Modeling the Risk of Progression to Kidney Failure in Patients With Primary Hyperoxaluria Type 1 Treated With Lumasiran Relative to a Natural History Cohort Not Treated With Lumasiran

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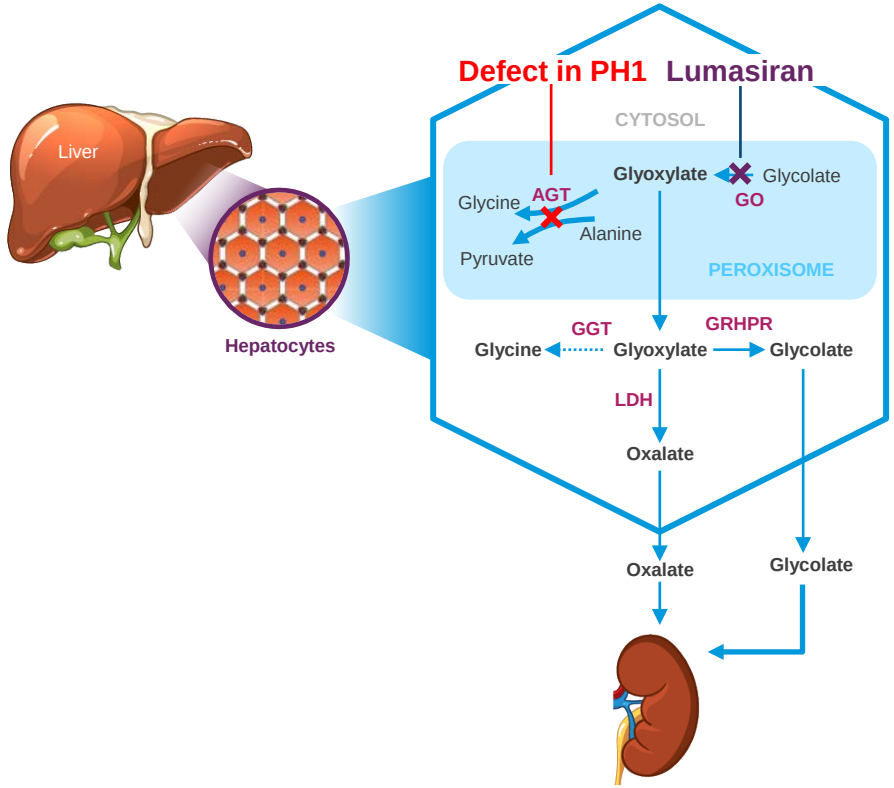
Primary Hyperoxaluria Type 1 and Lumasiran

- Patients with PH1 overproduce oxalate due to a deficiency in the hepatic peroxisomal enzyme AGT[1,2]
- Excretion of excess oxalate by the kidneys can lead to recurrent kidney stones, nephrocalcinosis, progressive kidney failure, and multiorgan damage from systemic oxalosis[1-3]
- The risk of kidney failure is positively associated with UOx excretion[4]
- Lumasiran, a subcutaneously administered RNAi therapeutic that decreases hepatic oxalate production by inhibiting the production of GO,[5-7] has been approved by the FDA for the treatment of PH1 to lower UOx levels in pediatric and adult patients[6]
- In the Phase 3 ILLUMINATE-A study (ClinicalTrials.gov: NCT03681184; EudraCT: 2018-001981-40), treatment with lumasiran resulted in substantial reductions in UOx with an acceptable safety profile in patients with PH1[8]



Here, we estimated the risk of progression to kidney failure in patients with PH1 treated with lumasiran, relative to patients not treated with lumasiran, using UOx excretion data from the ILLUMINATE-A study and natural history data on the relationship between UOx excretion and kidney failure

