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

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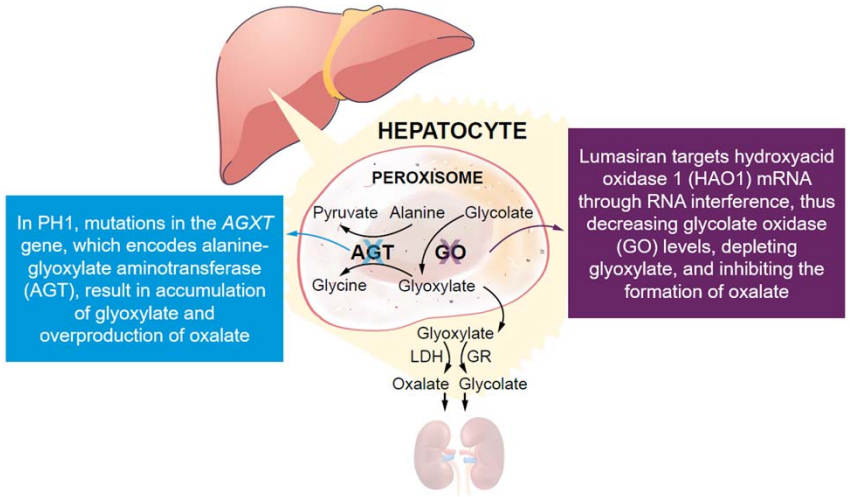
Introduction

- 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]
  - Pediatric patients with PH1 are characterized by presentation before adolescence (median: 3 years), nephrocalcinosis (43%), decreased eGFR at diagnosis (median: 52 mL/min/1.73m^2), and calcium oxalate monohydrate stone composition (median: 100%)[4]
- Lumasiran, the first approved RNAi treatment for PH1 with the longest duration of efficacy data, effectively lowers urinary oxalate in pediatric and adult patients[5,6]



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. Tasian Ge, et al. Distinguishing characteristics of pediatric patients with primary hyperoxaluria type 1 in PEDSnet. *J Pediatr Urol*. 2024 Feb;20(1):88.e1-88.e9. doi: 10.1016/j.jpurol.2023.10.001. **5.** 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. **6.** Oxlumo [package insert]. Cambridge, MA: Alnylam Pharmaceuticals; 2022.

Objective and Methods

- To evaluate long-term effects of lumasiran on kidney stone events (KSE) and nephrocalcinosis (NC) in patients with PH1

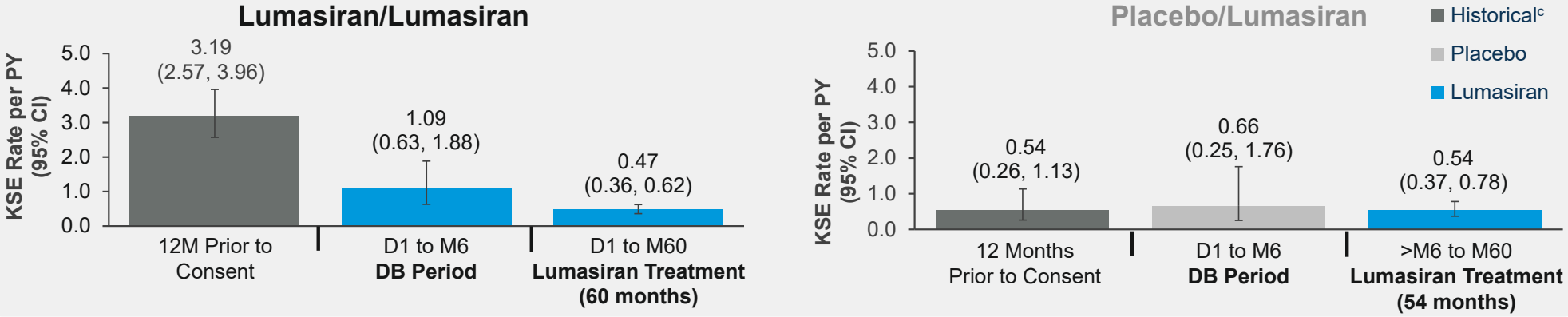
Study	Phase 3 ILLUMINATE-A N=39	Phase 3 ILLUMINATE-B N=18
Design	• Randomized, double-blind, placebo-controlled • 6-month primary analysis • 54-month extension period	• Single-arm, open-label • 6-month primary analysis • 54-month extension period
Patients	• PH1 • Age ≥6 years • eGFR ≥30 mL/min/1.73m^2	• PH1 • Age <6 years • eGFR >45 mL/min/1.73m^2[a]
Exploratory endpoints	• KSE rates • Medullary NC grade	• KSE rates • Medullary NC grade

