Efficacy and Safety of Lumasiran in Patients With Primary Hyperoxaluria Type 1: 24-Month Analysis of the ILLUMINATE-A Trial

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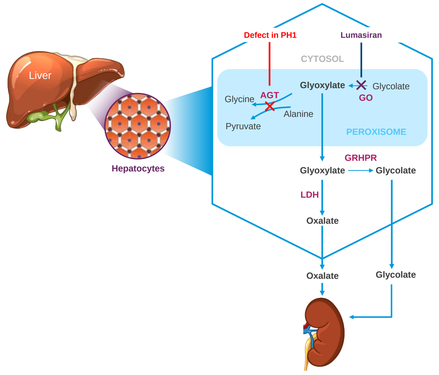
Conclusions

- **Long-term lumasiran treatment resulted in sustained reductions in UOx and POx through 24 months of treatment in the lumasiran/lumasiran group (mean UOx reduction: 58.1%; mean POx reduction: 56.0%) and 18 months of treatment in the placebo/lumasiran group (UOx: 48.7%; POx: 61.2%)**
- **Lower kidney stone event rates were observed after initiation of lumasiran, and event rates remained lower in the lumasiran/lumasiran group (historical: 3.19/person-year; 24 months of treatment: 0.80/person-year) and in the placebo/lumasiran group (historical: 0.54/person-year; 18 months of treatment: 0.28/person-year) through Month 24**
- **Lumasiran demonstrated an acceptable safety profile in patients with PH1**
  - **The most common AEs related to lumasiran were injection-site reactions, all of which were mild and transient**

Introduction

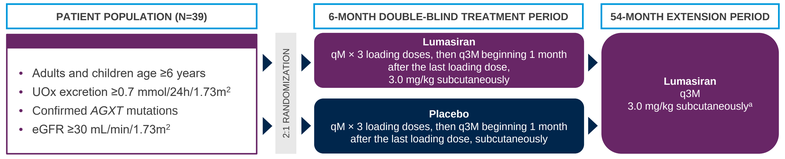
- Primary hyperoxaluria type 1 is a rare genetic disorder characterized by hepatic overproduction of oxalate[1,2]
- Excretion of excess oxalate by the kidneys can result in recurrent kidney stones, nephrocalcinosis, progressive kidney disease, and ultimately kidney failure[2,3]
- Lumasiran is a subcutaneously administered, liver-directed RNAi therapeutic to lower UOx levels in pediatric and adult patients with PH1[4,5]
  - Lumasiran decreases hepatic oxalate production by inhibiting the production of GO[4-6] (**Figure 1**)
- We report data from the 24-month analysis of ILLUMINATE-A, a randomized, double-blind, placebo-controlled Phase 3 trial designed to evaluate the efficacy and safety of lumasiran in children and adults with PH1 and eGFR ≥30 mL/min/1.73m^2

Figure 1. Defect in Glyoxylate Metabolism in Hepatocytes of Patients With PH1 and Lumasiran Therapeutic Hypothesis



Methods

Figure 2. ILLUMINATE-A Phase 3 Study Design



- Treatment arms were stratified at randomization based upon mean 24-hour UOx[b] from the first 2 valid samples collected during screening (≤1.70 mmol/24h/1.73m^2 vs >1.70 mmol/24h/1.73m^2)
- Oxalate was measured with a validated liquid chromatography-tandem mass spectrometry assay

NCT03681184; EudraCT Number: 2018-001981-40. [a]Patients 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. [b]1.70 mmol/24h/1.73m^2=153 mg/24h/1.73m^2 (1 mmol/24h/1.73m^2=90 mg/24h/1.73m^2).

