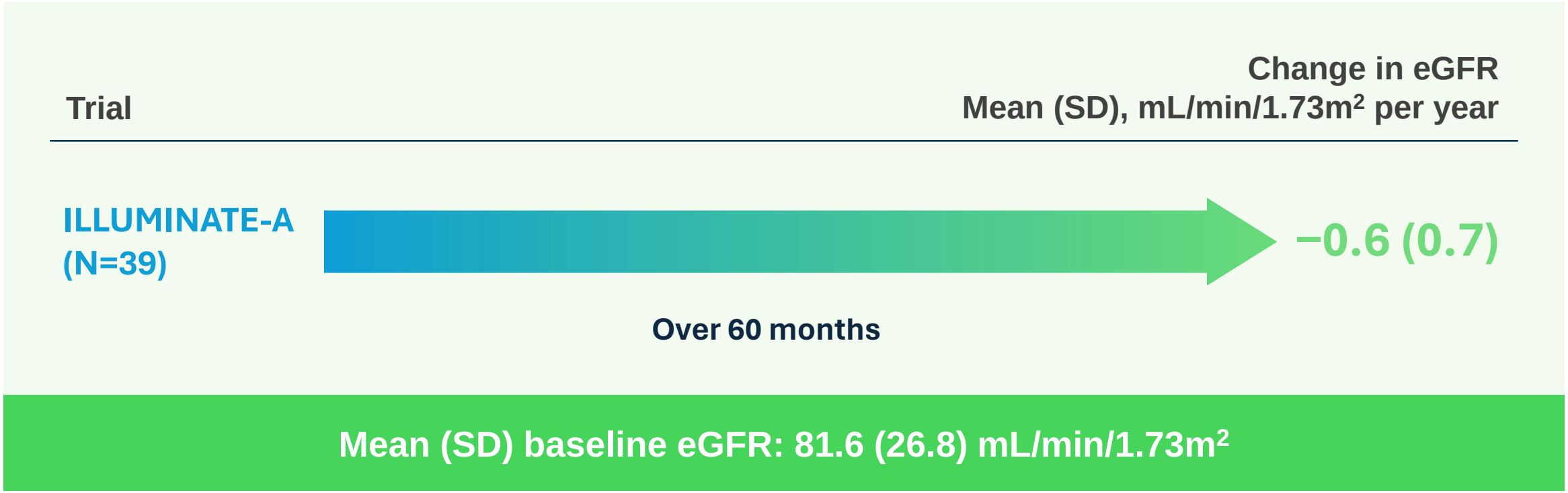

Values are mean (SEM).

aFor the lumasiran/lumasiran treatment sequence, baseline is defined as the mean of all measurements prior to the first dose date/time of lumasiran. For the placebo/lumasiran treatment sequence, baseline is the mean of the last 2 non-missing measurements prior to the first dose date/time of lumasiran.

[b]Visit is relative to the first dose of lumasiran.

