Long-Term Effects of Lumasiran on Kidney Stones and Nephrocalcinosis in Patients With Primary Hyperoxaluria Type 1

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Disclosures

Gregory Tasian: Scientific advisory board for Alnylam Pharmaceuticals and Novo Nordisk
Jeffrey M. Saland: Grants, personal fees, and nonfinancial support from Alnylam Pharmaceuticals
John C. Lieske: Grants from Alnylam Pharmaceuticals, Dicerna Pharmaceuticals, OxThera, Retrophin, and Siemens; other from Arbor, NovoBiome, and Orfan-BridgeBio; grants and other from Allena and Synlogic
Julien Hogan: Consultant for Alnylam Pharmaceuticals and Traverse; travel fees from Biocodex; research grant from CareDx
Yaacov Frishberg: Consultancy fees and membership in the safety review committee for Alnylam Pharmaceuticals
Martin Coenen: Nothing to disclose
Richard Willey, Mary Callanan, and **Desmond Murphy:** Employees of and shareholders in Alnylam Pharmaceuticals
Cristin Kaspar: Employee of Alnylam Pharmaceuticals
Sally-Anne Hulton: Travel expenses to participate in clinical research meetings, consultancy fee from advisory board, and consultancy fees paid to Birmingham Children's Hospital Renal Research Fund from Alnylam Pharmaceuticals; other from Chiesi Pharmaceuticals

Acknowledgments: On behalf of the study investigators, thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the lumasiran clinical studies. Medical writing and editorial assistance was provided by Peloton Advantage, LLC, an OPEN Health company, in accordance with Good Publication Practice (GPP 2022) guidelines and funded by Alnylam Pharmaceuticals.
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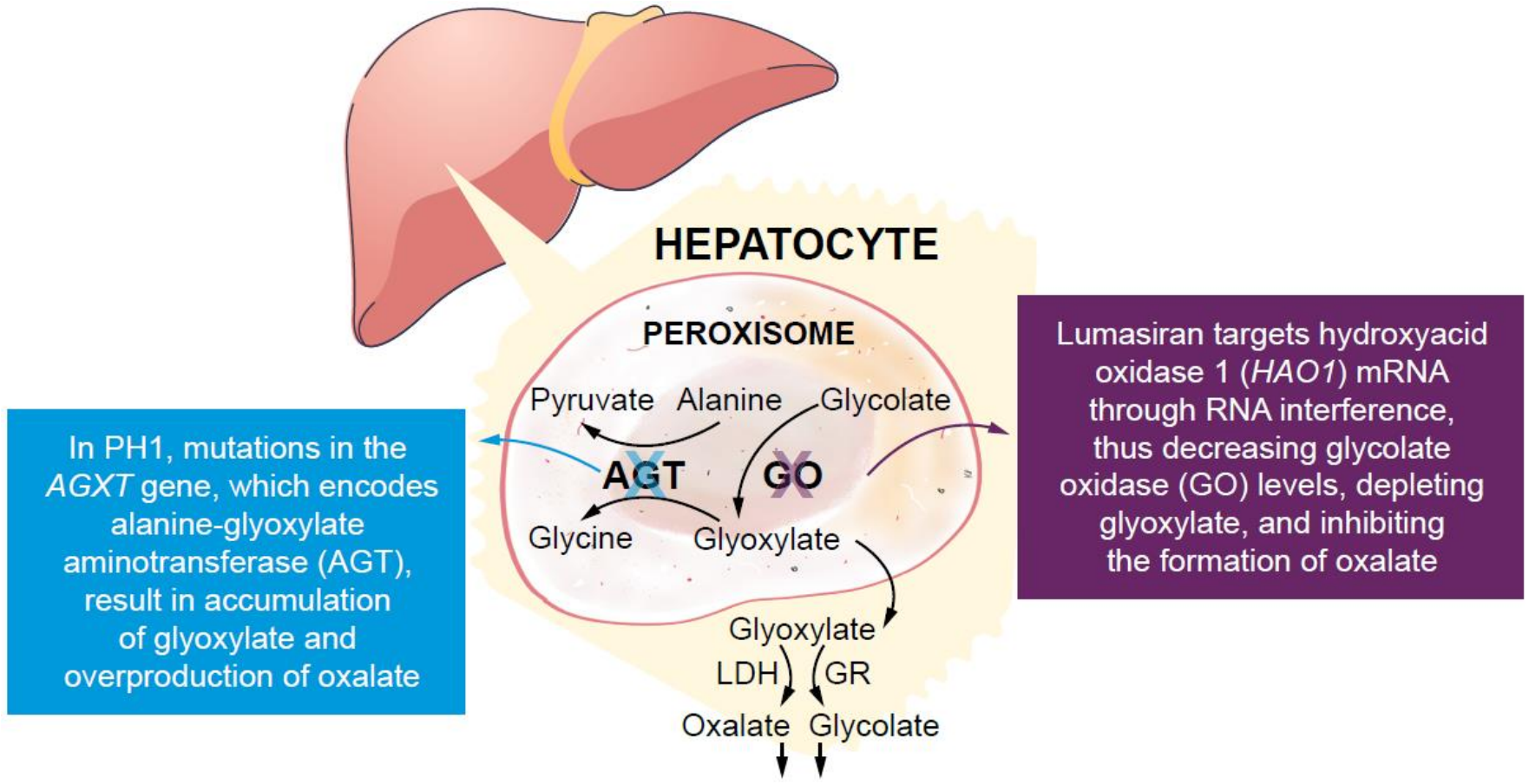
Funding: This study was funded by Alnylam Pharmaceuticals

