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 with any stage of kidney function.[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 a 54-month open label extension 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/1.73m^2).[5] The study was conducted at 16 study sites, in eight countries around the world. [8]

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 mean 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 absolute change from baseline in urinary oxalate levels, the proportion of patients with normal or near-normal 24-hour urinary oxalate levels (≤1.5 ULN*) and changes in the estimated glomerular filtration rate (eGFR) from baseline - all at month 6.
- Exploratory endpoints included nephrocalcinosis and kidney stone events.

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 m^2 or normal serum creatinine, if less than 12 months old.[6,7,9] 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 Endpoints[9]

- 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.

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- Select secondary endpoints evaluated the proportion of patients with normal or near-normal spot urinary oxalate:creatinine for age (≤1.5 ULN*), the proportion of patients with normal spot urinary oxalate:creatinine for age and changes in eGFR from baseline - all at month 6.
- Exploratory endpoints included kidney stone events and nephrocalcinosis.

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/1.73m^2 or elevated serum creatinine for patients <12 months of age), and conducted at 14 study sites across 11 countries around the world.[4,10] 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.[10] The dosing regimen is based on weight with three monthly starting doses followed by ongoing monthly or quarterly doses.[10]

ILLUMINATE-C Endpoints[10]

- The primary efficacy endpoint for Cohort A was the percent change in plasma oxalate from baseline to month 6, averaged across months 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 months 3 to 6.
- Select secondary endpoints evaluated absolute and percent change in plasma oxalate and urine oxalate levels from baseline to month 6. 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).[11]

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

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