# eGFR Stability

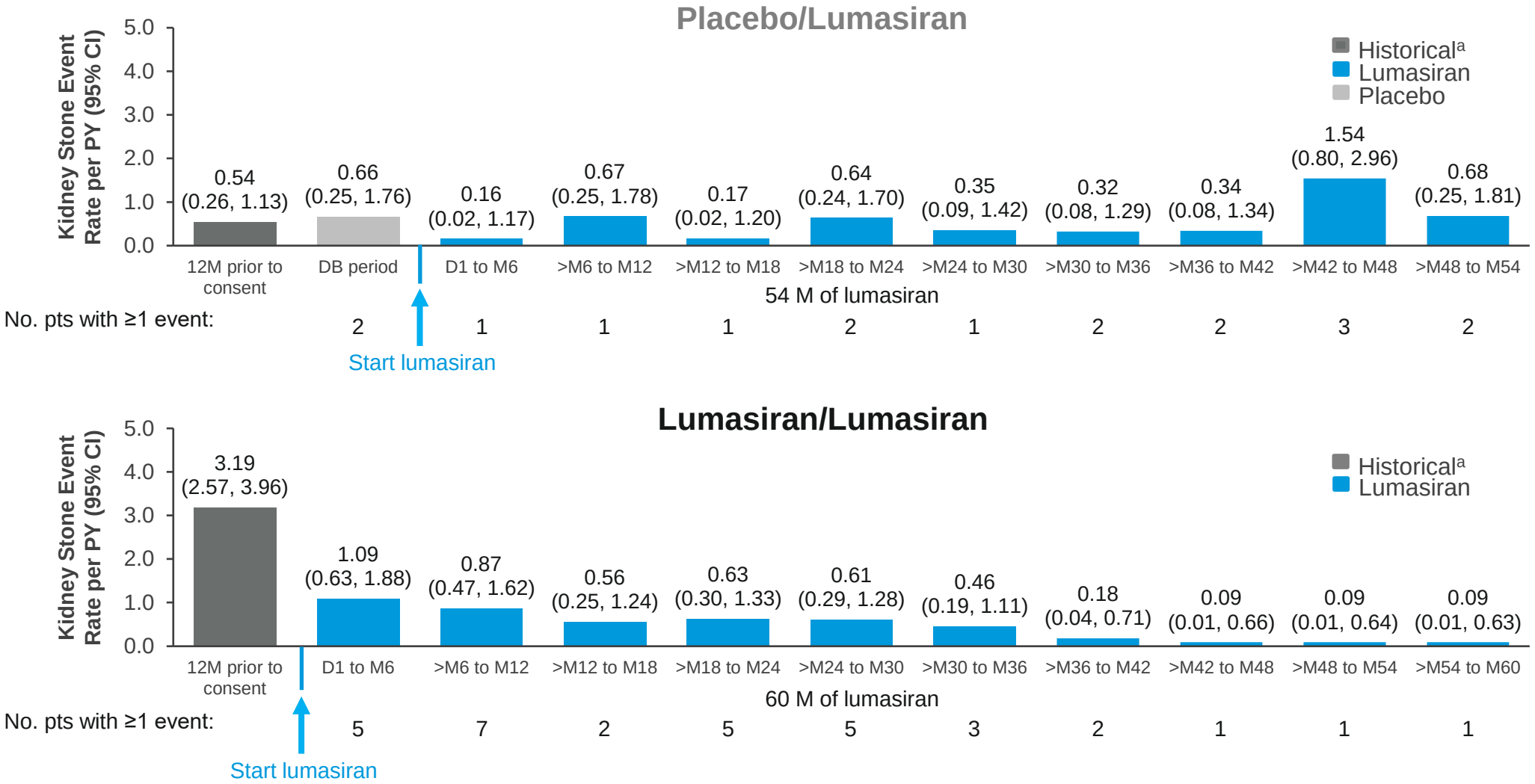
- Overall, in the all-lumasiran-treated set, the mean annual rate of eGFR change per year at Month 60 was minimal: −0.6 mL/min/1.73m$^2$




The calculation of eGFR is calculated from serum creatinine based on the Modification of Diet in Renal Disease formula for patients ≥18 years of age and the Schwartz Bedside Formula for patients <18 years of age at screening. The annual rate of eGFR change is calculated using simple linear regression.