Introduction

- Primary hyperoxaluria type 1 (PH1) is a rare genetic disorder associated with hepatic oxalate overproduction[1]
- In patients with PH1, recurrent kidney stones are a major cause of morbidity, and nephrocalcinosis is associated with an increased risk of kidney failure[2,3]



- Lumasiran, the first approved RNAi treatment for PH1 with the longest duration of efficacy data, effectively lowers urinary oxalate in pediatric and adult patients[4,5]

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

1. Cochat P, Rumsby G. *N Engl J Med*. 2013;369:649-658. **2.** Milliner DS, et al. Primary Hyperoxaluria Type 1. GeneReviews 1993 [update Nov 30, 2017]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1283/. Accessed: January 11, 2022. **3.** Danpure CJ. Primary hyperoxaluria. In: Valle DL, et al, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. doi:10.1036/ommbid. **4.** U.S. Food and Drug Administration. FDA Approves First Drug to Treat Rare Metabolic Disorder [press release]. 2020; www.fda.gov/news-events/press-announcements/fda-approves-first-drug-treat-rare-metabolic-disorder. Accessed January 12, 2022. **5.** Oxlumo [package insert]. Cambridge, MA: Alnylam Pharmaceuticals; 2022.

Objective

- We evaluated the long-term effects of lumasiran on kidney stones and medullary NC in patients with PH1 in 4 lumasiran clinical trials up to 60 months duration

Study	Phase 1/2 Part B[a] N=20	Phase 2 OLE N=20	Phase 3 ILLUMINATE-A N=39	Phase 3 ILLUMINATE-B N=18
ClinicalTrials.gov ID number	NCT02706886	NCT03350451	NCT03681184	NCT03905694
Design	• Multiple ascending doses	• Long-term open-label extension study of patients from Phase 1/2 Part B with up to 54 months of dosing	• 6-month double-blind, placebo-controlled period followed by a long-term extension period of up to 54 months	• Single-arm, open-label study with a 6-month primary analysis period followed by a long-term extension period of up to 54 months
Participants	• Patients with PH1 • 6-64 years old • eGFR >45 mL/min/1.73m^2	• Patients with PH1 who completed the Phase 1/2 study, Part B	• Patients with PH1 • ≥6 years old • eGFR ≥30 mL/min/1.73m^2	• Patients with PH1 • <6 years old • eGFR >45 mL/min/1.73m^2[b]
Relevant data	• Kidney stone-related AEs[c]	• Kidney stone-related AEs[c]	• KSE rates and medullary NC grade (exploratory endpoints)	• KSE rates and medullary NC grade (exploratory endpoints)

[a]Part A involved a single-blind, placebo-controlled, single dose in healthy adults. [b]Normal serum creatinine if <12 months old. [c]Medullary NC grade was not assessed.
AE, adverse event; eGFR, estimated glomerular filtration rate; KSE, kidney stone event; NC, nephrocalcinosis; OLE, open-label extension; PH1, primary hyperoxaluria type 1.

