Impact of Lumasiran on Long-Term Clinical Outcomes in Primary Hyperoxaluria Type 1 (PH1): a Cohort Simulation Model

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Conclusions

- Based on the sustained reduction in oxalate levels attributed to lumasiran, the current model suggests that in patients with PH1, lumasiran may prolong survival, delay progression to end-stage kidney disease and reduce the need for liver and kidney transplants compared with usual care.
- Early initiation of lumasiran may confer sustained clinical benefits by modifying the disease trajectory in patients with PH1 and improving long-term outcomes. While therapeutic benefits were estimated across all stages of disease severity, they were more pronounced in individuals with early-stage disease compared to those with advanced disease. These projected outcomes should be validated through clinical data as longer-term use of lumasiran continues

Background

PH1 is a rare genetic disorder in which endogenous hepatic oxalate overproduction can lead to recurrent kidney stones, chronic kidney disease (CKD) and kidney failure.

- Hepatic deficiency of the enzyme alanine-glyoxylate aminotransferase leads to an increase in oxalate concentration and crystallization of calcium oxalate.
- As kidney function declines, plasma oxalate (POx) increases producing systemic oxalosis and multi-organ damage.
- Historically, therapeutic options for PH1 have been limited (Table 1).

Table 1. Conventional therapeutic options (pre-RNAi)*

Therapy	Description	Limitations
Conservative measures	Hyperhydration, dietary restrictions, and crystallization inhibitors.	May delay but do not prevent renal function decline.
High-intensity dialysis	Used to remove oxalate; often employed as a bridge to transplantation.	Ineffective long-term as oxalate production exceeds removal capacity.
Combined liver–kidney transplant	Historically the only effective treatment for most patients in advance CKD stages.	Involves long waiting times, procedural risks, and lifelong immunosuppression.

* Liver-kidney transplant is a treatment for PH1 in advanced CKD (stages 4–5), but it is excluded as a comparator in the model outcomes.

- Lumasiran is the first FDA- and EMA-approved RNA interference (RNAi) therapy for PH1 and may slow progression to systemic oxalosis—potentially reducing the need for liver or combined liver-kidney transplantation in affected patients..

Objective

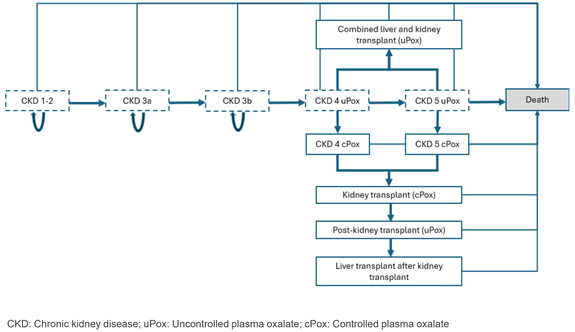
- To model and simulate the potential long-term clinical outcomes of lumasiran in PH1, including progression to end-stage kidney disease (ESKD), transplant rates, and mortality.

Methods

Long-term effects of lumasiran and usual care were simulated using a Markov model, with six-month cycles over a lifetime horizon

- The target population in the model consist of PH1 patients of any age without disease control.
- CKD distribution at the simulation start was informed by the baseline distribution of PH1 patients enrolled in the Rare Kidney Stone Consortium registry.
- The cohort transitioned through twelve health states defined by CKD stage, POx levels, transplant status (liver and/or kidney), and death.
- Comparator: Usual care, including standard therapies but excluding RNAi therapies (see table 1).
- Transitions between health states informed by lumasiran treatment effect (phase III ILLUMINATE trials), USA national transplant and mortality data, and publications. Transitions in the usual care cohort were informed by RKSC registry data and estimated annual eGFR decline across CKD stages in PH1.

Figure 1. Markov model structure



CKD: Chronic kidney disease; uPox: Uncontrolled plasma oxalate; cPox: Controlled plasma oxalate

Key assumptions and results of the cohort simulation model

Assumptions

- In early-stage CKD, patients in the lumasiran cohort maintained stable kidney function, with no progression observed, consistent with findings from ILLUMINATE-A
- The cohort entering the model in advanced stages started in an uncontrolled POx health state (oxalate supersaturation threshold of 50 µmol/L).
- The lumasiran cohort responding to treatment was expected to transition to controlled POx health states but the usual care cohort remained in uncontrolled POx.
  - The cohort in uncontrolled POx health states transitioned to combined liver-kidney transplant.
  - The cohort in controlled POx transitioned to isolated kidney transplant (avoiding the need for combined liver-kidney or liver transplant).
- If lumasiran is discontinued after isolated kidney transplant, patients may transition to “post-kidney transplant with uncontrolled POx,” followed by “liver transplant after kidney transplant
- Transition to less severe CKD stages was not permitted in either treatment group.
- Patients in all health states could transition to death at any time.