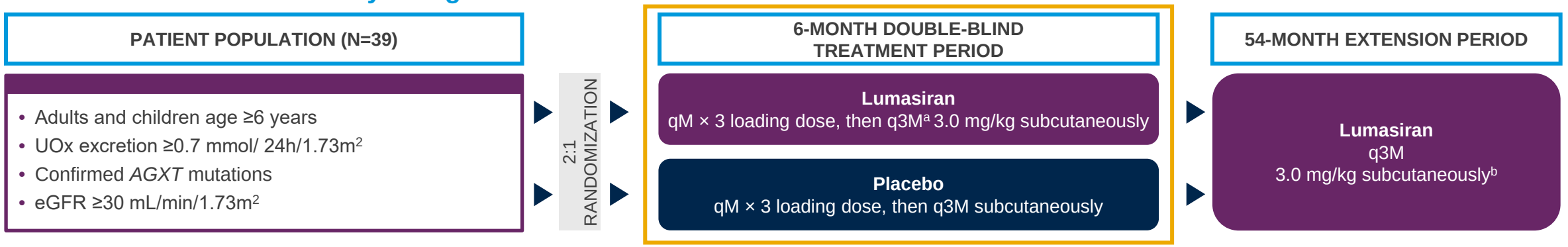
AGT, alanine–glyoxylate aminotransferase; FDA, US Food and Drug Administration; GGT, glutamate-glyoxylate aminotransferase; GO, glycolate oxidase; GRHPR, glyoxylate reductase/hydroxypyruvate reductase; LDH, lactate dehydrogenase; PH1, primary hyperoxaluria type 1; RNAi, RNA interference; UOx, urinary oxalate.

1. Cochat P, Rumsby G. *N Engl J Med*. 2013;369:649-58. 2. Danpure CJ. *The Online Metabolic and Molecular Bases of Inherited Disease*. New York, NY: The McGraw-Hill Companies, Inc.; 2019. 3. Lieske JC, et al. *Am J Nephrol*. 2005;25:290-6. 4. Zhao F, et al. *Clin J Am Soc Nephrol.* 2016;11:119-26. 5. Liebow A, et al. *J Am Soc Nephrol.* 2017;28:494-503. 6. Oxlumo [package insert]. Cambridge, MA: Alnylam Pharmaceuticals; 2020. 7. Oxlumo [summary of product characteristics]. Amsterdam, Netherlands: Alnylam Netherlands; 2020. 8. Garrelfs SF, et al. *N Engl J Med*. 2021;384:1216-26.

Methods

- A skewed-normal distribution of 24-hour UOx values for patients with PH1 was simulated based on reported summary UOx values (median, minimum, maximum, and IQR) from the RKSC PH Registry among patients who were not in kidney failure at diagnosis and did not receive lumasiran[1]
  - Median (Q1, Q3) age at diagnosis was 8.1 (4.0, 18.2) years[1]
  - Kidney failure was defined as an eGFR <15 mL/min/1.73m^2 or start of dialysis or kidney transplantation[1]
- Data from the 6-month, double-blind treatment period of the ILLUMINATE-A trial of lumasiran were used to build a log-linear model of post-lumasiran treatment steady-state UOx as a function of baseline UOx and treatment (lumasiran vs placebo)
- This model was applied to the simulated 24-hour UOx values of the RKSC cohort, considered as pretreatment baseline, to predict the distribution of steady-state UOx values for RKSC patients in a scenario in which they were treated with lumasiran