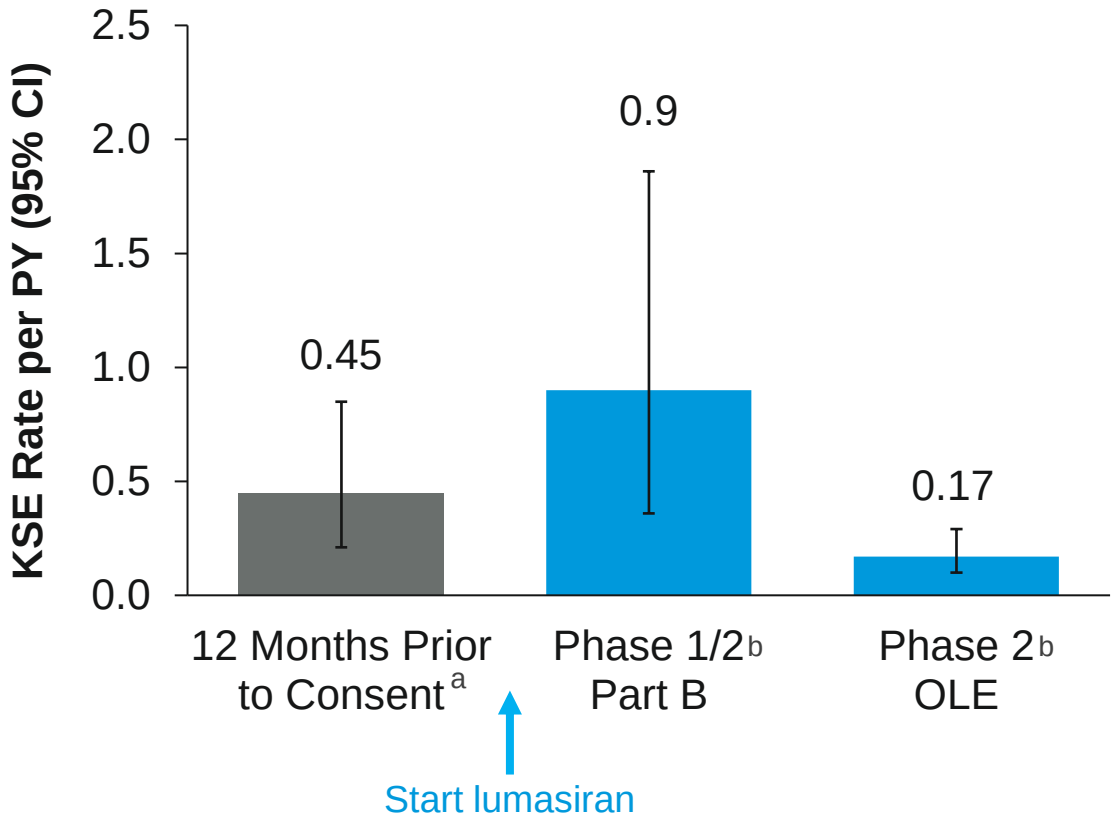
Methods

- **KSEs[a] (kidney stone events)** were defined[b] as any of the following:
  - Visit to healthcare provider because of a kidney stone
  - Medication for renal colic
  - Stone passage
  - Macroscopic hematuria due to a kidney stone
- **Medullary NC** in each kidney was graded on a validated, semiquantitative, standardized 4-point scale with a higher grade indicating greater severity[1]
  - Kidney ultrasounds were graded centrally by a single radiologist blinded to timepoint (ILLUMINATE-A and ILLUMINATE-B) and treatment arm (ILLUMINATE-A)
  - Data were available up to Month 60 (ILLUMINATE-A) and Month 30 (ILLUMINATE-B) at the time of the analysis

[a]For Phase 2, kidney stone-related AEs were defined as any kidney stone meeting the AE definition and reported as an AE and were identified by medical review.
[b]For ILLUMINATE-A and ILLUMINATE-B.
AE, adverse event; KSE, kidney stone event; NC, nephrocalcinosis.
1. Dick PT, et al. *Pediatr Radiol*. 1999;29:68-72.

Kidney Stone Event Rates in Phase 1/2 and Phase 2 OLE Studies

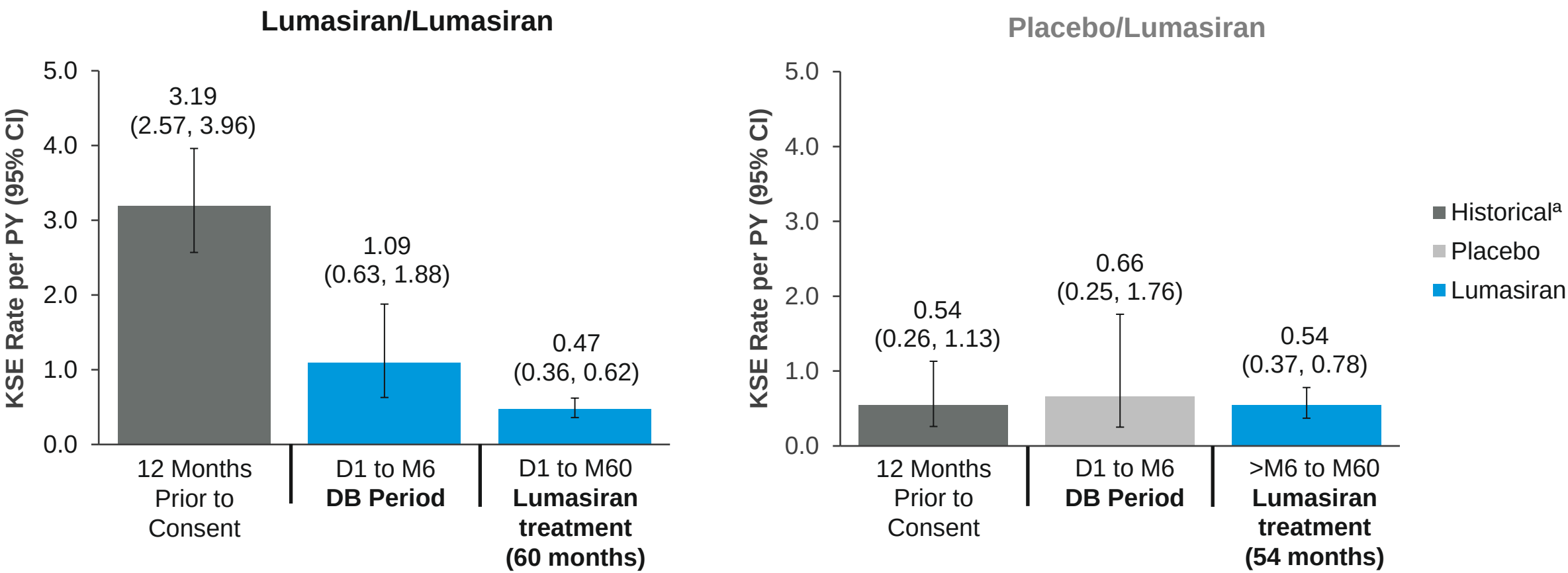
- In this Phase 2 OLE study (N=20), 14 KSEs were reported in 5/20 patients during lumasiran treatment (total duration: 54 months)



