Targeting Glycolate Oxidase for the Treatment of Primary Hyperoxaluria Type 1: Development and Clinical Characterization of Lumasiran, an RNAi Therapeutic

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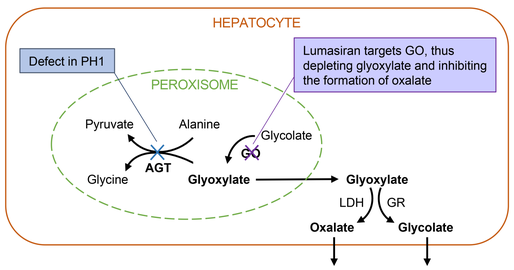
Conclusions

- **Lumasiran is the first approved treatment for PH1[1]**
- **Lumasiran has been evaluated in clinical trials in 98 patients with PH1, with follow-up of up to 5 years**
- **Clinical trial data support the efficacy and safety of lumasiran in patients of all ages and varying levels of disease severity[2]**
- **With long-term lumasiran treatment, urine and plasma oxalate levels were reduced, kidney stone event rates and medullary nephrocalcinosis were generally stable or improved, and kidney function remained stable**
- **Lumasiran demonstrated an acceptable safety profile, with injection site reactions being the most commonly reported lumasiran-related AE[3,4]**

Lumasiran for the Treatment of PH1

- PH1, an autosomal recessive disease caused by deficient activity of the hepatic enzyme AGT, is associated with oxalate overproduction, progressive kidney damage, and eventual systemic oxalosis[1]
- Lumasiran is a liver-directed siRNA that reduces oxalate levels by targeting mRNA encoding GO (**Figure 1**)
- The approval of lumasiran for the treatment of PH1[3,4] in 2020 introduced the first disease-modifying option in the management of PH1[2]

Figure 1. Mechanism of Action of GO Inhibition for the Treatment of PH1[5,6]



GO Is a Favorable Target for Therapeutic Intervention

- GO has a number of characteristics that make it an attractive target for therapeutic intervention in PH1,[7,8] including:
  - Targeting GO specifically addresses the defect in PH1, as GO lies upstream of the molecular defect in PH1[5]
  - The physiological role of GO is thought to be restricted to metabolism of glycolate to glyoxylate, with no role in the Cori cycle, the Krebs cycle, or glucose availability[9]
  - GO has a highly restricted tissue distribution, being specifically expressed in the liver[10]
  - Mouse knockout models with complete inhibition of GO exhibit a normal phenotype, with only asymptomatic elevation of urine glycolate[5,11]
  - A rare human null mutation with lifelong GO knockout exhibited no clinical phenotype[12]

Lumasiran Clinical Development Program

- The lumasiran clinical development program is robust, comprising trials that enrolled a total of 98 patients with a wide range of ages and varying levels of PH1 severity, including patients undergoing intensive hemodialysis (**Table**)
- A large, prospective, observational study (BONAPH1DE; NCT04982393) is being conducted to examine the long-term, real-world safety and effectiveness of lumasiran in patients with PH1
  - Patients diagnosed with PH1 are managed and treated per standard of care
  - The study is currently recruiting; estimated enrollment is 200 patients

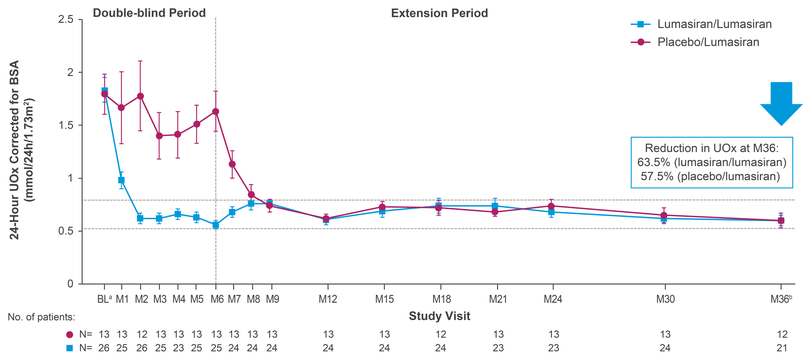
Table. Clinical Trials of Lumasiran in PH1