# Kidney Stone Events on Lumasiran

- Kidney stone event rates were low during lumasiran treatment

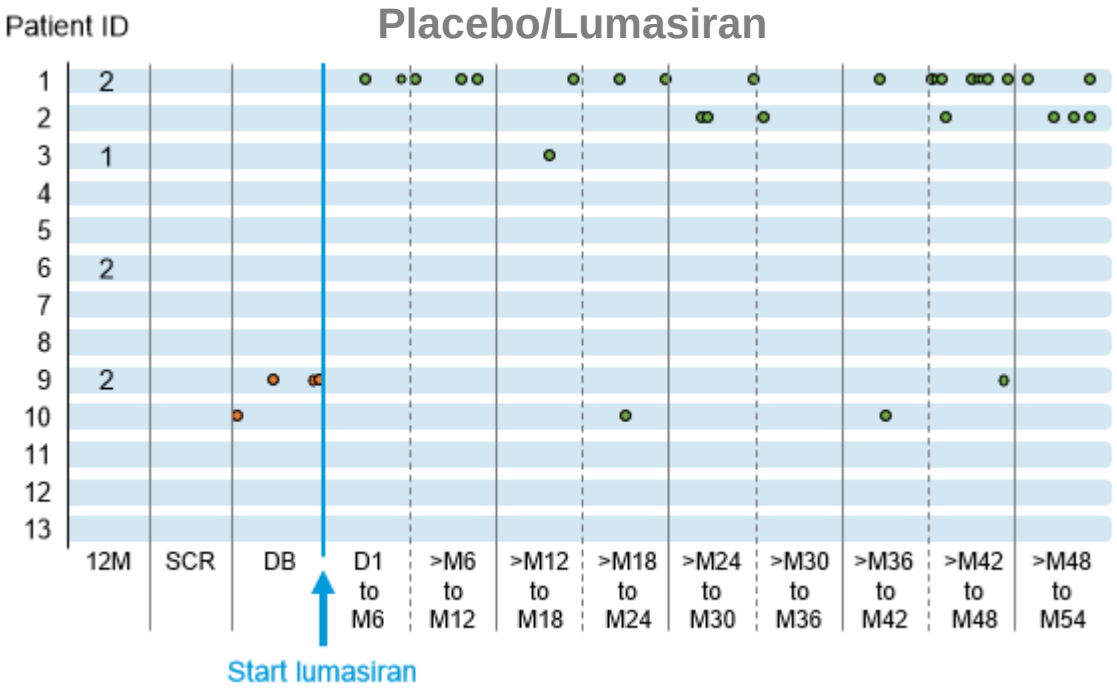