[a]Number of symptomatic kidney stone events reported for the 12 months prior to consent in the Phase 1/2 study. [b]In the Phase 1/2 Part B and Phase 2 OLE studies, kidney stones were described as kidney stone-related adverse events.
KSE, kidney stone event; OLE, open-label extension; PY, patient-year.

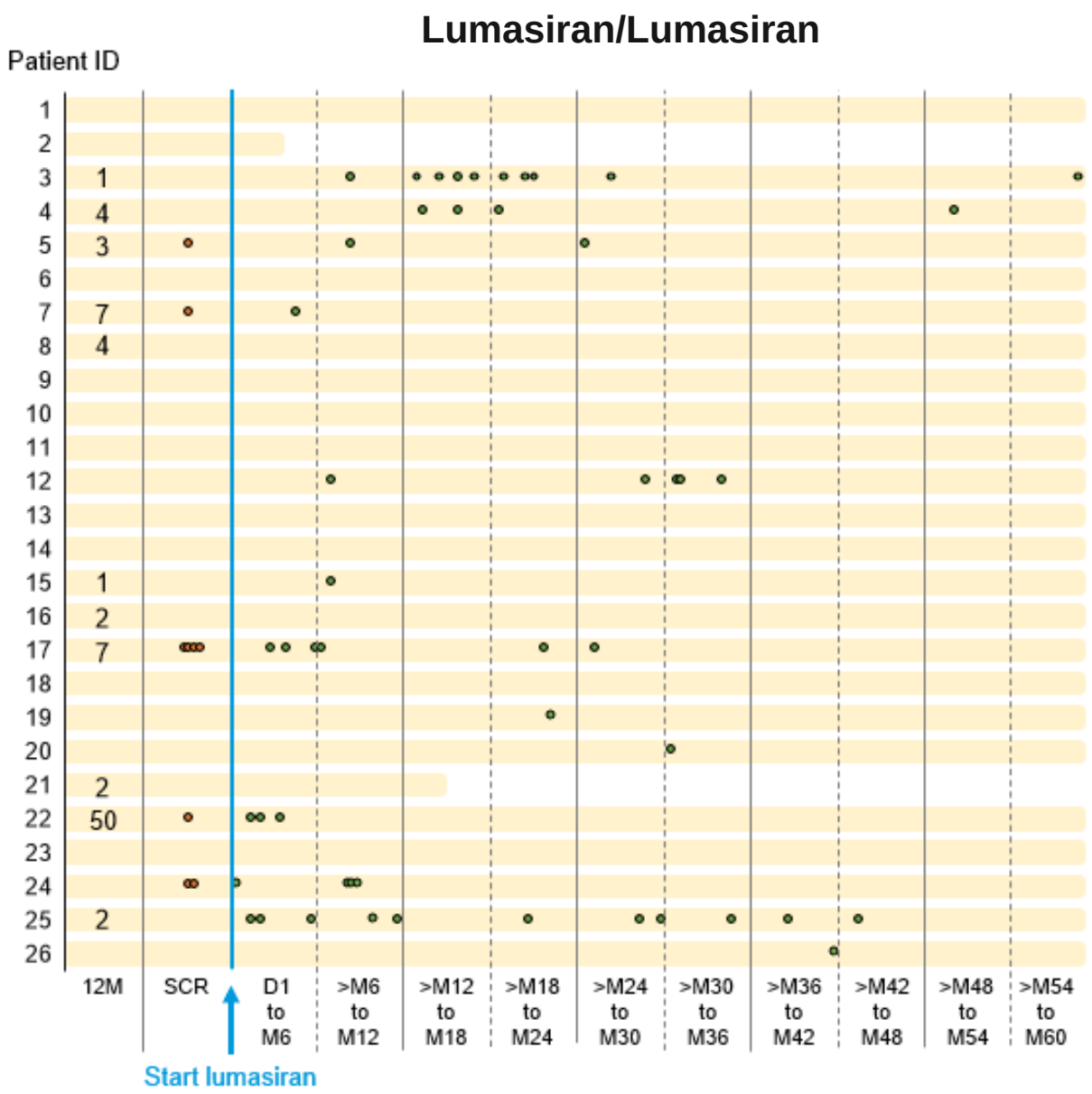
Kidney Stone Event Rates in Phase 3 ILLUMINATE-A

