

ILLUMINATE: Lumasiran Clinical Development Program

Lumasiran is a subcutaneously administered RNAi interference (RNAi) therapeutic, approved by the U.S. Food and Drug Administration on November 23, 2020 as OXLUMO® (lumasiran) for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary oxalate levels in pediatric and adult patients. On October 6, 2022, the FDA approved a supplemental New Drug Application (sNDA) for OXLUMO, which is now indicated for the treatment of PH1 to lower urinary and plasma oxalate levels in pediatric and adult patients. Please see the full US Prescribing Information [here](#). OXLUMO is a subcutaneous injection administered by a healthcare professional.¹ Lumasiran targets the messenger RNA of the *hydroxyacid oxidase 1* gene (*HAO1*), which encodes glycolate oxidase (GO), the liver enzyme involved in the overproduction of oxalate and upstream of the alanine-glyoxylate aminotransferase (AGT) enzyme deficient in patients with PH1.¹

PH1 is an ultra-rare, inherited disease characterized by overproduction of oxalate – an unneeded end-product of metabolism. The excess production of oxalate results in the deposition of calcium oxalate crystals in the kidneys and urinary tract and can lead to the formation of painful and recurrent kidney stones and nephrocalcinosis, which can progress to kidney failure. PH1 can also lead to oxalate deposition in multiple organs beyond the kidney, a condition known as systemic oxalosis.^{2,3} The goal of the ILLUMINATE clinical program is to evaluate the safety and efficacy of lumasiran in pediatric and adult PH1 patients across the spectrum of disease onset and severity.^{4,5,6}



ILLUMINATE-A

ILLUMINATE-A is a randomized, double-blind, placebo-controlled multinational Phase 3 study (N=39) with a 6-month primary analysis period and an extended 54-month dosing period to evaluate the efficacy and safety of lumasiran in children (aged six or older) and adults with PH1 with relatively preserved kidney function (an estimated glomerular filtration rate [eGFR] ≥ 30 mL/min/1.73m²).⁵ The study is being conducted at 17 study sites, in eight countries around the world and is the largest interventional study of PH1.

Patients were randomized 2:1 to receive three monthly starting doses of lumasiran (3 mg/kg) or placebo followed by ongoing quarterly doses. The 6-month primary analysis of the study was completed in December 2019. A total of 38 out of 39 patients completed the primary analysis period and all eligible patients continued to the ILLUMINATE-A open-label extension period.⁵

ILLUMINATE-A Endpoints^{5,7}

- The primary endpoint of ILLUMINATE-A was the percent change in 24-hour urinary oxalate excretion corrected for body surface area from baseline to month 6 (averaged from months 3 to 6), relative to placebo.
- Key secondary endpoints evaluated additional measures of urinary and plasma oxalate, and changes in estimated glomerular filtration rate (eGFR).
- Exploratory endpoints included nephrocalcinosis and kidney stone events.

ILLUMINATE-A Results^{1,7,8,9}

- Lumasiran achieved the primary efficacy endpoint and all tested secondary endpoints.
- For the primary efficacy endpoint, patients receiving lumasiran experienced a 65% least-squares mean reduction in 24-hour urinary oxalate from baseline to month 6 vs a 12% least-squares mean reduction reported in response to placebo, resulting in a mean treatment difference of 53% relative to placebo ($p=1.7 \times 10^{-14}$). These reduced oxalate levels were maintained through month 24.
- In accessing select secondary endpoints, the majority (21/25 or 84%) of patients randomized to lumasiran achieved 24-hour urinary oxalate levels at or below 1.5 times the upper limit of normal ($1.5 \times \text{ULN} = 0.771$ mmol/24hr/1.73m²) ($p=8.3 \times 10^{-7}$) at month 6. Approximately half (13/25 or 52%) of the lumasiran-treated patients achieved urinary oxalate levels within the normal range (less than or equal to 0.514 mmol/24hr/1.73m²) ($p=0.001$). In contrast, none of the patients (0/13) in the placebo arm achieved normal or near-normal levels of oxalate.