ILLUMINATE-A Phase 3 Study Design



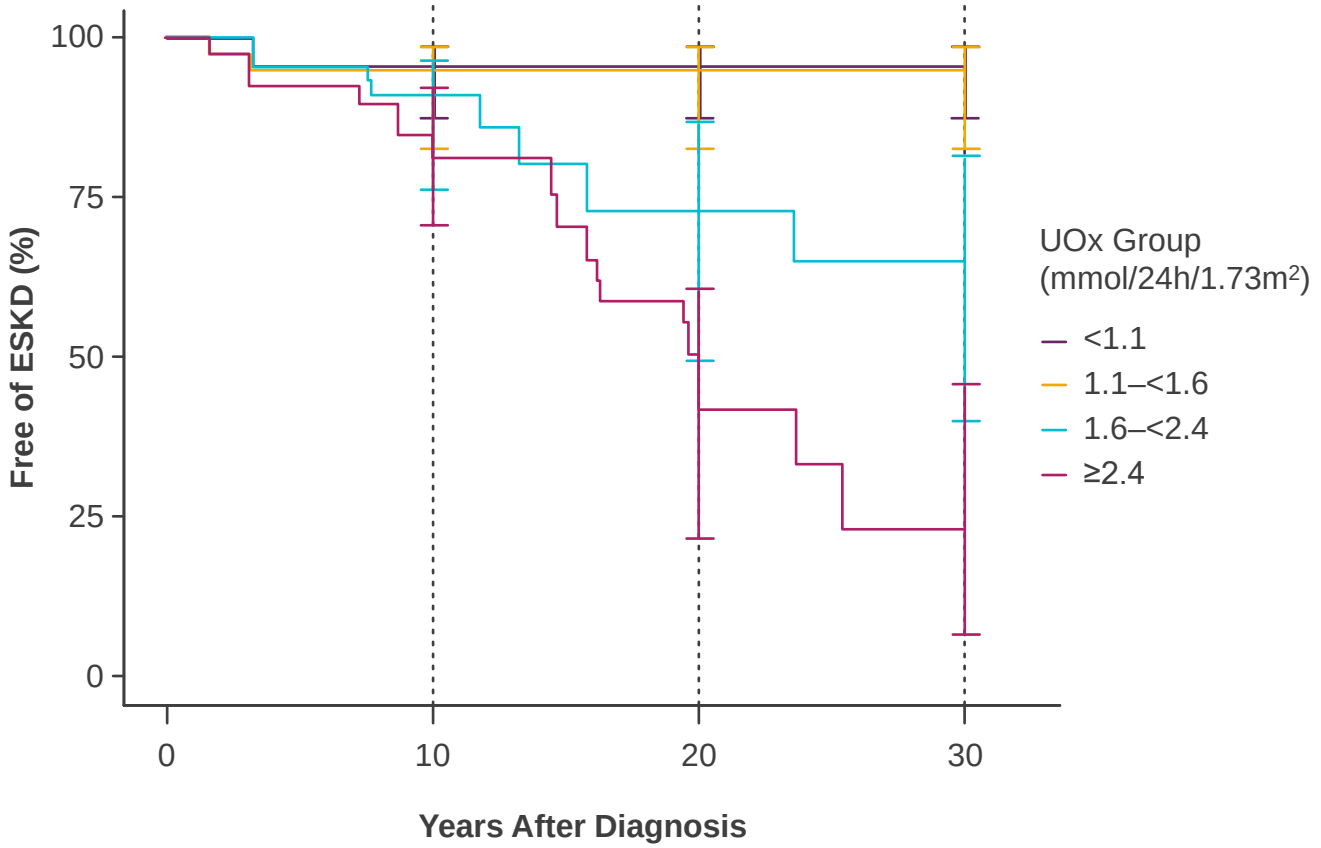
- Treatment arms were stratified at randomization based upon mean 24-hour UOx from the first 2 valid samples collected during screening (≤1.70[c] vs >1.70[c] mmol/24h/1.73m^2)
- Oxalate was measured with a validated liquid chromatography-tandem mass spectrometry assay

[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/24h/1.73m^2 = 153 mg/24h/1.73m^2 (1 mmol/24h/1.73m^2 = 90 mg/24h/1.73m^2).
Data from the 6-month double-blind treatment period (gold box) were used to build the log-linear model of post-lumasiran treatment steady-state UOx.
eGFR, estimated glomerular filtration rate; IQR, interquartile range; PH1, primary hyperoxaluria type 1; Q, quartile; q3M, once every 3 months; qM, once monthly; qM × 3, once monthly for 3 consecutive months; RKSC, Rare Kidney Stone Consortium; UOx, urinary oxalate.
1. Zhao F, et al. *Clin J Am Soc Nephrol.* 2016;11:119-26.

Methods (cont'd)

- Kidney failure rates per 100 patients (with 95% CIs) in the RKSC PH1 cohort, had all received lumasiran, were estimated at 10-year intervals using the following data sources in conjunction with one another:
  - A model of kidney failure risk as a function of 24-hour UOx excretion, based on published Kaplan-Meier curves of kidney survival (RKSC)[1]
  - Predicted on-treatment UOx values (as described in the previous slide) for patients in the RKSC PH1 cohort, had all received lumasiran
- 95% CIs were estimated, via the Greenwood method, based on the predicted number of events during the interval of interest and the number of patients at risk at the start of the interval
- To allow estimation of the number of events avoided with lumasiran, kidney failure rates in a scenario without lumasiran treatment (i.e., with even distribution of patients across UOx quartiles) were also calculated from the RKSC model

Kaplan-Meier Plot of Kidney Survival by Quartile of UOx Excretion at Diagnosis



Probability with estimated 95% CIs was extracted from the RKSC PH1 cohort.[1]