	Phase 1/2[13]	Phase 2 Open-label Extension[14]	ILLUMINATE-A[15]	ILLUMINATE-B[16]	ILLUMINATE-C[17]
Clinical Trials.gov identifier	NCT02706886	NCT03350451	NCT03681184	NCT03905694	NCT04152200
Phase	1/2	2	3	3	3
Design	Single-blind, placebo-controlled, single dose (Part A, healthy adults) and multiple ascending dose (Part B) study	Open-label extension for patients from Part B of the Phase 1/2 trial	Randomized, double-blind, placebo-controlled study with extension period	Single-arm, open-label study with extension period	Single-arm, open-label study with extension period
Participants (N)	20 in Part B → 20		39	18	21
Inclusion criteria	Part B: • PH1 • 6–64 years of age • 24-hour UOx excretion >0.7 mmol/24h/1.73m² • eGFR >45 mL/min/1.73m²	• Completed Phase 1/2 study (Part B) • In the opinion of the investigator, tolerated the study drug	• PH1 • ≥6 years of age • 24-hour UOx excretion >0.7 mmol/24h/1.73m² • eGFR ≥30 mL/min/1.73m²	• PH1 • <6 years of age • UOx:Cr greater than ULN for age • eGFR >45 mL/min/1.73m² if ≥12 months of age or normal serum creatinine if <12 months of age	• PH1 • All ages eligible • POx ≥20 µmol/L • eGFR ≤45 mL/min/1.73m² if ≥12 months of age or elevated serum creatinine if <12 months of age • Not on hemodialysis (Cohort A) or on stable hemodialysis regimen (Cohort B)
Status	Completed	Completed	Active, not recruiting; M36 data presented[18]	Active, not recruiting; M30 data presented[19]	Active, not recruiting; M12 data presented[20]
Total study duration	6 months	Up to 54 months	Up to 60 months	Up to 60 months	Up to 60 months

- Lumasiran is associated with rapid and sustained reduction in oxalate levels and favorable impacts on clinically important outcomes (kidney function, kidney stones, medullary nephrocalcinosis)

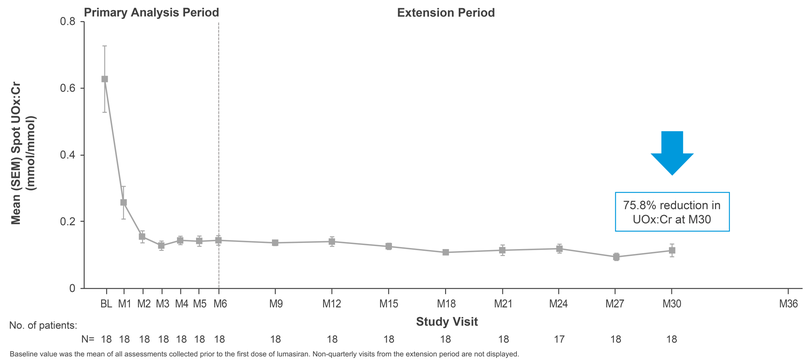
Urinary Oxalate

Figure 2. Mean (SEM) 24-Hour UOx in ILLUMINATE-A



Dotted horizontal lines represent the ULN of 0.514 mmol/24h/1.73m² (1 mmol/24h/1.73m² = 90 mg/24h/1.73m²) and 1.5 x ULN (0.771 mmol/24h/1.73m²) for 24-hour UOx excretion.
[a]Baseline is the median of all valid 24-hour urine assessments collected prior to the first dose of study drug (lumasiran or placebo) without any non-protocol–related sample issues.
[b]At Month 36, the lumasiran/lumasiran group had received 36 months of lumasiran treatment, and the placebo/lumasiran group had received 30 months of lumasiran treatment.

