Clinical Outcomes in Phase 3 Studies of Lumasiran in Pediatric and Adult Patients with Primary Hyperoxaluria Type 1

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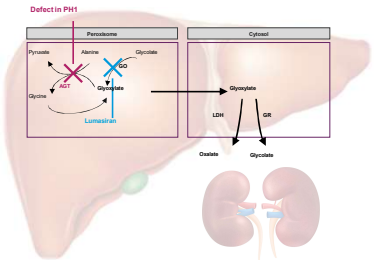
Conclusions

- **Lumasiran treatment, previously shown to reduce urinary oxalate excretion, demonstrated encouraging early results on clinical outcomes in infants, children, and adult patients with PH1**
  - **eGFR remained stable**
  - **Kidney stone event rates either decreased or were low and unchanged**
  - **Nephrocalcinosis improved or remained stable in the majority of patients treated with lumasiran; continued treatment with lumasiran beyond 6 months resulted in an increase in the percentage of patients experiencing unilateral and bilateral improvement**
- **Data on the effect of lumasiran on kidney function, kidney stone events, and nephrocalcinosis will continue to be collected in the extension periods of both studies**

Introduction

- Patients with PH1 overproduce oxalate due to a deficiency in the hepatic peroxisomal enzyme AGT[1,2] (**Figure 1**)
- Excess oxalate can lead to recurrent kidney stones, nephrocalcinosis, progressive kidney disease, and multiorgan damage from systemic oxalosis[1,2]
  - Kidney stones, as well as associated hospitalizations and stone removal procedures, are a major cause of morbidity in PH1[3]
  - Presence of nephrocalcinosis is associated with risk of kidney failure[4]
  - eGFR decline in most patients is gradual but can be unpredictable[3]
- Due to the causal role of urinary oxalate in kidney stone formation, nephrocalcinosis, and kidney function decline,[1,2] a substantial reduction in urinary oxalate levels is expected to confer clinical benefit in patients with PH1[3]
- Lumasiran is an RNAi therapeutic approved by the FDA for the treatment of PH1 to reduce urinary oxalate levels in pediatric and adult patients[5]
- Lumasiran decreases hepatic oxalate production by inhibiting the production of GO[6] (**Figure 1**)

Figure 1. Defect in Glyoxylate Metabolism in Hepatocytes of Patients With Primary Hyperoxaluria Type 1 and Lumasiran Therapeutic Hypothesis



- In the Phase 3 ILLUMINATE-A (NCT03681184) and ILLUMINATE-B (NCT03905694) studies, treatment with lumasiran resulted in substantial reductions in urinary oxalate with an acceptable safety profile in patients with PH1, from infants through adults[7-9]
  - ILLUMINATE-A: The primary endpoint was the percent reduction from baseline in 24-hour urinary oxalate excretion corrected for BSA averaged over Months 3 through 6. Lumasiran reduced 24-hour urinary oxalate excretion by 53.5% relative to placebo ($P=1.7\times10^{-14}$). Reductions in 24-hour urinary oxalate were sustained through Month 12 in patients initially randomized to lumasiran and replicated in the patients who crossed over from placebo to lumasiran at Month 6[7,8]
  - ILLUMINATE-B: Lumasiran led to a LS mean reduction of 72.0% in spot urinary oxalate:creatinine ratio from baseline to Month 6 in infant and pediatric patients with PH1 <6 years old[9]
- In this analysis, we evaluated clinical outcomes from the ILLUMINATE-A and ILLUMINATE-B studies, including changes in eGFR, kidney stone event rates, and medullary nephrocalcinosis grade after up to 12 months of lumasiran treatment

Methods

Study Design

- ILLUMINATE-A is a randomized, double-blind, placebo-controlled, Phase 3 trial (**Figure 2**)

Figure 2. ILLUMINATE-A Phase 3 Study Design

NCT03681184; EudraCT Number: 2018-001981-40; *Maintenance dose of 3.0 mg/kg (qSM) started 1 month after last loading dose. ^aPatients randomized to placebo received loading doses of 3.0 mg/kg lumasiran at Months 6, 7, and 8; patients randomized to lumasiran received a maintenance dose of 3.0 mg/kg lumasiran at Month 6, and placebo at Months 7 and 8. ^≤1.70 mmol/24hr/1.73m² = 153 mg/24hr/1.73m² (1 mmol/24hr/1.73m² = 90 mg/24hr/1.73m²).

- ILLUMINATE-B is a single arm, open-label Phase 3 trial (**Figure 3**)

Figure 3. ILLUMINATE-B Phase 3 Study Design

NCT03905694; EudraCT Number: 2018-004014-17; *Continued weight-based dosing.† Patients <10 kg received loading doses 6.0 mg/kg once monthly for 3 months and then maintenance doses 3.0 mg/kg once monthly; patients ≥10 to <20 kg received loading doses 6.0 mg/kg once monthly for 3 months and then maintenance doses 6.0 mg/kg once every 3 months; patients ≥20 kg received loading doses 3.0 mg/kg once monthly for 3 months and then maintenance doses 3.0 mg/kg once every 3 months. The maintenance dose began 1 month after the last loading dose.