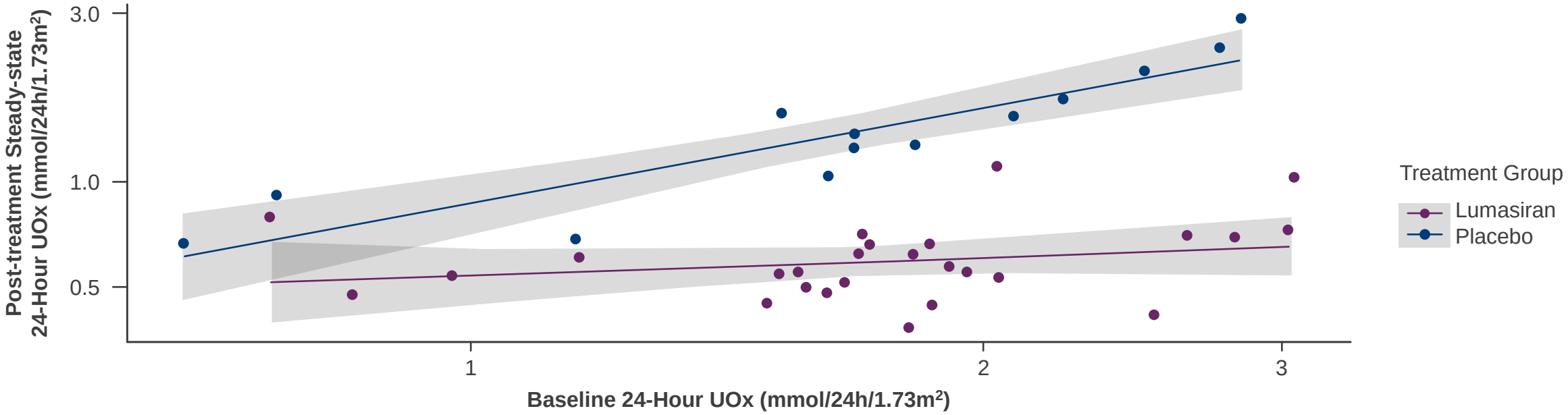
CI, confidence interval; ESKD, end-stage kidney disease; PH1, primary hyperoxaluria type 1; RKSC, Rare Kidney Stone Consortium; UOx, urinary oxalate.

1. Zhao F, et al. *Clin J Am Soc Nephrol.* 2016;11:119-26.

Modeling of 24-Hour UOx Excretion

- The RKSC Registry included 192 patients with PH1 who did not have kidney failure at diagnosis[1]
- The log-linear model derived from ILLUMINATE-A data predicted a substantial reduction in UOx excretion across all levels of baseline UOx, with greater reductions seen in patients with higher baseline 24-hour UOx excretion

Estimated Lumasiran Treatment Effect on 24-Hour UOx Excretion in ILLUMINATE-A



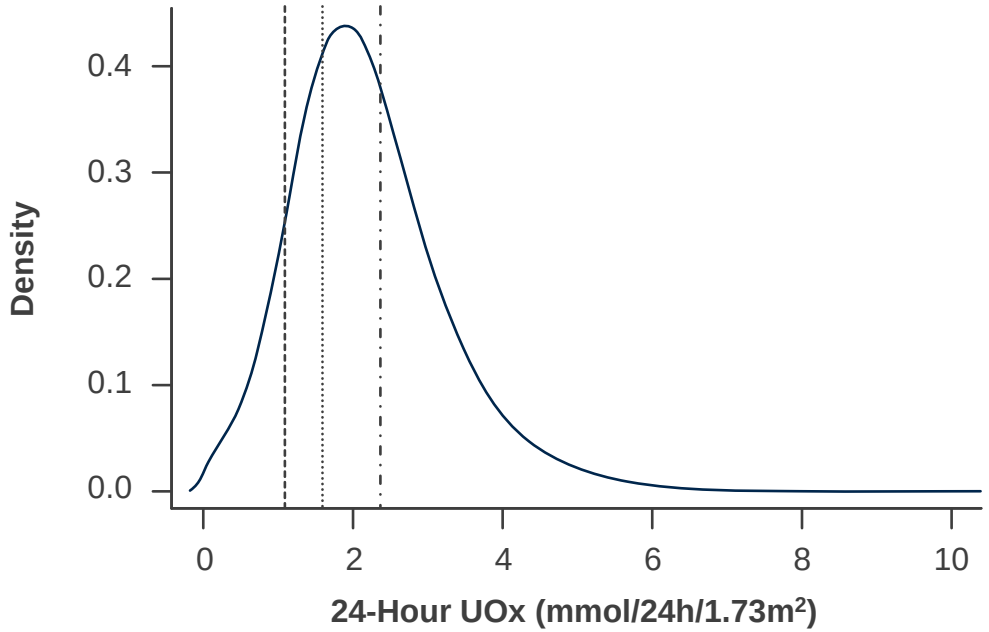
PH1, primary hyperoxaluria type 1; RKSC, Rare Kidney Stone Consortium; UOx, urinary oxalate.