- No serious or severe adverse events (AEs) were reported. Injection site reactions (ISRs) were the most common drug-related adverse reaction, reported in 10 out of 26, or 38%, of patients receiving OXLUMO. No ISRs were reported in patients receiving placebo. ISRs occurred throughout the study period and included erythema, pain, pruritis, and discomfort. These symptoms were generally mild and resolved within one day of the injection and did not lead to discontinuation of treatment.⁸



ILLUMINATE-B

ILLUMINATE-B is a single arm, open-label, multinational Phase 3 study (N=18) with a 6-month primary analysis period and an extended 54-month dosing period to evaluate the safety and efficacy of lumasiran in patients with PH1 under the age of six, with an eGFR of > 45 mL/min/1.73 m² or normal serum creatinine, if less than 12 months old.^{6,7,10} The study is being conducted at nine study sites, in five countries around the world.⁶ Dosing regimen is based on weight, with three monthly starting doses followed by ongoing monthly or quarterly doses.¹

ILLUMINATE-B Endpoints¹⁰

- The primary endpoint of the study was the percent change from baseline to month 6 in spot urinary oxalate:creatinine ratio averaged across months 3 to 6.
- Select secondary endpoints evaluated additional measures of urinary and plasma oxalate, and changes in eGFR.
- Exploratory endpoints included kidney stone events and nephrocalcinosis.

ILLUMINATE-B Results^{10,11,12}

- For the primary efficacy endpoint, patients receiving lumasiran experienced a 72% least-squares mean reduction in spot urinary oxalate:creatinine ratio from baseline to month 6, averaged across months 3 to 6. The percent reduction in urinary oxalate excretion was maintained with continued OXLUMO treatment through month 12.
- At 6 months, lumasiran also demonstrated positive results across secondary endpoints including proportion of patients (9/18 or 50%) achieving urinary oxalate levels at or below 1.5 times ULN and (1/18 or 6%) achieving urinary oxalate levels at or below ULN.*
- The overall safety and tolerability profile of lumasiran was consistent with that observed in the ILLUMINATE-A study.¹



ILLUMINATE-C

ILLUMINATE-C is a single arm, open-label, multinational Phase 3 study with a 6-month primary analysis period and an extended 54-month dosing period to evaluate the safety and efficacy of lumasiran in PH1 patients of all ages with severe kidney impairment (eGFR ≤ 45 mL/min/1.73m² or elevated serum creatinine for patients <12 months of age), and conducted at 14 study sites across 11 countries around the world.^{4,13} Patients on peritoneal dialysis were excluded from the study. Cohort A enrolled six patients with advanced PH1 who did not require dialysis at study start, and Cohort B enrolled 15 patients on hemodialysis.¹³ The dosing regimen is based on weight with three monthly starting doses followed by ongoing monthly or quarterly doses.¹³

ILLUMINATE-C Endpoints¹³

- The primary efficacy endpoint for Cohort A was the percent change in plasma oxalate from baseline to month 6, averaged across month 3 to 6, and the primary endpoint for Cohort B was the percent change in pre-dialysis plasma oxalate from baseline to month 6, averaged across month 3 to 6.
- Secondary endpoints evaluated additional measures of plasma oxalate and changes in urinary oxalate. Kidney function, frequency and mode of dialysis, frequency of kidney stone events, and measures of systemic oxalosis, including clinical manifestations, will also be evaluated in the extension period of the study.

*ULN for urinary oxalate:creatinine is age dependent, ranging from 0.22 mmol/mmol in patients 1-6 months old to 0.07 mmol/mmol for patients 5-7 years old. (1 mmol/mmol=0.796 mg/mg).¹⁵

ILLUMINATE-C 6M Primary Analysis Results^{13,14}

- For the primary endpoint, from baseline to month 6, there was a 33% LS mean reduction in plasma oxalate in Cohort A and a 42% LS mean reduction in pre-dialysis plasma oxalate in Cohort B, averaged across months 3 to 6.
- Positive results across secondary endpoints were observed for patients on lumasiran, including reductions in plasma oxalate between dialysis sessions from baseline to month 6 in Cohort B, as well as consistent reductions in urinary oxalate in Cohort A.
- ISRs were the most common drug-related AE reported in 24% (5/21) of patients, all of which were mild and transient. There were no deaths and no serious or severe AEs related to lumasiran.

For more information on ILLUMINATE-A ([NCT03681184](https://clinicaltrials.gov/ct2/show/study/NCT03681184)), ILLUMINATE-B ([NCT03905694](https://clinicaltrials.gov/ct2/show/study/NCT03905694)), and ILLUMINATE-C ([NCT04152200](https://clinicaltrials.gov/ct2/show/study/NCT04152200)) please visit www.clinicaltrials.gov or contact media@alnylam.com.

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