Results

- Patient characteristics at baseline are shown in **Table 1**. Of 39 patients enrolled, 24/26 in the lumasiran/lumasiran group and 13/13 in the placebo/lumasiran group entered the extension period

Table 1. ILLUMINATE-A: Baseline Characteristics

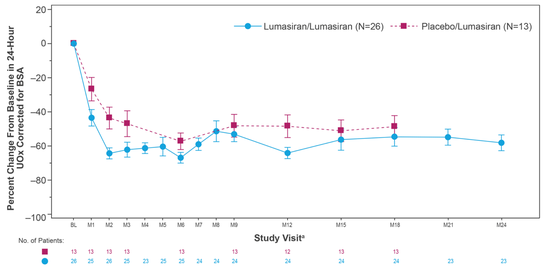
Baseline Characteristic[a]	Placebo/ Lumasiran (N=13)	Lumasiran/ Lumasiran (N=26)	All Lumasiran (N=39)
Age at informed consent, mean (range), years	17.0 (6–60)	18.7 (6–47)	18.1 (6–60)
Male, n (%)	8 (62)	18 (69)	26 (67)
Race, n (%)			
White	9 (69)	21 (81)	30 (77)
Asian	3 (23)	3 (12)	6 (15)
Other or >1 race	1 (8)	2 (8)	3 (8)
24-Hour UOx excretion corrected for BSA[b], mean (SD), mmol/24h/1.73m^2	1.63 (0.67)	1.84 (0.60)	1.77 (0.62)
POx, mean (SD), µmol/L[c]	19.3 (9.5)	14.8 (7.6)	16.3 (8.4)
eGFR, mean (SD), mL/min/1.73m^2	78.8 (30.0)	83.0 (25.5)	81.6 (26.8)
Patients reporting history of kidney stone events[d], n (%)			
Lifetime	10 (77)	23 (88)	33 (85)
12 months prior to consent	4 (31)	11 (42)	15 (38)

[a]Baseline is defined as the last non-missing value prior to the first dose of lumasiran. [b]ULN is 0.514 mmol/24h/1.73m^2=45 mg/24h/1.73m^2 (1 mmol/24h/1.73m^2=88 mg/24h/1.73m^2). [c]ULN is 12.11 µmol/L. [d]A kidney stone event is defined as an event that includes at least one of the following: visit to healthcare provider because of a kidney stone, medication for renal colic, stone passage, or macroscopic hematuria due to a kidney stone.

Percent Change in 24-Hour UOx During Lumasiran Treatment

- Patients initially randomized to lumasiran (lumasiran/lumasiran) had a sustained reduction in 24-hour UOx through Month 24 (mean reduction from baseline at Month 24: 58.1%) (**Figure 3**)
- Patients initially randomized to placebo who crossed over to lumasiran after 6 months (placebo/lumasiran) demonstrated a similar time course and magnitude of 24-hour UOx reduction after 18 months of lumasiran treatment (mean reduction: 48.7%) (**Figure 3**)

Figure 3. Percent Change in 24-Hour UOx During Lumasiran Treatment

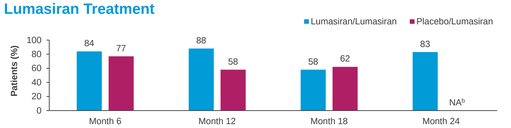


Data cutoff: April 26, 2021. Data in graph are mean ± SEM. [a]Visit is relative to the first dose of lumasiran.

Proportion of Patients With 24-Hour UOx ≤1.5 × ULN During Lumasiran Treatment

- After 24 months of lumasiran treatment, 83% of lumasiran/lumasiran patients achieved near normalization or normalization of 24-hour UOx (**Figure 4**)
- After 18 months of lumasiran treatment, 62% of placebo/lumasiran patients achieved near normalization or normalization of 24-hour UOx (**Figure 4**)

Figure 4. Proportion of Patients With 24-Hour UOx ≤1.5 × ULN During Lumasiran Treatment

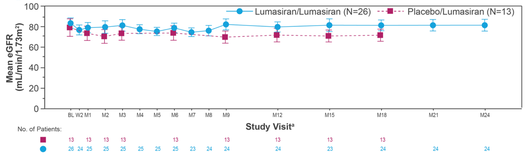


Data cutoff: April 26, 2021. [a]Visit is relative to the first dose of lumasiran. [b]Data are not available for the placebo/lumasiran group at Month 24 because patients received only 18 months of lumasiran treatment.