1. Zhao F, et al. *Clin J Am Soc Nephrol.* 2016;11:119-26.

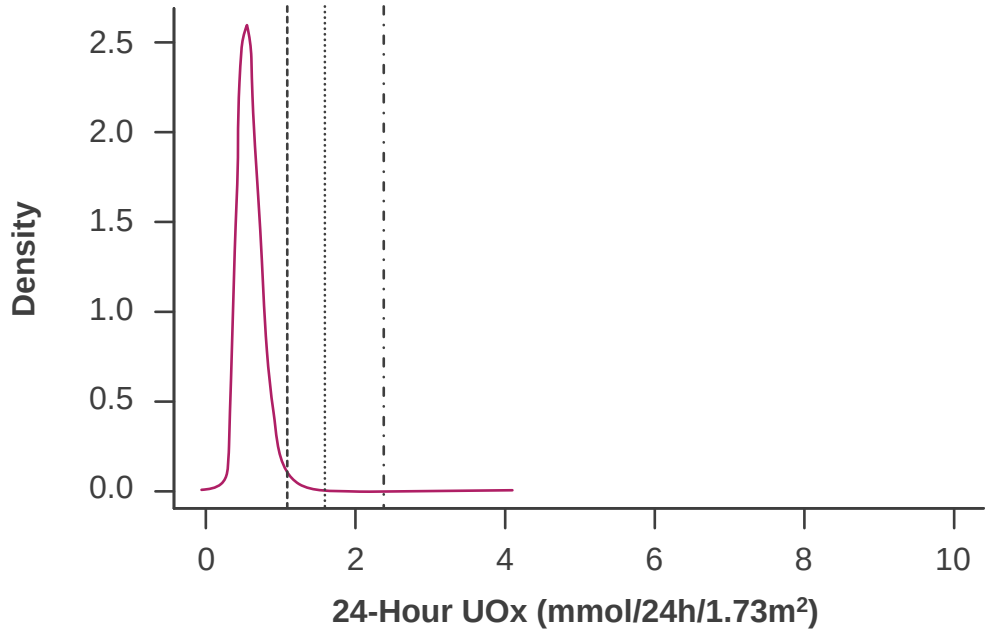
Modeling of 24-Hour UOx Excretion (cont'd)

- The mean (SD) 24-hour UOx excretion for the RKSC PH1 cohort was 2.2 (1.1) mmol/24h/1.73m^2 in the absence of lumasiran treatment and was predicted to decrease to 0.62 (0.17) mmol/24h/1.73m^2 in the model that simulated the effect of lumasiran administration

Simulated Distribution of 24-Hour UOx Excretion in Patients From the RKSC Not Treated With Lumasiran



Predicted Distribution of 24-Hour UOx Excretion in Patients From the RKSC Had They Been Treated With Lumasiran