Figure 3. Mean (SEM) Spot UOx:Cr in ILLUMINATE-B



Baseline value was the mean of all assessments collected prior to the first dose of lumasiran. Non-quarterly visits from the extension period are not displayed.

eGFR

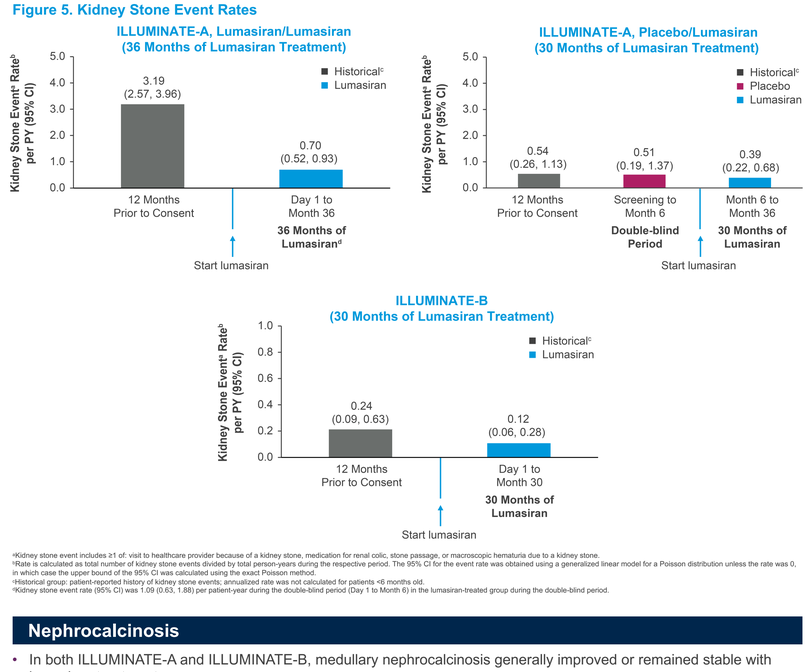
- In the Phase 2 OLE study, mean eGFR values remained stable through Month 54

Figure 4. Mean (SEM) eGFR in ILLUMINATE-A, ILLUMINATE-B, and ILLUMINATE-C

[a]In ILLUMINATE-A, eGFR is calculated from serum creatinine based on the Modification of Diet in Renal Disease formula for patients ≥18 years of age and the Schwartz Bedside Formula for patients <18 years of age at screening. In ILLUMINATE-B, eGFR is calculated based on the Schwartz Bedside Formula in patients ≥12 months of age at the time of the assessment. In ILLUMINATE-C, eGFR is calculated based on the Schwartz Bedside Formula for patients ≥12 months to <18 years of age at the time of the assessment and the Modification of Diet in Renal Disease formula for patients ≥18 years of age at screening.
[b]In ILLUMINATE-A, baseline is the last assessment prior to the first dose of study drug (lumasiran or placebo).
[c]At Month 36, the lumasiran/lumasiran group had received 36 months of lumasiran treatment, and the placebo/lumasiran group had received 30 months of lumasiran treatment.

Kidney Stone Events

Figure 5. Kidney Stone Event Rates



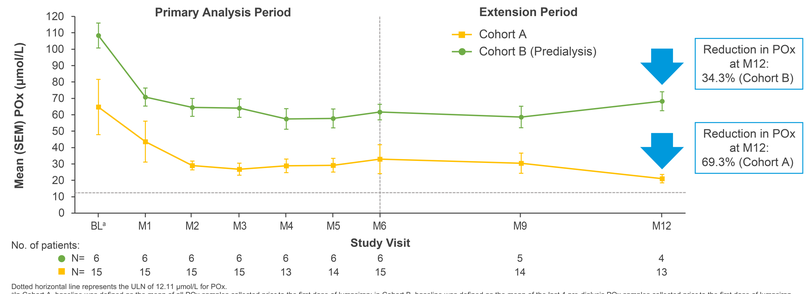
[a]Kidney stone event includes ≥1 of: visit to healthcare provider because of a kidney stone, medication for renal colic, stone passage, or macroscopic hematuria due to a kidney stone.
[b]Rate is calculated as total number of kidney stone events divided by total person-years during the respective period. The 95% CI for the event rate was obtained using a generalized linear model for a Poisson distribution unless the rate was 0, in which case the upper bound of the 95% CI was calculated using the exact Poisson method.
[c]Historical group: patient-reported history of kidney stone events; annualized rate was not calculated for patients <6 months old.
[d]Kidney stone event rate (95% CI) was 1.09 (0.63, 1.88) per patient-year during the double-blind period (Day 1 to Month 6) in the lumasiran-treated group during the double-blind period.