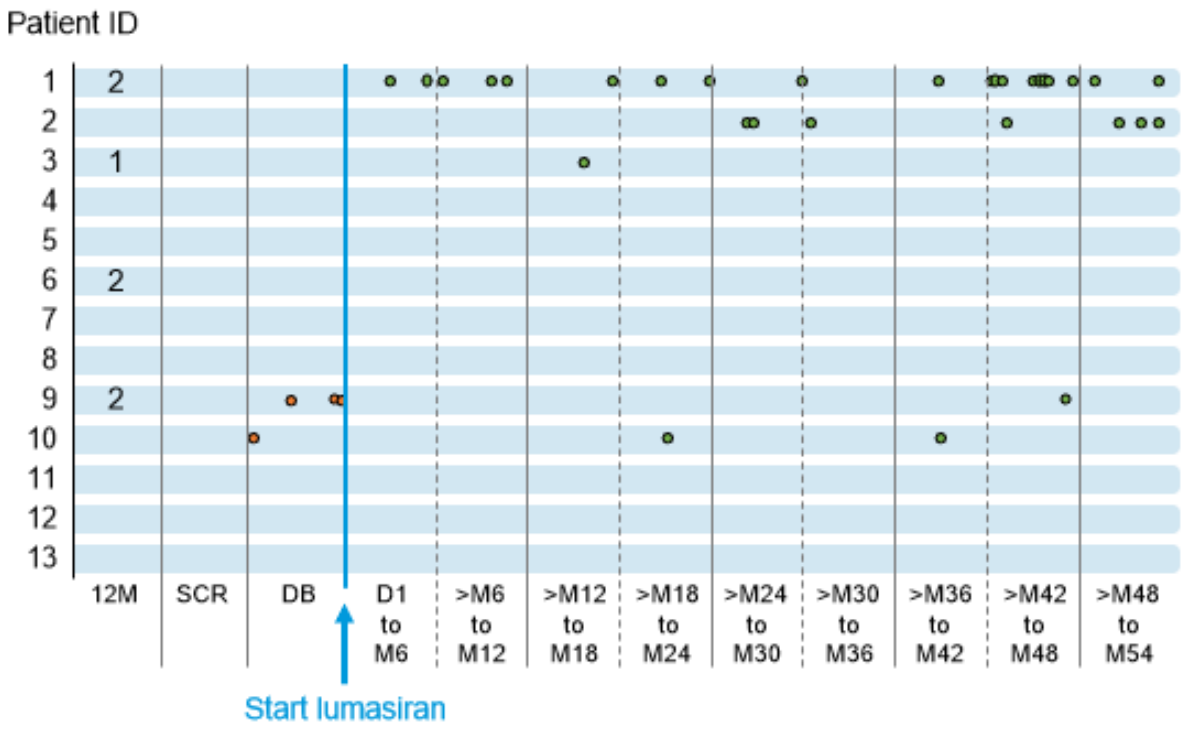
- In ILLUMINATE-A, 21/39 (54%) patients had no KSEs during lumasiran treatment and 7/39 (18%) patients had only 1 KSE



Post hoc analysis. Patients in ILLUMINATE-A were not stratified by KSE history.
[a]Patient-reported history of KSEs.
D, day; DB, double-blind; CI, confidence interval; KSE, kidney stone event; M, month; OLE, open-label extension; PY, patient-year.