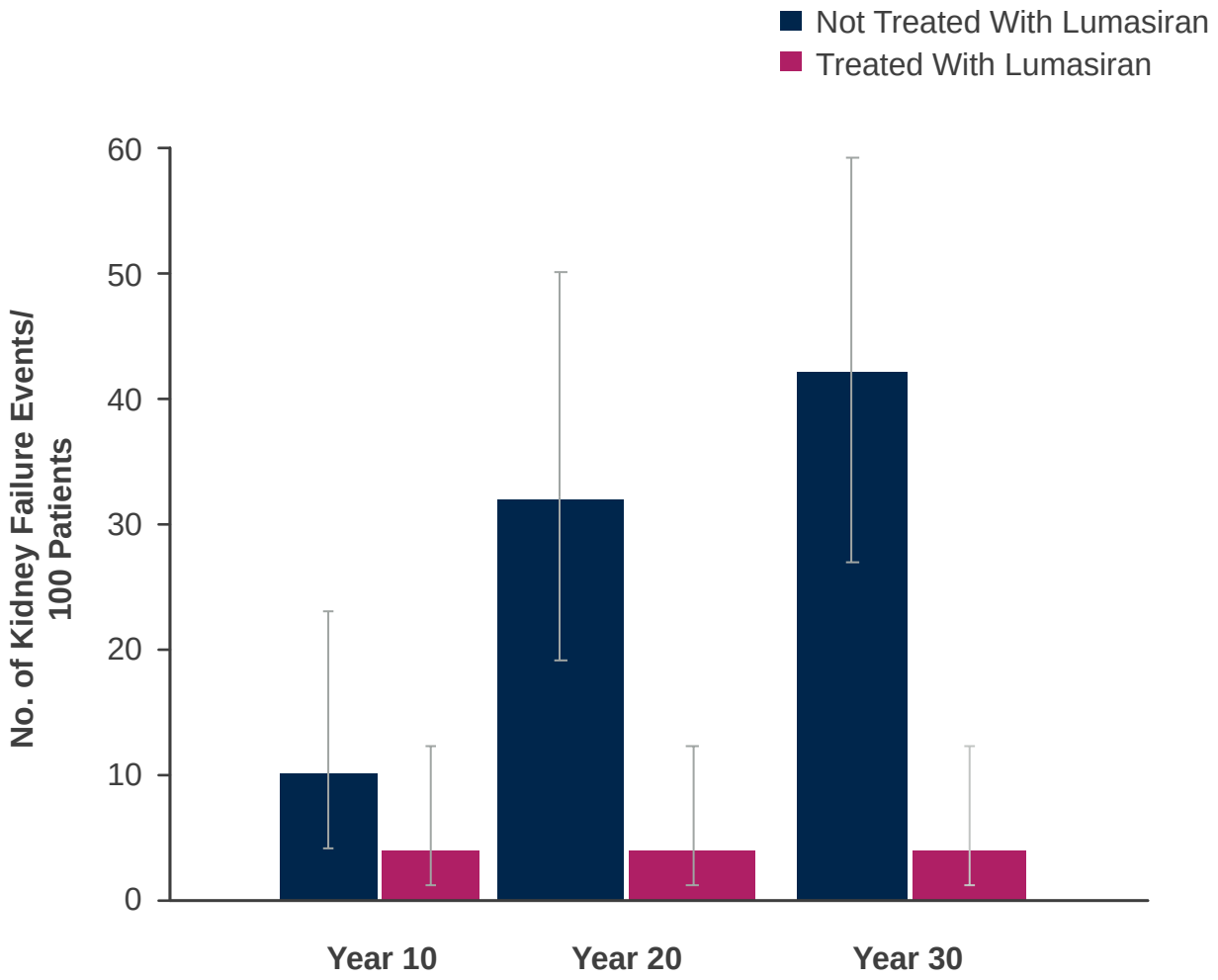


Vertical dashed lines represent 24-hour UOx excretion rates of 1.1, 1.6, and 2.4 mmol/24h/1.73m^2.
PH1, primary hyperoxaluria type 1; RKSC, Rare Kidney Stone Consortium; SD, standard deviation; UOx, urinary oxalate.

Kidney Failure Events

- Based on simulated 24-hour UOx distribution and the probability of kidney failure:
  - The predicted number of kidney failure events/100 patients (95% CI) using the model for patients not treated with lumasiran at 10, 20, and 30 years, was 10 (4, 23), 32 (19, 50), and 42 (27, 59), respectively
  - The estimated cumulative number of kidney failure events/100 patients (95% CI) using the model of patients treated with lumasiran was 4 (1, 12) at 10 years and remained unchanged at 20 and 30 years
- Treatment effects assume the treatment was initiated promptly after diagnosis, very early in life
  - The model presented may overestimate treatment benefits in a scenario where treatment is initiated later in life, especially after CKD has occurred

Predicted Number of Kidney Failure Events/100 Patients



CI, confidence interval; CKD, chronic kidney disease; UOx, urinary oxalate.

Summary

- PH1 is a rare, devastating disease, with high morbidity and mortality
- As oxalate overproduction is the key causative factor of PH1, substantial reductions in UOx predict clinical benefit in patients with relatively preserved kidney function
- This analysis predicts a long-term reduction in kidney failure risk among patients with PH1 treated with lumasiran, assuming prompt treatment at diagnosis

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PH1, primary hyperoxaluria type 1; UOx, urinary oxalate.