- KSEs defined as any of the following: visit to healthcare provider because of a kidney stone, medication for renal colic, stone passage, gross 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 ILLUMINATE-B)

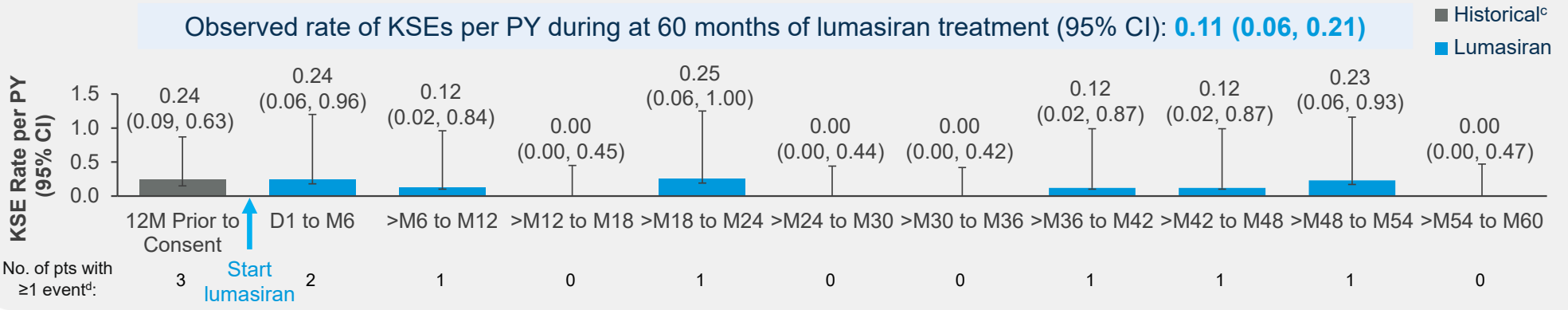
[a]Normal serum creatinine if <12 months old.
eGFR, estimated glomerular filtration rate; KSE, kidney stone event; NC, nephrocalcinosis; PH1, primary hyperoxaluria type 1.
1. Dick PT, et al. *Pediatr Radiol*. 1999;29:68-72.

Kidney Stone Event Rates in ILLUMINATE-A and ILLUMINATE-B

- In **ILLUMINATE-A**[a,b], 21/39 (54%) patients had no KSEs; 7/39 (18%) patients had only 1 KSE



- In **ILLUMINATE-B**[a], 14/18 (78%) patients had no KSEs; 2/18 (11%) patients had only 1 KSE