Kidney Stone Events by Patient in Phase 3 ILLUMINATE-A



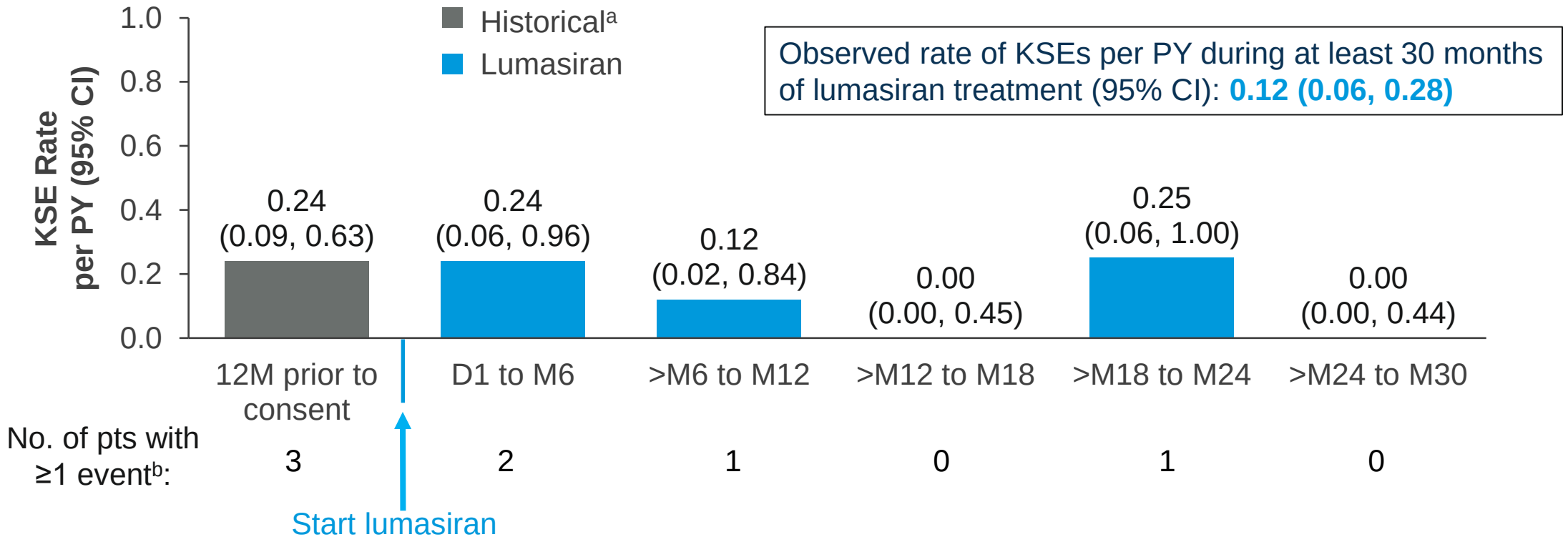


Patients were screened within 60 days prior to study drug administration. Each line represents 1 patient. Each data point indicates 1 KSE. The timing for historical events (prior 12 months) was not documented.

DB, double-blind; M, month; OLE, open-label extension; SCR, screening; Y, year.

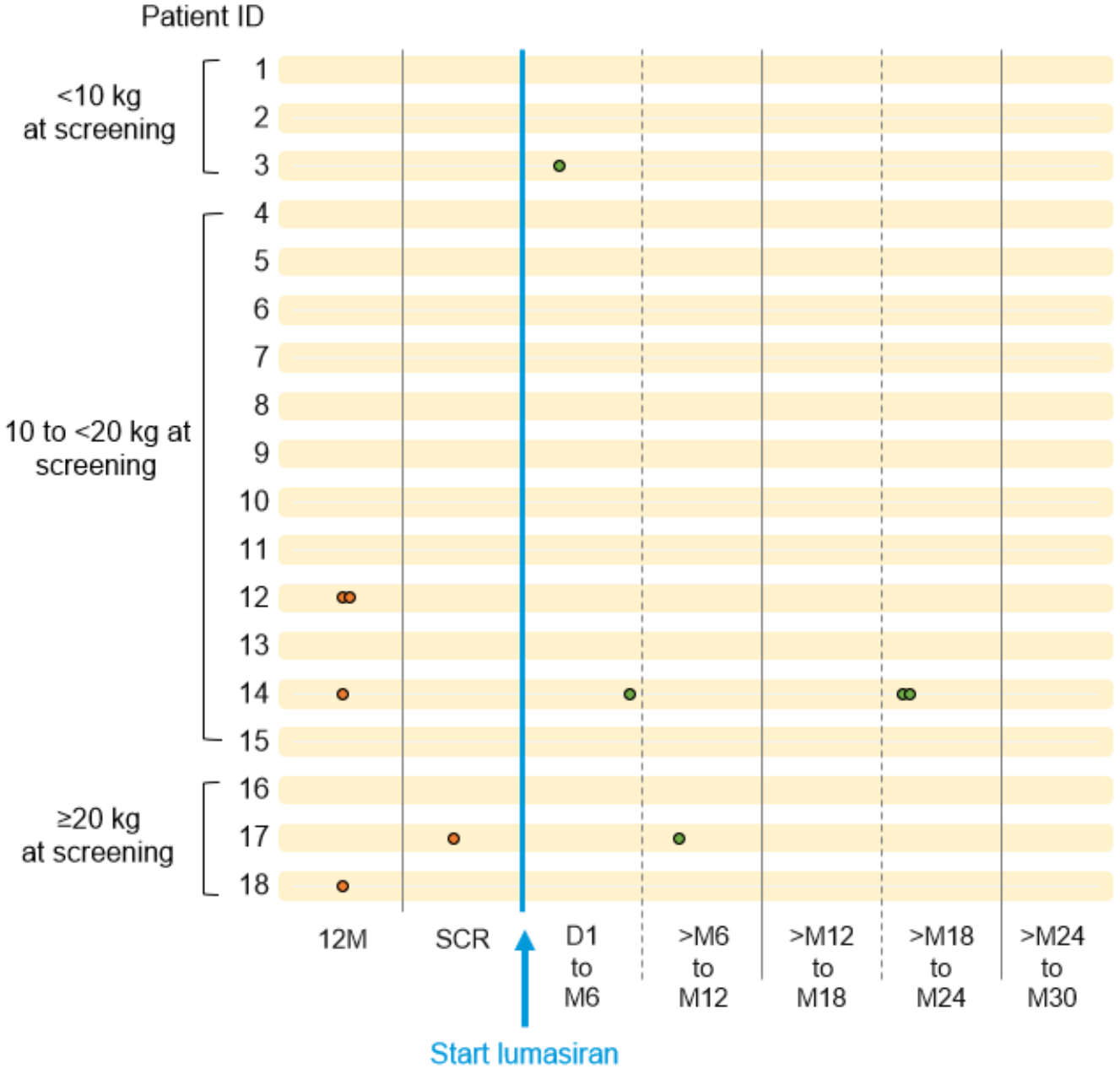
Kidney Stone Event Rates in Phase 3 ILLUMINATE-B

