Effect of Lumasiran on Kidney Stones and Nephrocalcinosis in Patients With Primary Hyperoxaluria Type 1

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Introduction

- PH1 is a rare, progressive, genetic disease characterized by hepatic overproduction of oxalate[1]
- In the kidneys, excess oxalate leads to the formation of insoluble calcium oxalate crystals, resulting in recurrent kidney stones, NC, and progressive kidney damage[1,2]
  - In patients with PH1, recurrent kidney stones are a major cause of morbidity[3]
  - Development of NC is associated with an increased risk of kidney failure[4]
  - A substantial reduction in urinary oxalate excretion is expected to improve clinical outcomes in patients with PH1[3]
- Lumasiran is an RNAi therapeutic indicated for the treatment of PH1 to lower urinary oxalate in pediatric and adult patients[5]
- In 4 clinical trials to date, lumasiran has demonstrated efficacy in lowering the urinary oxalate excretion of patients with PH1: a Phase 1/2 trial (NCT02706886),[6] a Phase 2 OLE (NCT03350451),[7] the Phase 3 ILLUMINATE-A trial (NCT03681184),[8] and the Phase 3 ILLUMINATE-B trial (NCT03905694)[9,10]
- We analyzed data from these 4 clinical trials to evaluate the effect of lumasiran treatment on KSE rates and medullary NC in pediatric and adult patients with PH1

Methods

Study Design

- Lumasiran data included in this analysis are shown in **Table 1**

Table 1. Summary of the Lumasiran Clinical Studies That Contributed Data in the Current Analysis[6-10]

Study	Phase 1/2 Study Part B (NCT02706886) N=20	Phase 2 Open-Label Extension Study (NCT03350451) N=20	Phase 3 ILLUMINATE-A Study (NCT03681184) N=39	Phase 3 ILLUMINATE-B Study (NCT03905694) N=18
Design	• Multiple ascending doses	• Long-term extension study with up to 54 months of dosing	• 6-month double-blind, placebo-controlled period followed by a long-term extension period of up to 54 months	• Single-arm, open-label study with a 6-month primary analysis period followed by a long-term extension period of up to 54 months
Patient population	• Patients with PH1 • 6–64 years old • eGFR >45 mL/min/1.73m^2	• Patients with PH1 who completed the Phase 1/2 study, Part B	• Patients with PH1 • ≥6 years old • eGFR ≥30 mL/min/1.73m^2	• Patients with PH1 • <6 years old • eGFR >45 mL/min/1.73m^2[a]
Relevant data	• Kidney stone-related AEs	• Kidney stone-related AEs	• KSE[b] rates and medullary NC grade were exploratory endpoints	• KSE rates and medullary NC grade were exploratory endpoints

[a]Normal serum creatinine if <12 months old.
[b]A KSE was defined as one of the following: visit to healthcare provider because of a kidney stone, medication for renal colic, stone passage, macroscopic hematuria due to a kidney stone.

Analyses

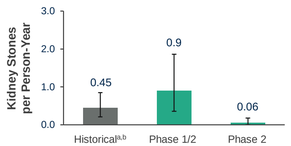
- KSE rates were calculated as the total number of KSEs divided by the total patient exposure time during the respective period (event per PY) and presented with 95% CI
- Kidney stone-related AEs (Phase 1/2 and Phase 2 OLE)
  - Defined as any kidney stone meeting the AE definition and reported as an AE; kidney stone AEs were identified by medical review
- KSEs (ILLUMINATE-A and ILLUMINATE-B)
  - A KSE was defined as an event that included at least 1 of the following:
    - Visit to a 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
- Medullary NC (ILLUMINATE-A and ILLUMINATE-B)
  - NC was not prospectively assessed in the Phase 1/2 Part B and Phase 2 OLE studies
  - In ILLUMINATE-A and ILLUMINATE-B, kidney ultrasounds were graded centrally by a single radiologist blinded to timepoint, 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 NC in each kidney was graded on a validated, semiquantitative, standardized 4-point scale, with a higher grade indicating greater severity[11]