Changes in POx and eGFR During Lumasiran Treatment

- Mean percent reduction from baseline in POx was 56.0% in the lumasiran/lumasiran group after 24 months of lumasiran treatment and 61.2% in the placebo/lumasiran group after 18 months of lumasiran treatment
- Mean eGFR remained stable in both groups during lumasiran treatment (**Figure 5**)

Figure 5. Mean eGFR Values During Lumasiran Treatment

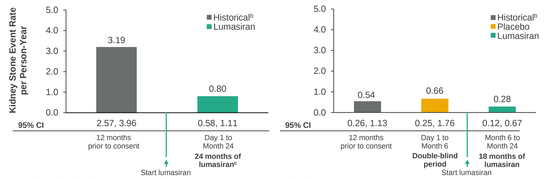


Data cutoff: April 26, 2021. Error bars represent SEM. [a]Visit is relative to the first dose of lumasiran.

Kidney Stone Events

- Kidney stone event rates decreased from 3.19/person-year during the 12 months prior to consent to 0.80/person-year in the lumasiran/lumasiran group from Day 1 to Month 24 (24 months of lumasiran treatment) (**Figure 6**)
- In the placebo/lumasiran group, kidney stone event rates decreased from 0.54/person-year during the 12 months prior to consent to 0.28/person-year from Month 6 to Month 24 (18 months of lumasiran treatment) (**Figure 6**)

Figure 6. Kidney Stone Event Rates[a]



Data cutoff: April 26, 2021. [a]Kidney stone event is defined as an event that includes at least one of the following: visit to healthcare provider because of a kidney stone, medication for renal colic, stone passage, or macroscopic hematuria due to a kidney stone. [b]Patient-reported history of kidney stone events. [c]Kidney stone event rate was 1.09 (0.63, 1.88) per person-year during the double-blind period (Day 1 to Month 6).

Safety Results

- Overall total mean duration of lumasiran exposure was 21.2 months (range: 2.8–26.9) with 389 doses given
  - 32 patients were treated for ≥18 months and 9 patients were treated for ≥24 months
- The majority of AEs were mild in severity
- The most common related AEs were mild, transient injection-site reactions (**Table 2**)
  - Erythema, pain, pruritus, and swelling at the injection site were the most common signs and symptoms
- Three patients had serious AEs, including abdominal pain (N=1), urosepsis (N=1), and a post-procedural complication (N=1); none were considered related to study drug (**Table 2**)
- There were no treatment interruptions or discontinuations related to lumasiran; no deaths occurred (**Table 2**)

Table 2. Safety Overview in Patients With PH1 During Lumasiran Treatment

Event, n (%)	Placebo/ Lumasiran (N=13)	Lumasiran/ Lumasiran (N=26)	All Lumasiran (N=39)
AEs	11 (85)	24 (92)	35 (90)
Serious AE[a]	0	3 (12)	3 (8)
Severe AE[b]	0	2 (8)	2 (5)
AE leading to discontinuation of study treatment[c]	0	1 (4)	1 (3)
AEs occurring in ≥15% of patients			
Injection-site reactions[d]	6 (46)	12 (46)	18 (46)
Abdominal pain	1 (8)	6 (23)	7 (18)
Headache	2 (15)	5 (19)	7 (18)
Death	0	0	0

Safety data from first dose of lumasiran to data cutoff date: April 26, 2021. [a]Abdominal pain, urosepsis, and post-procedural complication, considered not related to study drug by the investigator. [b]Urosepsis and post-procedural complication, considered not related to study drug. [c]Fatigue and disturbance in attention, considered not related to study drug. [d]Includes AEs of injection-site reaction, injection-site pain, injection-site erythema, and injection-site discomfort.

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