Values in parentheses represent 95% CI.

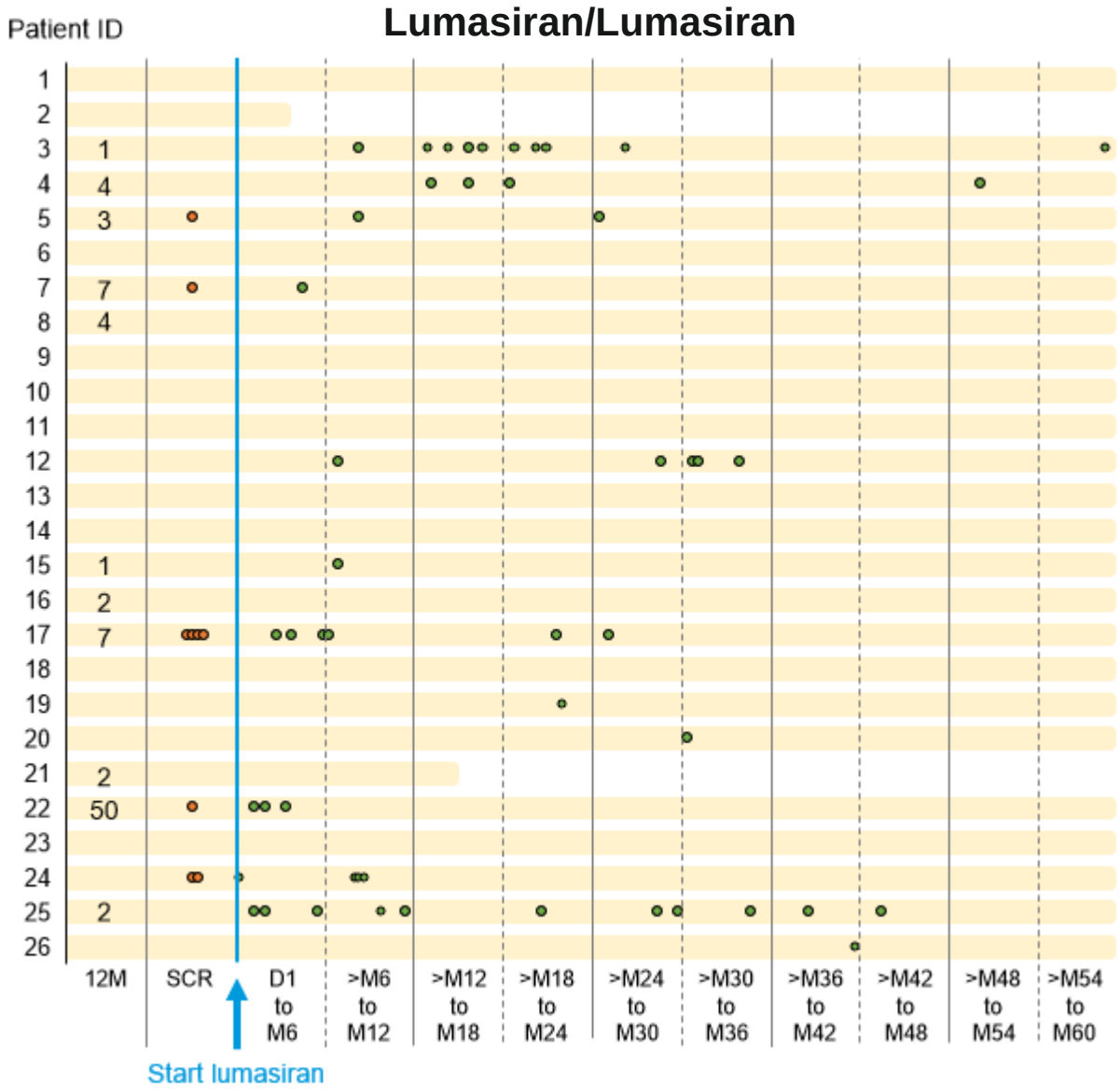
[a]Patient-reported history of kidney stone events.