Results

Kidney Stone-Related AEs

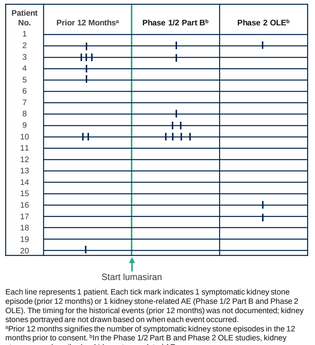
- Phase 1/2 Part B and Phase 2 OLE studies (**Figure 1**)
  - 6/20 patients reported ≥1 kidney stone for the 12 months prior to consent
  - During Part B of the Phase 1/2 trial, 4/20 patients reported kidney stone-related AEs with lumasiran treatment
  - After continuing to the Phase 2 OLE, 3/20 patients reported kidney stone-related AEs
  - Kidney stone-related AEs by patient are shown in **Figure 2**

Figure 1. Kidney Stones in the Phase 1/2 Part B and Phase 2 OLE Studies



Error bars represent 95% CI.
Duration of follow-up: historical, 20 person-years; Phase 1/2 Part B, 7.8 person-years; OLE, 48.0 person-years.
[a]Patient-reported number of kidney stones in the 12 months prior to enrollment in the Phase 1/2 study. Historical describes the number of symptomatic kidney stone episodes in the 12 months prior to consent. [b]In the Phase 1/2 Part B and Phase 2 OLE studies, kidney stones were described as kidney stone-related AEs. [c]Data from the ongoing Phase 2 OLE up to the March 1, 2021, data cut are presented.

Figure 2. Kidney Stones by Patient in the Phase 1/2 Part B and Phase 2 OLE Studies



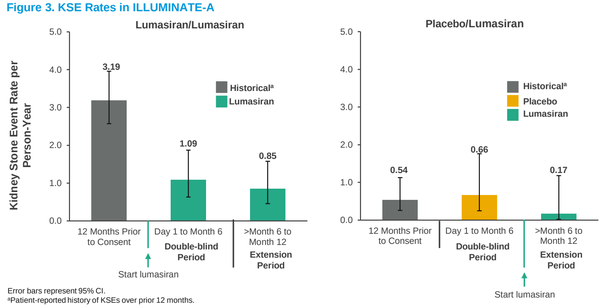
Each line represents 1 patient. Each tick mark indicates 1 symptomatic kidney stone episode (prior 12 months) or 1 kidney stone-related AE (Phase 1/2 Part B and Phase 2 OLE). The timing for the historical events (prior 12 months) was not documented; kidney stones portrayed are not drawn based on when each event occurred.
[a]Prior 12 months signifies the number of symptomatic kidney stone episodes in the 12 months prior to consent. [b]In the Phase 1/2 Part B and Phase 2 OLE studies, kidney stones were described as kidney stone-related AEs.

KSE Rates

ILLUMINATE-A (Patients ≥6 Years Old)

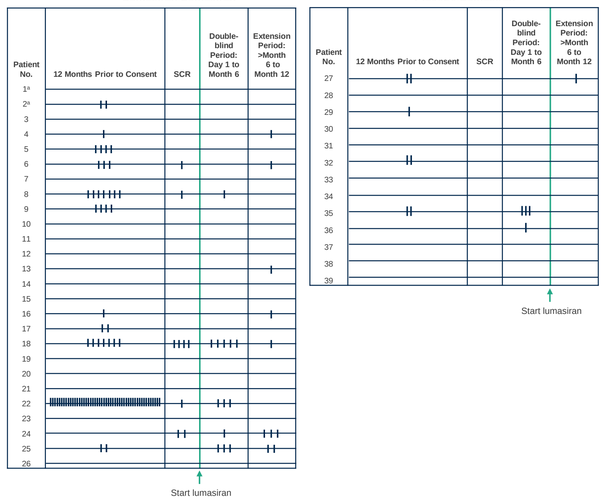
- In ILLUMINATE-A, KSE rates decreased during the first 6 months of lumasiran treatment in the patients initially randomized to lumasiran, relative to the 12 months prior to consent; this reduction was maintained after an additional 6 months of treatment (**Figure 3**)
  - In the patients initially randomized to placebo, KSE rates remained unchanged during the 6 months of placebo administration, relative to the 12 months prior to consent; after these patients crossed over from placebo to lumasiran, KSE rates appeared to decrease after 6 months of lumasiran treatment (**Figure 3**)
- KSEs by patient are shown in **Figure 4**
  - In the lumasiran/lumasiran group, KSEs appeared lower by Month 6; this reduction was sustained through Month 12 compared with the number of events for the 12 months prior to consent
  - In the placebo/lumasiran group, the number of KSEs during the 12 months prior to consent and during the 6-month placebo-controlled period were similar. During lumasiran treatment, the number of KSEs appeared to decrease compared with the prior 12-month and placebo-controlled periods