- In ILLUMINATE-B, 14/18 (78%) patients had no KSEs during at least 30 months of lumasiran treatment and 3/18 (17%) patients had only 1 KSE



[a]Patient-reported history of KSEs.
[b]A single patient had a single KSE noted beyond the M30 time point.
CI, confidence interval; D, day; KSE, kidney stone event; M, month; PY, patient-year.

Kidney Stone Events by Patient in Phase 3 ILLUMINATE-B



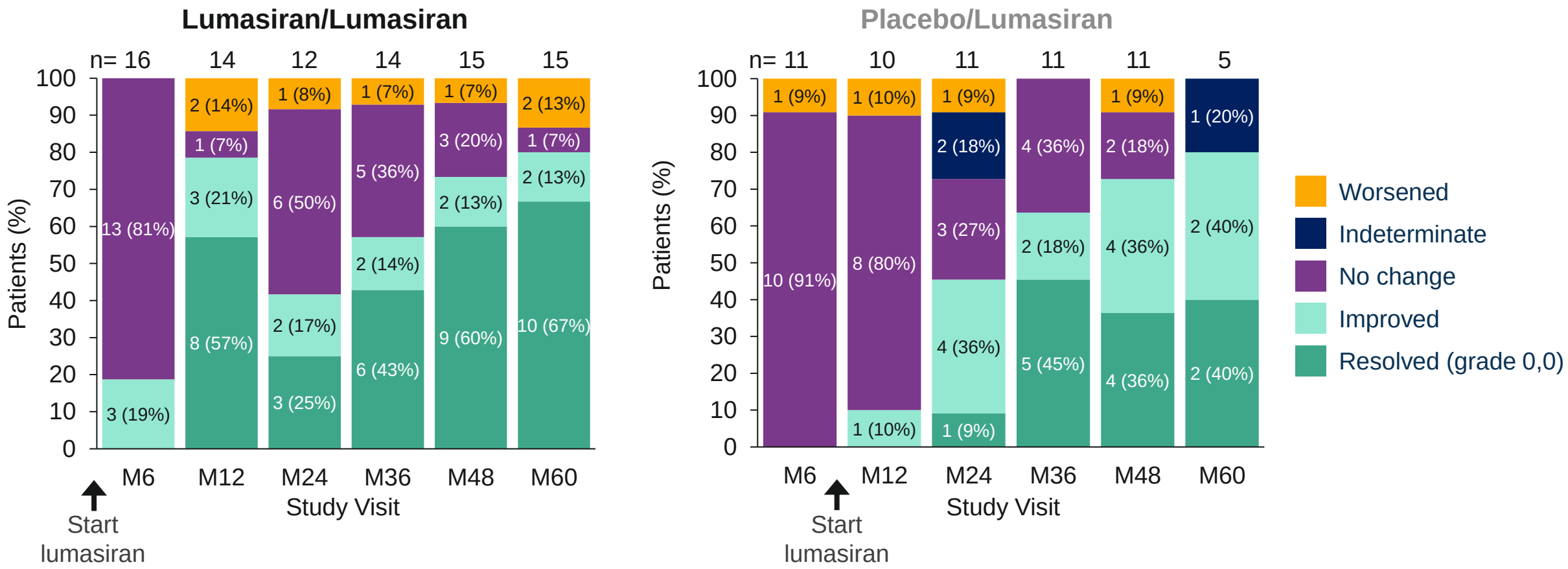
Each line represents 1 patient. Each data point indicates 1 KSE. Weight is at time of screening. The timing for historical events (prior 12 months) was not documented. KSEs portrayed for prior 12 months and screening are not drawn based on when each event occurred.

A single patient had a single KSE noted beyond the M30 time point.

D, day; KSE, kidney stone event; M, month; SCR, screening.

