

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. OXLUMO is a subcutaneous injection administered by a healthcare professional.¹ Lumasiran targets the messenger RNA of the *hydroxyacid oxidase 1* gene, which encodes glycolate oxidase, or 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 Lumasiran is also being investigated for the treatment of PH1 in patients with advanced renal disease, including those on dialysis.²

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, nephrocalcinosis, progression to kidney failure, and multiorgan dysfunction.^{3,4} 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.^{2,5,6}



ILLUMINATE-A

ILLUMINATE-A is a randomized, double-blind, placebo-controlled multinational Phase 3 study (N=39) with an extended dosing period (54 months) to evaluate the efficacy and safety of lumasiran in children (aged six or older) and adults with PH1 with relatively preserved renal function (an estimated glomerular filtration rate [eGFR] \geq 30 mL/min/1.73m²).⁵ The study is being conducted at 16 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 eGFR.
- Exploratory endpoints included nephrocalcinosis and renal stone events.

ILLUMINATE-A Results^{1,7}

- Lumasiran achieved the primary efficacy endpoint and all tested secondary endpoints.
- Specifically, treatment with lumasiran resulted in a 65% mean reduction in urinary oxalate relative to baseline versus 12% reduction reported in response to placebo, resulting in a mean treatment difference of 53% relative to placebo ($p=1.7 \times 10^{-14}$).
- At month 6, the majority (21/25 or 84%) of patients randomized to lumasiran achieved urinary oxalate levels at or below 1.5 times the upper limit of normal ($1.5 \times \text{ULN} = 0.771 \text{ mmol}/24\text{hr}/1.73\text{m}^2$) ($p=8.3 \times 10^{-7}$). Approximately half (13/25 or 52%) of the lumasiran-treated patients achieved urinary oxalate levels within the normal range (less than or equal to $0.514 \text{ mmol}/24\text{hr}/1.73\text{m}^2$) ($p=0.001$). 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 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, pruritus, and swelling. These symptoms were generally mild and resolved within one day of the injection and did not lead to discontinuation of treatment.



ILLUMINATE-B

ILLUMINATE-B is a single arm, open-label, multinational Phase 3 study (N=18) to evaluate the safety and efficacy of lumasiran in patients with PH1 under the age of six (range: 3-72 months), with an eGFR of ≥ 45 mL/min/1.73 m² or normal serum creatinine, if less than 12 months old.^{6,7} The study is being conducted at nine study sites, in five countries around the world. Dosing regimen is based on weight, with three monthly starting doses followed by ongoing monthly and quarterly doses.¹

ILLUMINATE-B Endpoints⁶

- 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.
- Key secondary endpoints evaluated additional measures of urinary and plasma oxalate, and changes in eGFR.
- Exploratory endpoints included renal stone events and nephrocalcinosis.

ILLUMINATE-B Results⁸

- Treatment with lumasiran led to a 72% mean reduction in spot urinary oxalate:creatinine ratio from baseline to month 6, averaged across months 3 to 6.
- 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 (≤ 0.771 mmol/24 hr/1.73 m²).
- The overall safety and tolerability profile of lumasiran was consistent with that observed in the ILLUMINATE-A study.



ILLUMINATE-C

ILLUMINATE-C is a single arm, open-label, multinational Phase 3 study to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of lumasiran in PH1 patients with advanced renal disease, including patients on dialysis. The trial is enrolling PH1 patients of all ages with advanced renal disease (eGFR ≤ 45 mL/min/1.73m²), at clinical centers worldwide.² The dosing regimen is based on weight with three monthly starting doses followed by ongoing monthly or quarterly doses.⁹

ILLUMINATE-C Endpoints²

- The primary endpoint of the study is the percent change in plasma oxalate from baseline to month 6.
- Key secondary endpoints will evaluate additional measures of plasma oxalate and changes in urinary oxalate, renal function, frequency and mode of dialysis, frequency of renal stone events, and measures of systemic oxalosis.

ILLUMINATE-C topline results are planned to be reported in 2021.

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

References:

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- ⁷ Garrelfs SF, Frishberg Y, Hulton SA, et al. ILLUMINATE-A, a Phase 3 study of lumasiran, an investigational RNAi therapeutic, in children and adults with primary hyperoxaluria type 1 (PH1). Presented at: European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) - Virtual Meeting. 7th June 2020
- ⁸ Deschenes G, Cochat P, Magen D, et al. ILLUMINATE-B, a Phase 3 Open-Label Study to Evaluate Lumasiran, an RNAi Therapeutic, in Young Children with Primary Hyperoxaluria Type 1 (PH1). Presented at: American Society of Nephrology (ASN) Annual Virtual Meeting, October 22, 2020
- ⁹ Data on file. Alnylam Pharmaceuticals, Inc. 2020