ILLUMINATE-C: A Phase 3 Single-Arm Study to Evaluate Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Lumasiran in Patients with Advanced Primary Hyperoxaluria Type 1

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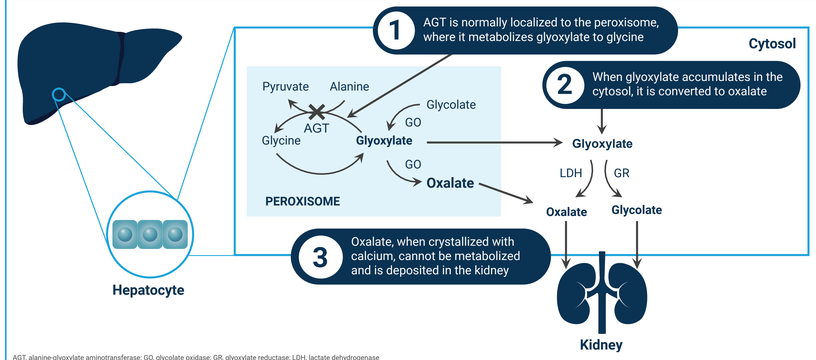
Background

Primary Hyperoxaluria Type 1 (PH1)

- PH1 is a rare autosomal recessive disease that is characterized by excessive hepatic oxalate, which is excreted almost entirely by the kidney, and that is caused by mutations in the alanine-glyoxylate aminotransferase *(AGXT)* gene (**Figure 1**)[1]

Figure 1. PH1 Is Caused by Error of Glyoxylate Metabolism



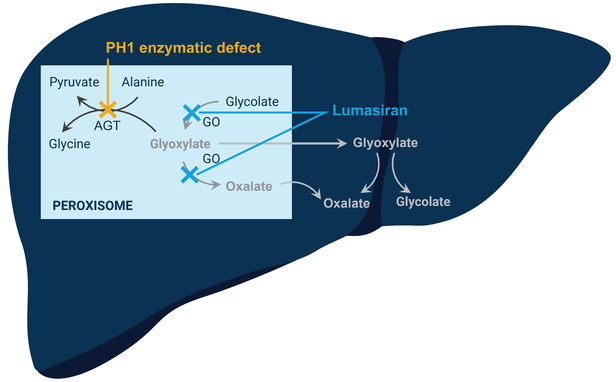
AGT, alanine-glyoxylate aminotransferase; GO, glycolate oxidase; GR, glyoxylate reductase; LDH, lactate dehydrogenase
Adapted from Cochat. *Kidney Int* 1999;55:2533–47

- Excess urinary oxalate results in recurrent nephrolithiasis and/or nephrocalcinosis and progressive renal function decline, subsequent multisystem accumulation of calcium oxalate crystals, and severe end-organ damage[2]
- The estimated prevalence of PH1 is 1–3 patients per million people in Europe and North America,[2,3] with a higher prevalence in some North African and Middle Eastern countries[2,4,5]; however, the disease is often misdiagnosed due to heterogeneous clinical presentation, and the true prevalence may be even greater[6]
- PH1 affects patients of all ages, from infants to adults[7]
- There are no approved therapies to treat PH1. The current standard of care is based on supportive measures such as high fluid intake and use of crystallization inhibitors, which do not prevent disease progression and are burdensome to patients and families
  - For patients with PH1 with specific mutations, pyroxidine (vitamin B6) is the only therapeutic known to lower oxalate production[8]; however, <5% of patients have a complete response[9]
  - The only potentially curative treatment is dual liver/kidney transplant,[6,7] a complicated procedure that is limited by organ availability and accompanied by serious risks, including graft dysfunction and death[10-13]

Lumasiran

- Lumasiran is an investigational RNA-interfering (RNAi) therapeutic targeting glycolate oxidase, which catalyzes the oxidation of glycolate to glyoxylate, a major substrate required for oxalate production (**Figure 2**)[14]
  - Lumasiran is subcutaneously administered and harnesses the natural RNAi mechanism to target the messenger RNA for *HAO1*, which encodes GO in the liver
  - The decreased production of GO reduces hepatic oxalate production[14]
- Phase 1/2 data demonstrated that patients receiving lumasiran experienced significant and sustained reductions in urinary and plasma oxalate to normal or near-normal levels[15]
  - In this study, reported adverse events (AEs) were mild or moderate in severity, and the majority were assessed to be unrelated to study drug[15]