# Kidney Stone Events on Lumasiran by Patient

- No KSEs occurred in 8/13 (62%) placebo/lumasiran patients and 13/26 (50%) lumasiran/lumasiran patients while on lumasiran




No. of pts with ≥1 event: 2 1 1 1 2 1 2 2 3 2

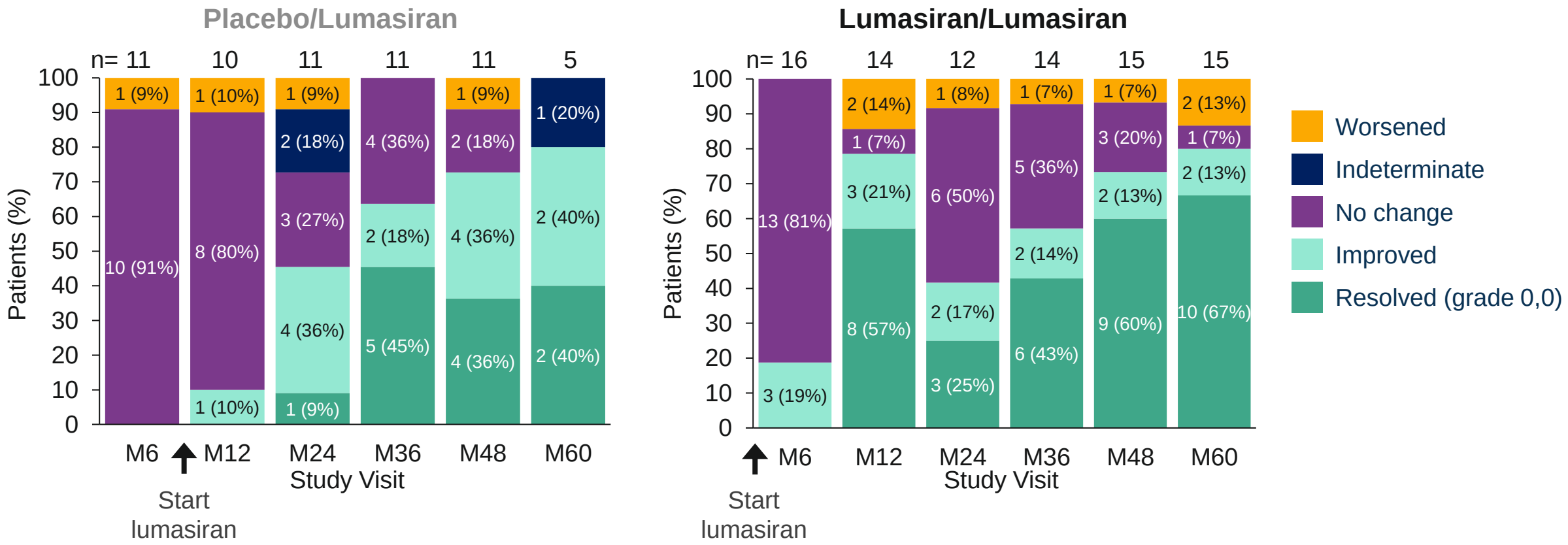



No. of pts with ≥1 event: 5 7 2 5 5 3 2 1 1 1

Patients were screened within 60 days prior to study drug administration. Each line represents 1 patient. Each data point indicates 1 KSE. The timing for historical events (prior 12 months) was not documented.

# Medullary Nephrocalcinosis

- Medullary NC grade generally improved or remained stable in patients with NC at baseline
- Medullary NC grade improved in 16/20 (80%) patients with NC at baseline and an assessment at end of study




- Medullary NC grade remained stable (no change) in 3/3 (100%) patients without NC at baseline and an assessment at end of study

Post hoc analysis. Indeterminate indicates improvement in one kidney and worsening in the other.

# ILLUMINATE-A 60-Month Safety Results

| Event, n (%) | Placebo/Lumasiran (n=13) | Lumasiran/Lumasiran (n=26) | All Lumasiran (N=39) |
|---|---|---|---|
| **Any AE** | 12 (92) | 25 (96) | 37 (95) |
| **AE related to study drug** | 6 (46) | 13 (50) | 19 (49) |
| **Serious AE[a]** | 1 (8) | 5 (19) | 6 (15) |
| **Severe AE[b]** | 0 | 4 (15) | 4 (10) |
| **AE leading to discontinuation of study treatment[c]** | 0 | 1 (4) | 1 (3) |
| **AEs occurring in ≥15% of patients (during lumasiran treatment)** | | | |
| **Injection site reactions[d]** | 5 (38) | 9 (35) | 14 (36) |
| **Abdominal pain** | 1 (8) | 8 (31) | 9 (23) |
| **COVID-19** | 4 (31) | 4 (15) | 8 (21) |
| **Headache** | 2 (15) | 5 (19) | 7 (18) |
| **Nasopharyngitis** | 2 (15) | 4 (15) | 6 (15) |
| **Death** | 0 | 0 | 0 |

[a]Abdominal pain (n=2), dysuria (n=1), follicular lymphoma (n=1), postprocedural complication (n=1), postprocedural infection (n=1), renal impairment (n=1), urinary tract infection (n=1), and urosepsis (n=1), all considered not related to lumasiran by the investigator. [b]Acute pyelonephritis (n=1), follicular lymphoma (n=1), postprocedural complication (n=1), postprocedural infection (n=1), urinary tract infection (n=1), and urosepsis (n=1), all considered not related to lumasiran by the investigator. [c]Fatigue and disturbance in attention, considered not related to lumasiran by the investigator, which began during the double-blind period. [d]All were transient, considered mild in severity, and resolved without sequelae.

# Conclusions

- This completes the planned data analyses for the Phase 3, long-term ILLUMINATE-A study
- Treatment of both pediatric and adult PH1 patients with lumasiran for up to 60 months led to marked and sustained reductions in UOx with acceptable safety results
- Clinical outcomes data included stable eGFR, minimal kidney stone events while on treatment, and improvement in medullary nephrocalcinosis

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**Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the lumasiran clinical studies**