Kidney Function, Kidney Stone Events, and Nephrocalcinosis

- Change in eGFR was a secondary endpoint in both studies
  - eGFR was calculated for patients ≥12 months of age with the Modification of Diet in Renal Disease formula for patients ≥18 years of age and the Schwartz Bedside Formula for patients ≥12 months and <18 years of age[10,11]
    - Patients <12 months were excluded from the eGFR analysis, as the Schwartz Bedside Formula is not validated for this age group
- Change in kidney stone event rates was an exploratory endpoint in both studies
  - A kidney stone event was defined as an event that included at least one of the following:
    - Visit to healthcare provider (eg, outpatient clinic, urgent care, emergency department, procedure) because of a kidney stone
    - Medication for renal colic
    - Stone passage
    - Macroscopic hematuria due to a kidney stone
  - The kidney stone event rate was calculated as total number of kidney stone events divided by total patient exposure time during the respective period (event per person-year), and presented with 95% CIs
- Change in medullary nephrocalcinosis grade was an exploratory endpoint in both studies
  - Medullary nephrocalcinosis was assessed by kidney ultrasound at baseline, Month 6, and Month 12, and centrally read by a radiologist who was blinded to time point and, in ILLUMINATE-A, also blinded to treatment arm
    - Data were available up to Month 12 for ILLUMINATE-A and Month 6 for ILLUMINATE-B at the time of the analysis
  - Degree of medullary nephrocalcinosis in each kidney was graded on a standardized 4-point scale, with a higher grade indicating greater severity (**Table 1**)[12]
    - The intra- and inter-observer reliability of the ultrasonography grading scale used to grade the severity of nephrocalcinosis was evaluated and reported by others and has been published[12]

Table 1. Medullary Nephrocalcinosis Grading Scale[12]

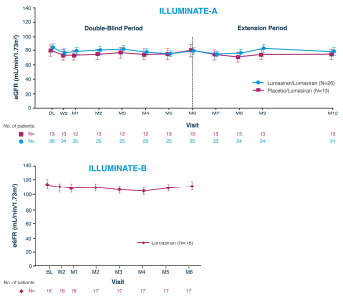
Grade	Grading Scale
Grade 0	No abnormal echogenicity of the medullary pyramids
Grade 1	Mild increase in echogenicity around the border of the medullary pyramids
Grade 2	Mild diffuse increase in echogenicity of the entire medullary pyramids
Grade 3	Greater, more homogeneous increase in the echogenicity of the entire medullary pyramids

Results

eGFR

- eGFR remained stable with lumasiran treatment through Month 12 in ILLUMINATE-A and through Month 6 in ILLUMINATE-B (**Figure 4**)

Figure 4. eGFR (A) From Baseline to Month 12 in ILLUMINATE-A; (B) From Baseline to Month 6 in ILLUMINATE-B

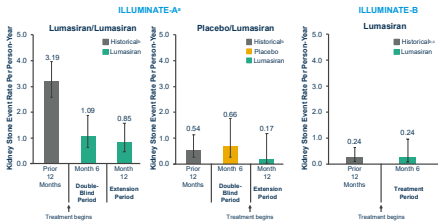


Data in graph are presented as mean ± SEM of observed values.

Kidney Stone Event Rates

- In ILLUMINATE-A, kidney stone event rates decreased during the first 6 months of lumasiran treatment in the patients initially randomized to lumasiran, relative to the 12 months prior to consent. This reduction was maintained after an additional 6 months of treatment (**Figure 5**)
  - In the patients initially randomized to placebo, kidney stone event rates remained unchanged during the 6 months of placebo treatment, relative to the 12 months prior to consent. After these patients crossed over from placebo to lumasiran, kidney stone event rates decreased after 6 months of lumasiran treatment (**Figure 5**)
- In ILLUMINATE-B, the low rates of kidney stone events were unchanged from 12 months prior to consent through the first 6 months of lumasiran treatment (**Figure 5**)

Figure 5. Kidney Stone Event Rates 12 Months Prior to Consent and 6 or 12 Months After Treatment with Lumasiran in ILLUMINATE-A and ILLUMINATE-B

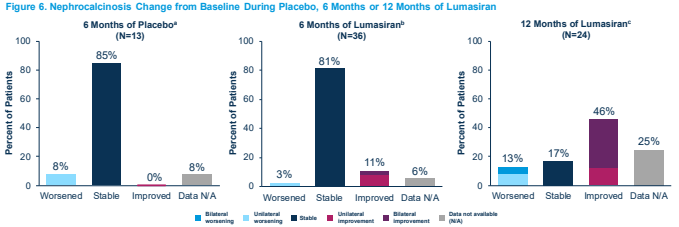


Error bars represent 95% CI.
^aRandomization was not stratified by kidney stone events at baseline. ^bPatient reported history of kidney stone events. ^cAnnualized rate was not calculated for patients <6 months old.

