Efficacy and Safety of Lumasiran in Patients with Primary Hyperoxaluria Type 1: 36-Month Analysis of the ILLUMINATE-A Trial

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Conclusions

- **In patients with PH1, treatment with lumasiran for up to 36 months led to sustained UOx reduction with an acceptable safety profile. The most common lumasiran-related AEs were mild injection site reactions**
- **Clinical outcomes data were encouraging, including stable eGFR, improved kidney stone event rate, and, in a number of patients, an improvement or complete resolution of medullary nephrocalcinosis**

Introduction

- PH1 is a rare genetic disorder characterized by overproduction of hepatic oxalate, increased oxalate excretion by the kidneys, and formation of calcium oxalate crystals in the kidneys and urinary tract[1]
- Patients with PH1 may experience recurrent nephrolithiasis and/or develop nephrocalcinosis, which can ultimately progress to kidney failure and systemic oxalosis[1]
- Lumasiran is an RNAi therapeutic that targets and promotes degradation of the mRNA encoding glycolate oxidase (GO), thereby reducing hepatic oxalate production[2]
- Lumasiran is approved in the United States for the treatment of PH1 to lower UOx and POx levels in pediatric and adult patients, and in the European Union to treat PH1 in all age groups[3,4]
- Here we report data from a 36-month analysis of the ILLUMINATE-A study of lumasiran in patients with PH1 (ClinicalTrials.gov: NCT03681184; EudraCT: 2018-001981-40)

Methods

- ILLUMINATE-A is an ongoing, multinational (Europe, North America, Middle East) Phase 3 trial
- Eligible patients were age ≥6 years at study entry with genetically confirmed PH1 and eGFR ≥30 mL/min/1.73m^2
- There was a 6-month, double-blind, placebo-controlled period, during which participants were randomized 2:1 to receive lumasiran or placebo, followed by an extension period of up to 54 months
- Lumasiran 3 mg/kg is administered as a loading dose once monthly for 3 doses, followed by a maintenance dose every 3 months beginning 1 month after the last loading dose[3]
- The degree of medullary nephrocalcinosis in each kidney was graded using a validated 4-point scale[5]
  - Medullary nephrocalcinosis was categorized as stable (ie, no change in either kidney), improving (ie, both kidneys improving or 1 kidney improving and 1 with no change), worsening (ie, both kidneys worsening or 1 kidney worsening and 1 with no change), or indeterminate (ie, 1 kidney improving and 1 worsening)

Results

- Of 39 patients enrolled, 24/26 in the lumasiran/lumasiran group and 13/13 in the placebo/lumasiran group entered and continue in the extension period
- Baseline characteristics were generally well balanced between groups (**Table 1**)

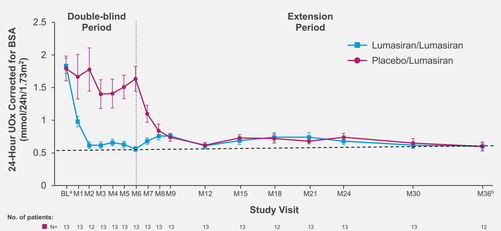
Table 1. Baseline Demographic and Clinical Characteristics[a]

Characteristic	Placebo/Lumasiran (N=13)	Lumasiran/Lumasiran (N=26)
Age at informed consent, mean (range), y	17.0 (6–60)	18.7 (6–47)
Male, n (%)	8 (62)	18 (69)
Race, n (%)		
Asian	3 (23)	3 (12)
White	9 (69)	21 (81)
Other or >1 race	1 (8)	2 (8)
24-hour UOx excretion corrected for BSA,[b] mean (SD), mmol/24h/1.73m^2	1.6 (0.7)	1.8 (0.6)
POx, mean (SD), µmol/L[c]	19.3 (9.5)	14.8 (7.6)
eGFR, mean (SD), mL/min/1.73m^2	78.8 (30.0)	83.0 (25.6)
Patients reporting history of kidney stone events,[d] n (%)		
Lifetime	10 (77)	23 (88)
12 months prior to consent	4 (31)	11 (42)

[a]Baseline is defined as the last nonmissing 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 = 90 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.

- At Month 36, mean percent reduction from baseline in 24-hour UOx was 63% in the lumasiran/lumasiran group (after 36 months of lumasiran treatment) and 58% in the placebo/lumasiran group (after 30 months of lumasiran treatment; **Figure 1**)

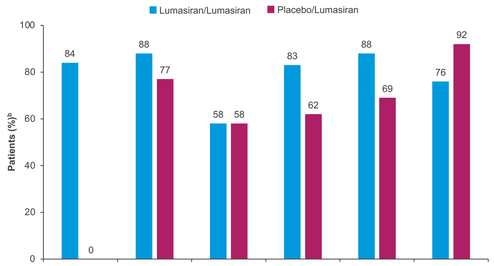
Figure 1. Mean (SEM) 24-Hour UOx Over Time



Dotted line represents the ULN of 0.514 mmol/24h/1.73m^2 (1 mmol/24h/1.73m^2 = 90 mg/24h/1.73m^2) for 24-hour UOx excretion.
[a]Baseline is the median of all valid 24-hour urine assessments collected prior to the first dose date/time of study drug (lumasiran or placebo) without any nonprotocol-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.