Nephrocalcinosis

- In both ILLUMINATE-A and ILLUMINATE-B, medullary nephrocalcinosis generally improved or remained stable with lumasiran treatment
  - ILLUMINATE-A: At Month 36, in the lumasiran/lumasiran group, 39% of patients had improvement, 50% were stable, and 11% had worsening (after 36 months of lumasiran). In the placebo/lumasiran group, 54% of patients improved, 36% were stable, and 9% had worsening (after 30 months of lumasiran). Overall, 43% of patients with medullary nephrocalcinosis at baseline had complete resolution
  - ILLUMINATE-B: At Month 24, nephrocalcinosis grade improved in 67% of patients, remained stable in 28%, and was indeterminate in 6%

Plasma Oxalate

Figure 6. Mean (SEM) POx Values in ILLUMINATE-C Over 12 Months



Dotted horizontal line represents the ULN of 12.11 µmol/L for POx.
[a]In Cohort A, baseline was defined as the mean of all POx samples collected prior to the first dose of lumasiran; in Cohort B, baseline was defined as the mean of the last 4 pre-dialysis POx samples collected prior to the first dose of lumasiran.

Safety

- ILLUMINATE-A: The most common AEs (≥15% of patients in the all-lumasiran-treated set during lumasiran treatment) were injection site reactions (49%), abdominal pain (21%), headache (18%), and COVID-19 (15%); 4 patients (10%) had serious AEs, none of which were considered related to the study drug
- ILLUMINATE-B: Lumasiran-related AEs were reported by 28% of patients, most commonly mild, transient injection site reactions (17%); there were no clinically relevant changes in laboratory measures, vital signs, or electrocardiograms related to lumasiran
- ILLUMINATE-C: At 12 months, the most common lumasiran-related AEs were mild, transient injection site reactions (24%); there were no serious or severe AEs related to lumasiran

Abbreviations: AE, adverse event; AGT, alanine-glyoxylate aminotransferase; BL, baseline; BSA, body surface area; CI, confidence interval; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GO, glycolate oxidase; GR, glyoxylate reductase; LDH, lactate dehydrogenase; M, month; NC, nephrocalcinosis; OLE, open-label extension; PH, primary hyperoxaluria; POx, plasma oxalate; PY, person-year; SEM, standard error of the mean; siRNA, small interfering ribonucleic acid; ULN, upper limit of normal; UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio.

Disclosures: HS-L: principal investigator for Alnylam Pharmaceuticals; travel and accommodation expenses from Alnylam Pharmaceuticals to attend international investigators' meetings. **AD:** Principal investigator for Alnylam Pharmaceuticals; received consultancy fees from Alnylam Pharmaceuticals. **FG-E:** Principal investigator for Alnylam Pharmaceuticals. **WH:** travel and accommodation expenses from Alnylam Pharmaceuticals to attend an international investigators' meeting. **JH:** consultancy fees from Alnylam Pharmaceuticals. **SAH:** travel expenses to participate in clinical research meetings, consultancy fee from Advisory Board, and consultancy fees paid to Birmingham Children's Hospital Renal Research Fund from Alnylam Pharmaceuticals, and other from Dicerna Pharmaceuticals and Chiesi Pharmaceuticals. **DM:** research funding, consultancy fees, and non-financial support from Alnylam Pharmaceuticals. **CM:** Nothing to disclose. **JSO:** institutional research funding from Alnylam Pharmaceuticals. **JMS:** grants, personal fees, and non-financial support from Alnylam Pharmaceuticals. **RS:** Primary investigator for Alnylam Pharmaceuticals; secondary investigator for Novartis, and serves on the institutional review board. **DJS:** grants and other from Alnylam Pharmaceuticals and personal fees from Advicenne. **ES:** principal investigator for Alnylam Pharmaceuticals; travel and accommodation expenses from Alnylam Pharmaceuticals to attend international investigators' meeting. **RS:** principal investigator for Alnylam Pharmaceuticals; travel and accommodation expenses from Alnylam Pharmaceuticals to attend international investigators' meeting. **NM & CK:** employment by Alnylam Pharmaceuticals. **JMG:** employee of and shareholder in Alnylam Pharmaceuticals. **ALS-L:** consultancy fees from Alnylam Pharmaceuticals and Dicerna Pharmaceuticals, and principal investigator for research funded by OxThera.
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