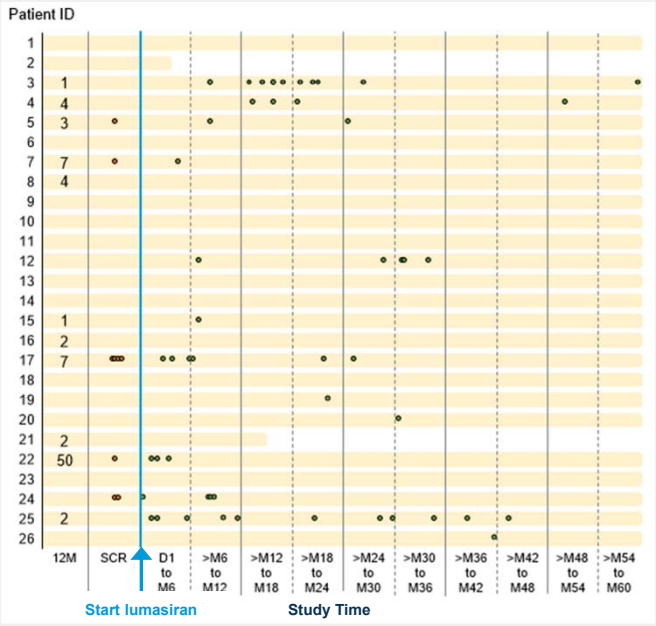


[a]Post hoc analysis. [b]Patients in ILLUMINATE-A were not stratified by KSE history. [c]Patient-reported history of KSE. [d]A single patient had a single KSE noted beyond the M30 time point.
D, day; DB, double-blind; CI, confidence interval; KSE, kidney stone event; M, month; PY, patient-year.

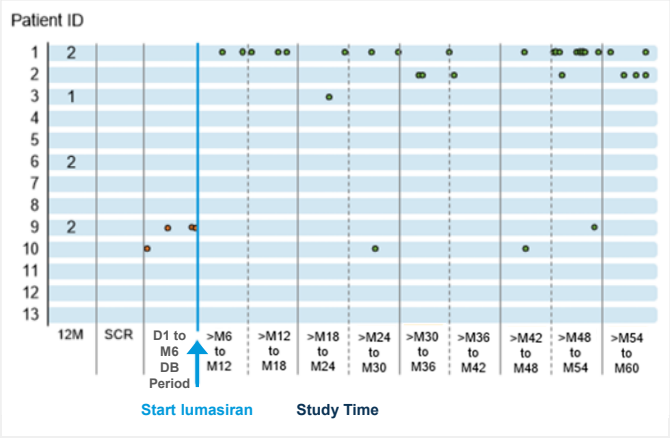
Kidney Stone Events by Patient in ILLUMINATE-A and ILLUMINATE B

ILLUMINATE-A[a,b]

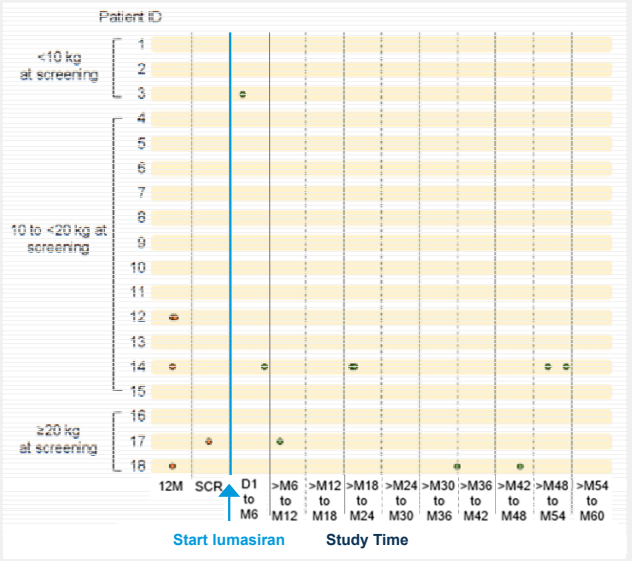
Lumasiran/Lumasiran



Placebo/Lumasiran



ILLUMINATE-B[a,c]