Figure 3. KSE Rates in ILLUMINATE-A



Error bars represent 95% CI.
[a]Patient-reported history of KSEs over prior 12 months.

Figure 4. KSEs by Patient in ILLUMINATE-A

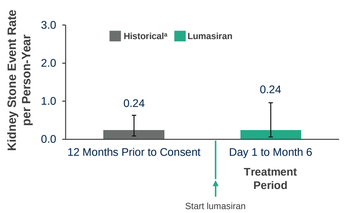


Each line represents 1 patient. Each tick mark indicates 1 KSE. The timing for the historical events (prior 12 months) was not documented; KSEs portrayed are not drawn based on when each event occurred.
[a]Patients 1 and 2 discontinued treatment or withdrew from the study during the 6-month double-blind period and did not receive lumasiran in the extension period. Patient 2 discontinued treatment after Month 3 and completed the 6-month double-blind period.

ILLUMINATE-B (Patients <6 Years Old)

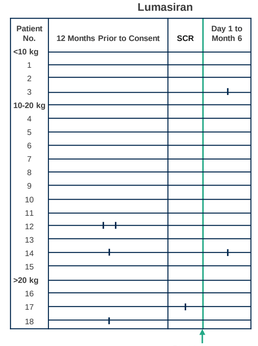
- In ILLUMINATE-B, the low rates of KSEs were unchanged from 12 months prior to consent through the first 6 months of lumasiran treatment (**Figure 5**)
- KSEs by patient are shown in **Figure 6**

Figure 5. KSE Rates in ILLUMINATE-B



Error bars represent 95% CI.
[a]Patient-reported history of KSEs; annualized rate was not calculated for patients age <6 months.

Figure 6. KSEs by Patient in ILLUMINATE-B



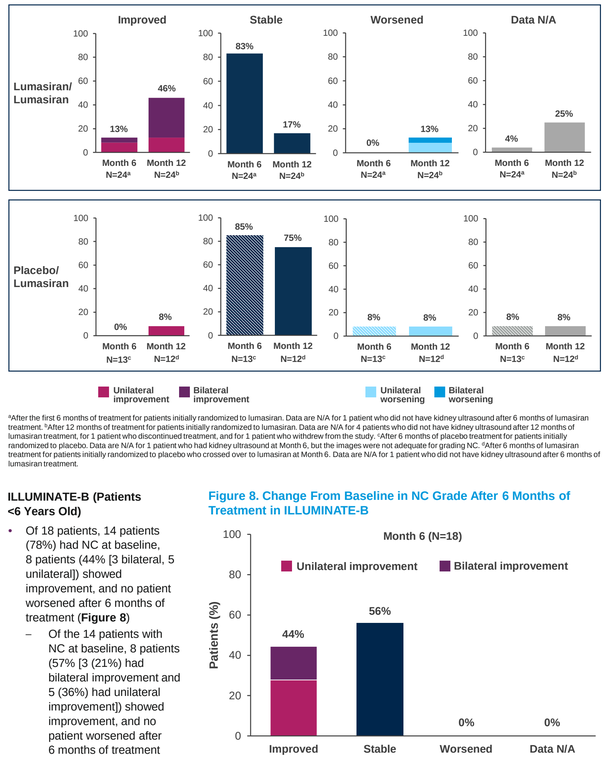
Each line represents 1 patient. Each tick mark indicates 1 KSE. The timing for the historical events (prior 12 months) was not documented; KSEs portrayed are not drawn based on when each event occurred.