Nephrocalcinosis in Phase 3 ILLUMINATE-A

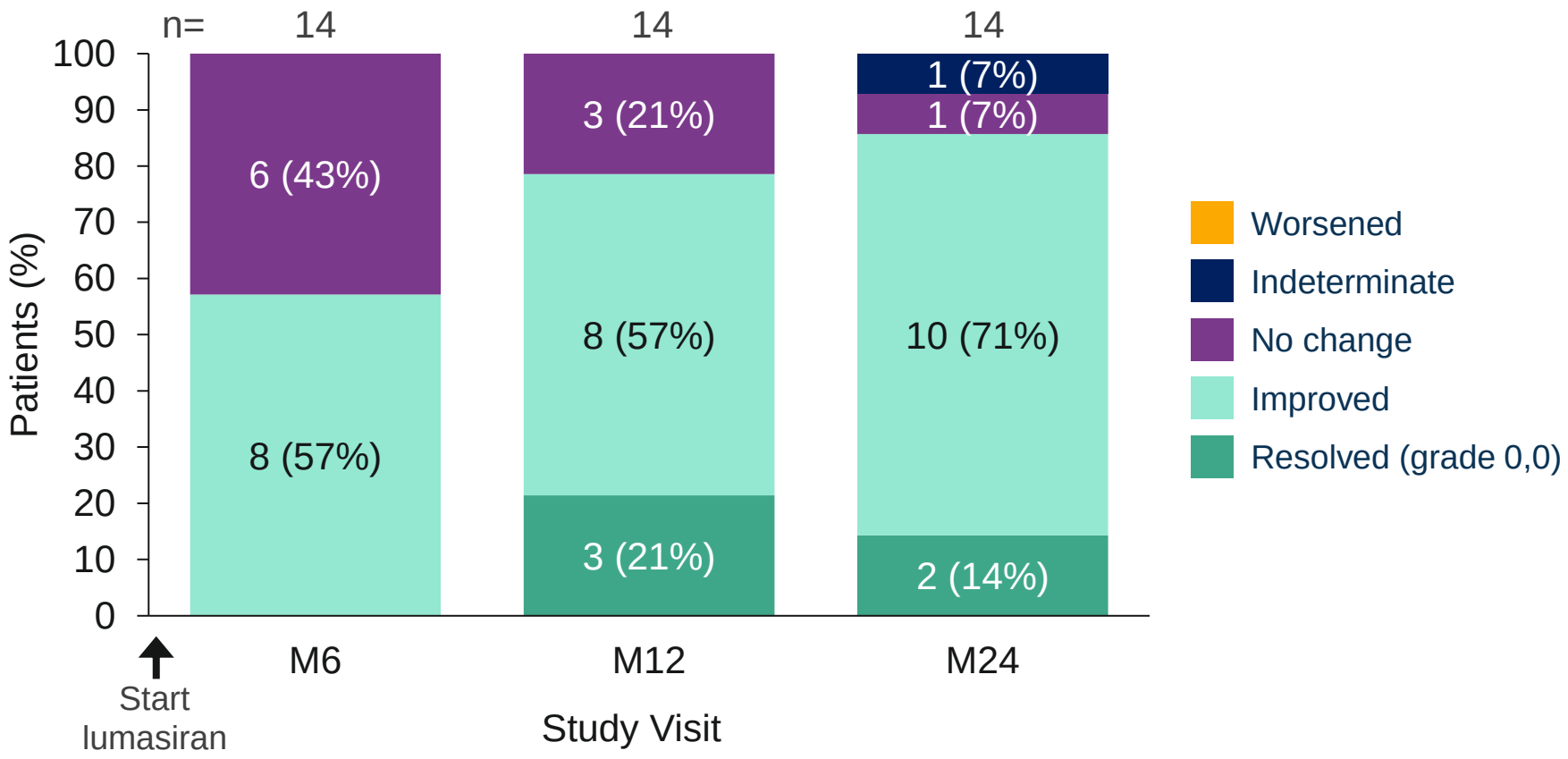
- Overall, 20 patients had NC at baseline and an assessment at end of study; among them, NC grade improved in 16 (80%) patients after 54 to 60 months of lumasiran treatment



Post hoc analysis. Indeterminate indicates improvement in one kidney and worsening in the other.
M, month; NC, nephrocalcinosis.

Nephrocalcinosis in Phase 3 ILLUMINATE-B

- In ILLUMINATE-B, 14 patients had NC at baseline and an assessment at end of study; among them, NC grade improved in 12 (86%) patients after 24 months of lumasiran treatment



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

Conclusions

- Long-term lumasiran treatment was associated with low occurrence of kidney stone events in the Phase 2 OLE study, ILLUMINATE-A, and ILLUMINATE-B
- Medullary NC grade frequently improved in patients treated with lumasiran for 5 years in ILLUMINATE-A and at least 30 months in ILLUMINATE-B
- A subset of patients exhibited complete resolution of nephrocalcinosis in ILLUMINATE-A and ILLUMINATE-B
- These are encouraging and clinically relevant trends that are consistent with the degree of urinary oxalate reduction while on lumasiran treatment

KSE, kidney stone event; NC, nephrocalcinosis; OLE, open-label extension.

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Thank You!