Nephrocalcinosis

- In ILLUMINATE-A, 46% of patients (11/24) had improved nephrocalcinosis grade (8 bilateral, 3 unilateral) and 13% (3/24) had worsening (1 bilateral, 2 unilateral) after 12 months of lumasiran treatment (**Figure 6**)
  - 92% (12/13) in the placebo group and 71% (17/24) in the lumasiran group had nephrocalcinosis at baseline
  - After 6 months of placebo, nephrocalcinosis grade remained stable in 85% (11/13) and worsened in 8% (1/13; unilateral)
  - After 6 months of lumasiran, nephrocalcinosis grade improved in 11% (4/36; 1 bilateral, 3 unilateral), remained stable in 81% (29/36), and worsened in 3% (1/36; unilateral)
  - Of patients with nephrocalcinosis and available ultrasounds, 15% (4/27) and 79% (11/14) showed improvement after 6 and 12 months, respectively; of those who improved, 73% (8/11) improved in both kidneys after 12 months of treatment

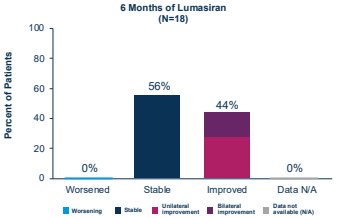
Figure 6. Nephrocalcinosis Change from Baseline During Placebo, 6 Months or 12 Months of Lumasiran



^aIncludes 6 months of placebo treatment for patients originally randomized to placebo. Data N/A for one patient who had kidney ultrasound at Month 6, but the images were not adequate for grading nephrocalcinosis. ^bIncludes first 6 months of treatment for patients originally randomized to lumasiran and the first 6 months of lumasiran treatment for patients originally randomized to placebo. Data N/A for 2 patients who did not have kidney ultrasound after 6 months of lumasiran treatment. ^cIncludes 12 months of treatment for patients originally randomized to lumasiran. Data N/A for 4 patients who did not have kidney ultrasound after 12 months of lumasiran treatment, for 1 patient who discontinued treatment, and for 1 patient who withdrew from the study. Two patients in the lumasiran group did not have valid kidney ultrasounds at baseline and were excluded from the current analysis. One placebo crossover patient did not have kidney ultrasound before the first dose of lumasiran and was also excluded from the current analysis.

- In ILLUMINATE-B, 78% (14/18) of patients had nephrocalcinosis at baseline; after 6 months of lumasiran treatment, nephrocalcinosis grade improved in 44% (8/18; 3 bilateral, 5 unilateral) and no patient worsened (**Figure 7**)
  - Of patients with nephrocalcinosis at baseline, nephrocalcinosis grade improved in 57% (8/14) after 6 months of lumasiran treatment

Figure 7. Nephrocalcinosis: Change From Baseline to Month 6 in ILLUMINATE-B



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Abbreviations: AGT, alanine-glyoxylate aminotransferase; BL, baseline; BSA, body surface area; CI, confidence interval; eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; GO, glycolate oxidase; GR, glyoxylate reductase/hydroxypyruvate reductase; LDH, lactate dehydrogenase; LS, least squares; M, month; N/A, not available; PH1, primary hyperoxaluria type 1; q3M, once every 3 months; qM, once monthly; qM × 3, once monthly for 3 consecutive months; RNAi, ribonucleic acid interference; SEM, standard error of the mean; W, week.

References: 1. Cochat P, Rumsby G. *N Engl J Med.* 2013;369:649-58. **2.** Millner DS, et al. *Gene Reviews®*. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1283. **3.** Millner DS, et al. *Clin J Am Soc Nephrol.*2020;15:1056-1065. **4.** Tang X, et al. *Kidney Int.* 2015;87:623-31. **5.** OXLUMO (lumasiran) [prescribing information]. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; 2020. **6.** Liebow A, et al. *J Am Soc Nephrol.* 2017;28:494-503. **7.** Garrelfs S, 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; June 2020; virtual. **8.** Saland J, et al. 12-Month Analysis of ILLUMINATE-A, a Phase 3 Study of Lumasiran: Sustained Oxalate Lowering and Kidney Stone Event Rates in Primary Hyperoxaluria Type 1. Presented at: American Society Nephrology Annual Meeting; October 2020; virtual. **9.** Deschênes G, 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 Nephrology Annual Meeting; October 2020; virtual. **10.** Levey AS, et al. *Ann Intern Med.* 2009;150:604-12. **11.** Schwartz GJ, et al. *J Am Soc Nephrol.* 2009;20:629-37. **12.** Dick PT, et al. *Pediatr Radiol.* 1999;29:68-72.

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