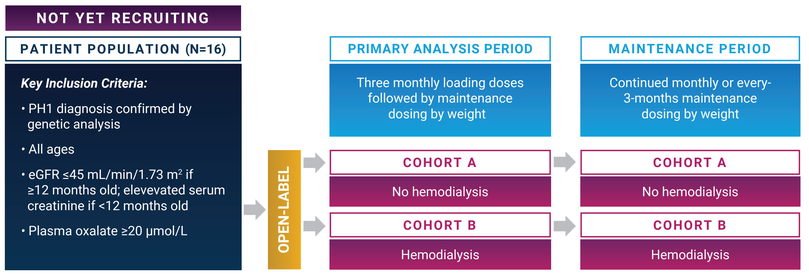
Figure 2. Lumasiran Is an Investigational RNAi Therapeutic for PH1



Trial Design

- ILLUMINATE-C (NCT04152200; EudraCT 2019-001346-17) is a single-arm study designed to evaluate the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics of lumasiran in patients with advanced PH1 (**Figure 3**)

Figure 3. ILLUMINATE-C Study Design



eGFR, estimated glomerular filtration rate

- Planned enrollment is 16 patients total:
  - Cohort A will enroll patients who do not yet require dialysis
  - Cohort B will enroll patients who are currently on a dialysis regimen
- Lumasiran will be administered subcutaneously monthly during the loading doses and either monthly or every 3 months during maintenance dosing; doses will be determined by weight
- Study endpoints are listed in **Table 1**

Table 1. Primary and Secondary Study Endpoints[a]

Primary	Percentage change in plasma oxalate from baseline (cohort A) or predialysis (cohort B) to 6 months
Secondary	• Percentage change in plasma oxalate AUC between dialysis sessions • Absolute change in plasma oxalate • Change in urinary oxalate • QOL assessed by PedsQL total score for patients ≥2 to <18 years of age at time of informed consent, and by KDQOL Burden of Kidney Disease and Effect of Kidney Disease on Daily Life subscales and SF-12 Physical Component Summary and Mental Component Summary in patients >18 years of age at time of informed consent • Plasma PK parameters of lumasiran • Frequency of AEs **Change in the following[b]:** • Nephrocalcinosis as assessed by renal ultrasound • Frequency and mode of dialysis • Frequency of renal stone events • Renal function by eGFR • Measures of systemic oxalosis in cardiac, dermatologic, skeletal, and ocular systems

AUC, area under the plasma drug concentration–time curve; KDQOL, Kidney Disease Quality of Life; PedsQL, Pediatric Quality of Life Inventory; QOL, quality of life; SF-12, Short Form 12
[a]For both the primary analysis period and the maintenance period unless otherwise noted
[b]Only for the maintenance period

Patient Eligibility

Inclusion Criteria

- PH1 diagnosis confirmed by genetic analysis
- Infants to adults
- Estimated glomerular filtration rate ≤45 mL/min/1.73 m^2 in patients ≥12 months of age; elevated serum creatinine for patients <12 months of age
- Plasma oxalate ≥20 µmol/L
- Stable pyridoxine therapy regimen (if applicable)
- Hemodialysis patients on a stable regimen (if applicable) for ≥4 weeks

Exclusion Criteria

- ALT, AST, bilirubin, INR, and hemoglobin in excess of specified laboratory parameters
- Active human immunodeficiency virus infection; evidence of current or chronic hepatitis C or hepatitis B virus infection
- Peritoneal dialysis or combination hemodialysis/peritoneal dialysis

Additional Information

For more information, please contact us at **clinicaltrials@alnylam.com** or visit our website at https://www.alnylam.com/alnylam-rnai-pipeline/clinical-trials/

Abbreviations

AGT, alanine-glyoxylate aminotransferase; *AGXT*, alanine-glyoxylate aminotransferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the plasma drug concentration–time curve; eGFR, estimated glomerular filtration rate; GO, glycolate oxidase; GR, glyoxylate reductase; INR, international normalized ratio; KDQOL, Kidney Disease Quality of Life; LDH, lactate dehydrogenase; PedsQL, Pediatric Quality of Life Inventory; PH1, primary hyperoxaluria type 1; PK, pharmacokinetic(s); RNAi, RNA-interfering; QOL, quality of life; SF-12, Short Form 12; ULN, upper limit of normal.

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