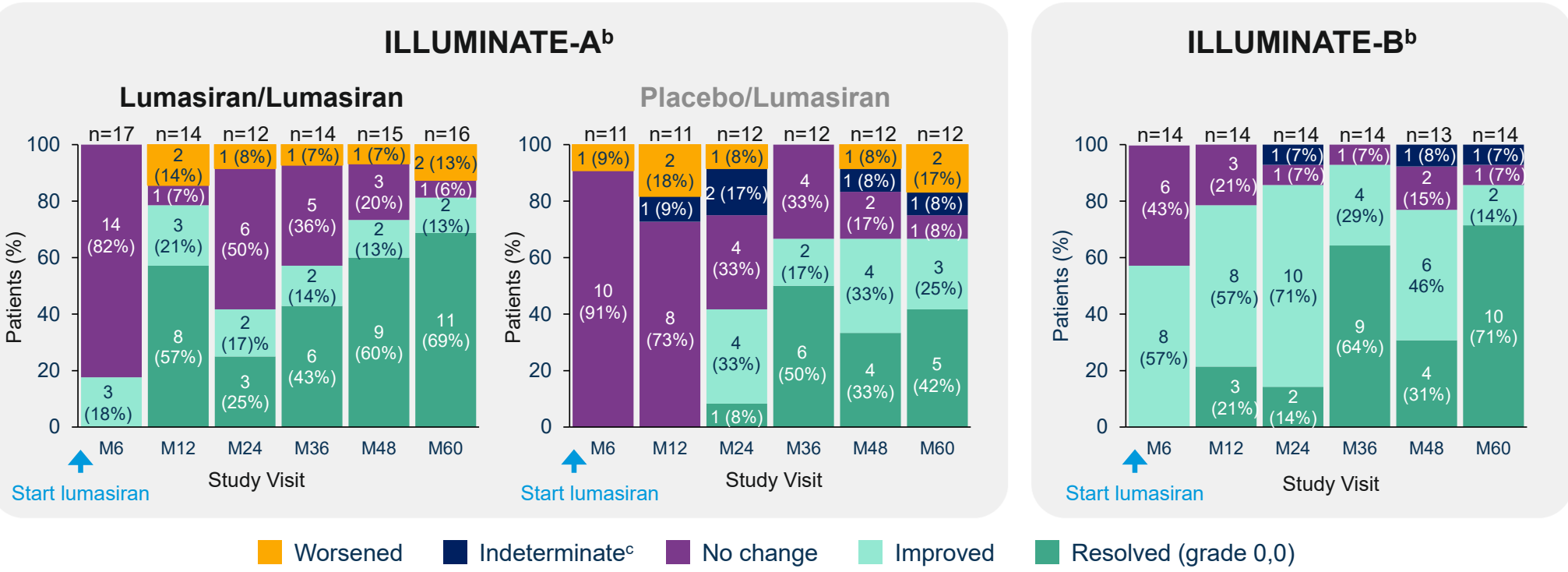


D, day; DB, double blind; KSE, kidney stone event; M, month; SCR, screening.

[a]Each line represents 1 patient. Each data point indicates 1 KSE. The timing for historical events (prior 12 months) was not document. KSE portrayed for 12M and SCR are not drawn based on when each event occurred. The 12M and SCR data points are centered; other data points are plotted showing when they occurred during the period. [b]Patients were screened within 60 days prior to study drug administration. [c]Weight is at time of screening.

Nephrocalcinosis in ILLUMINATE-A and ILLUMINATE-B

- At 60 months, NC grade improved in a majority of patients who had NC at baseline[a]
  - 21/28 (75%) patients in ILLUMINATE-A, 16 improved to grade 0 bilaterally
  - 12/14 (86%) patients in ILLUMINATE-B, 10 improved to grade 0 bilaterally
- In patients without NC (grade 0 bilaterally) at baseline, 7/7 (100%) in ILLUMINATE-A and 4/4 (100%) in ILLUMINATE-B had no change in NC grade at 60 months



[a]In patients who had NC at baseline and an assessment at end of study. [b]Post hoc analysis. [c]Indicates improvement in one kidney and worsening in the other.
M, month; NC, nephrocalcinosis.

Conclusions

- The majority of patients experienced 0 or 1 kidney stone events over long-term treatment of lumasiran
- Medullary nephrocalcinosis grade frequently improved in patients treated with lumasiran for 5 years in ILLUMINATE-A and 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

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