Cohort baseline characteristics

- Average age (years) at lumasiran initiation was 6.9 in children and 34 in adults, of whom 59% were male.
- Cohort distribution at baseline: 63.7% in CKD stages 0-3b, 9.5% in CKD stage 4, and 26.8% with ESKD

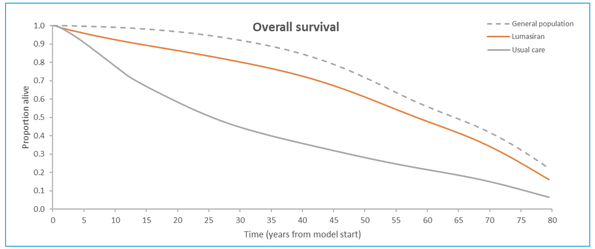
Limitations

- Limitations include gaps in literature on PH1 transplantation rates, long-term lumasiran data, and CKD stage–specific mortality. All model assumptions were reviewed by clinical experts and reflect real-world practice

Results

- The median time to death in the lumasiran cohort was 64.73 years (95% CI = 64.53, 64.93), compared to 30.79 years in the usual care cohort (95% CI = 30.60, 30.99; Figure 2).

Figure 2. Time to death curve



- Among preserved kidney function cohort, lumasiran had a lower proportion progressing to ESKD.
- Transplant rates were lower in the lumasiran arm independent of disease severity.

Table 2. Outcomes over lifetime

Patient Group	Outcome	Lumasiran Cohort	Usual Care Cohort
Preserved kidney function at baseline	Progression to ESKD	10%	92%
	Median time to ESKD	Not reached	11.5 years
	Lifetime transplant rate	5%	53%
Advanced kidney disease at initiation	Lifetime liver transplant rate	16%	66%
	Survival at 20 years	76%	49%

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References: 1. Groothoff JW, Metry E, Deesker L, et al. Clinical practice recommendations for primary hyperoxaluria: an expert consensus statement from ERKNet and OxalEurope. Nat Rev Nephrol. Mar 2023;19(3):194-211. **2.** Rumsby G, Cochat P. Primary hyperoxaluria. N Engl J Med. Nov 28 2013;369(22):2163. doi:10.1056/NEJMc1311606. **3.** Gang X LFaMJ. Lumasiran for. Front Pediatr 2023;10:1052625. **4.** Milliner DS HP, Sas DJ, et al. Primary Hyperoxaluria Type 1. GeneReviews® [Internet] Seattle (WA): University of Washington, Seattle. 2022. **5.** Danpure C. Primary hyperoxaluria. The Online Metabolic and Molecular Bases of Inherited Disease. 2019. **6.** Alnylam P. OXLUMO (lumasiran) injection, for subcutaneous use. Initial US approval. FDA. 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214103lbl.pdf. **7.** Saland JM, Lieske JC, Willey R, et al. Long-term Efficacy and Safety of Lumasiran in Patients with Primary Hyperoxaluria Type 1 in a Final Analysis of the ILLUMINATE-A Trial. Pediatric Academic Societies 2025. **8.** Alnylam P. OXLUMO (lumasiran) injection, for subcutaneous use. Initial US approval. FDA. 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214103lbl.pdf. **9.** Singh P VL, Schulte PJ, Sas DJ, Milliner DS, Lieske JC. Estimated GFR Slope Across CKD Stages in Primary Hyperoxaluria Type 1. American Journal of Kidney Diseases 2022. **10.** Garrelfs SF, Frishberg Y, Hulton SA, et al. Lumasiran, an RNAi Therapeutic for Primary Hyperoxaluria Type 1. N Engl J Med. Apr 01 2021;384(13):1216-1226. doi:10.1056/NEJMoa2021712. **11.** Hayes W, Sas DJ, Magen D, et al. Efficacy and safety of lumasiran for infants and young children with primary hyperoxaluria type 1: 12-month analysis of the phase 3 ILLUMINATE-B trial. Pediatr Nephrol. Apr 2023;38(4):1075-1086. **12.** Frishberg Y, Hayes W, Shasha-Lavsky H, et al. Efficacy and safety of lumasiran for infants and young children with primary hyperoxaluria type 1: 30-month analysis of the phase 3 ILLUMINATE-B trial. Front Pediatr. 2024;12:1392644. doi:10.3389/fped.2024.1392644. **13.** Michael M, Groothoff JW, Shasha-Lavsky H, et al. Lumasiran for Advanced Primary Hyperoxaluria Type 1: Phase 3 ILLUMINATE-C Trial. Am J Kidney Dis. Feb 2023;81(2):145-155.e1.doi:10.1053/j.ajkd.2022.05.012. **14.** Go AS CG, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296-305. **15.** Harambat J vSK, Espinosa L, Groothoff JW, Hulton SA, Cerkauskiene R, Schaefer F, Verrina E, Jager KJ, Cochat P, (ESPN/ERA-EDTA) ESfPNERA-EDaTA. Characteristics and outcomes of children with primary oxalosis requiring renal replacement therapy. Clin J Am Soc Nephrol. 2012;7(3):458-65. **16.** Jamieson NV EPTSG. A 20-year experience of combined liver/kidney transplantation for primary hyperoxaluria (PH1): the European PH1 transplant registry experience 1984-2004. Am J Nephrol. 2005;25(3):282-9. **17.** Organ Procurement and Transplantation Network (OPTN). https://optn.transplant.hrsa.gov/.