Nephrocalcinosis Grade

ILLUMINATE-A (Patients ≥6 Years Old)

- Overall, NC improved or remained stable in the majority of patients after 12 months of lumasiran treatment (**Figure 7**)

Figure 7. Change From Baseline in NC Grade After 6 Months and 12 Months of Treatment in ILLUMINATE-A



[a]After the first 6 months of treatment for patients initially randomized to lumasiran. Data are N/A for 1 patient who did not have kidney ultrasound after 6 months of lumasiran treatment. [b]After 12 months of treatment for patients initially randomized to lumasiran. Data are 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. [c]After 6 months of placebo treatment for patients initially randomized to placebo. Data are N/A for 1 patient who had kidney ultrasound at Month 6, but the images were not adequate for grading NC. [d]After 6 months of lumasiran treatment for patients initially randomized to placebo who crossed over to lumasiran at Month 6. Data are N/A for 1 patient who did not have kidney ultrasound after 6 months of lumasiran treatment.

ILLUMINATE-B (Patients <6 Years Old)

- Of 18 patients, 14 patients (78%) had NC at baseline, 8 patients (44% [3 bilateral, 5 unilateral]) showed improvement, and no patient worsened after 6 months of treatment (**Figure 8**)
  - Of the 14 patients with NC at baseline, 8 patients (57% [3 (21%) had bilateral improvement and 5 (36%) had unilateral improvement]) showed improvement, and no patient worsened after 6 months of treatment

Figure 8. Change From Baseline in NC Grade After 6 Months of Treatment in ILLUMINATE-B

Conclusions

- **Lumasiran treatment demonstrated encouraging results on kidney stone-related AEs/KSEs and NC in children and adults with PH1**
  - **A reduction in kidney stone-related AEs was observed in the Phase 2 OLE of the Phase 1/2 trial**
  - **A reduction in KSE rates was observed in ILLUMINATE-A; KSE rates remained stable in ILLUMINATE-B**
  - **NC grade stabilized or improved in ILLUMINATE-A and ILLUMINATE-B**
- **Longer-term data on KSE rates and NC continue to be collected**

Acknowledgments: Thank you to the patients, investigators, and study staff who participated in the studies. Editorial assistance was provided by Peloton Advantage, LLC, an OPEN Health company, in accordance with Good Publication Practice (GPP3) guidelines and funded by Alnylam Pharmaceuticals. This study was funded by Alnylam Pharmaceuticals. **Disclosures: JCL:** grants from Alnylam, other from Alnylam, during the conduct of the study; grants and other from Dicerna, grants from Allena, other from Orfan-Bridgebio, other from Synlogic, other from Novobiome, grants from OxThera, other from Oxidien, other from Dicerna, other from OxThera, outside the submitted work. **SFG:** nonfinancial support and grants from Alnylam Pharmaceuticals and grants from Dicerna Pharmaceuticals. **MM:** principal investigator for Alnylam Pharmaceuticals. **JMS:** grants, personal fees, and nonfinancial support from Alnylam Pharmaceuticals. **DJS**: grants and other from Alnylam Pharmaceuticals and personal fees from Advicenne. **TN** and **JMG**: employees of and shareholders in Alnylam Pharmaceuticals. **TLM:** previously employed by and is a shareholder in Alnylam pharmaceuticals. **YF:** consultancy fees from Alnylam Pharmaceuticals and member of the Scientific Review Committee.

Abbreviations: AE, adverse event; CI, confidence interval; eGFR, estimated glomerular filtration rate; KSE, kidney stone event; N/A, not available; NC, nephrocalcinosis; OLE, open-label extension; PH1, primary hyperoxaluria type 1; PY, person-years; RNAi, ribonucleic acid interference; SCR, screening.

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Presented at: the Annual Meeting of the American Urological Association (AUA); September 10–13, 2021; Las Vegas, NV