- At Month 36, 24-hour UOx excretion was ≤1.5 × ULN in 76% of patients in the lumasiran/lumasiran group (after 36 months of lumasiran treatment) and 92% in the placebo/lumasiran group (after 30 months of lumasiran treatment; **Figure 2**)

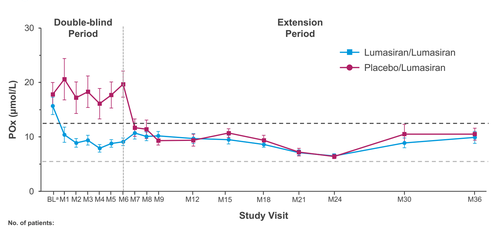
Figure 2. Patients with 24-Hour UOx Corrected for BSA ≤1.5 x ULN[a] Over Time



[a]ULN is 0.514 mmol/24h/1.73m^2 = 45 mg/24h/1.73m^2 (1 mmol/24h/1.73m^2 = 90 mg/24h/1.73m^2).
[b]Percentages are based upon the number of patients having 24-hour UOx corrected for BSA data at the visit.

- At Month 36, mean percent reduction from baseline in POx was 36% in the lumasiran/lumasiran group (after 36 months of lumasiran treatment) and 35% in the placebo/lumasiran group (after 30 months of lumasiran treatment; **Figure 3**)

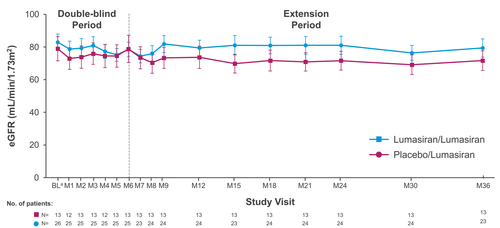
Figure 3. Mean (SEM) POx Levels Over Time



Dark gray dotted line represents the ULN of 12.11 µmol/L for POx. Light gray dotted line represents the lower limit of quantitation of the POx assay at 5.55 µmol/L; values below the lower limit of quantitation were assigned a value of 5.55 µmol/L.
[a]Baseline is the mean of all measurements prior to the first dose date/time of study drug in the study (lumasiran or placebo) in the 6-month double-blind period.

- In both the lumasiran/lumasiran group and the placebo/lumasiran group, eGFR remained stable through Month 36 (**Figure 4**)

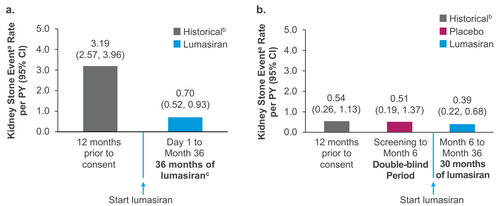
Figure 4. Mean (SEM) eGFR Over Time



[a]Baseline is the last assessment prior to the first dose of study drug (lumasiran or placebo) in the 6-month double-blind period.

- Kidney stone event rates decreased from 3.19/PY during the 12 months before consent to 0.70/PY in the lumasiran/lumasiran group, and from 0.54/PY to 0.39/PY in the placebo/lumasiran group (**Figure 5**)

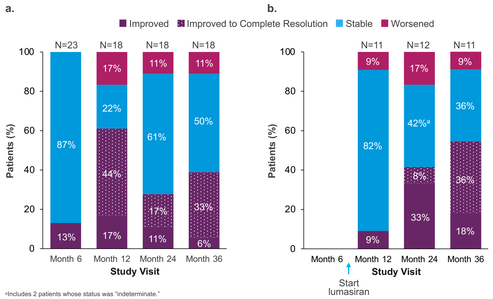
Figure 5. Kidney Stone Event Rates[a] in the (a) Lumasiran/Lumasiran and (b) Placebo/Lumasiran Groups



[a]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 (95% CI) was 1.09 (0.63, 1.88) per PY during the double-blind period (Day 1 to Month 6).

- Medullary nephrocalcinosis generally improved or remained stable (**Figure 6**)
- Forty-three percent of patients with medullary nephrocalcinosis at baseline had complete resolution of medullary nephrocalcinosis after long-term treatment
  - After 36 months of lumasiran treatment, 6 of the 13 (46%) patients in the lumasiran/lumasiran group with medullary nephrocalcinosis at baseline had no detectable nephrocalcinosis at Month 36
  - After 30 months of lumasiran treatment, 4 of the 10 (40%) patients in the placebo/lumasiran group with medullary nephrocalcinosis at baseline had no detectable nephrocalcinosis at Month 36

Figure 6. Change in Medullary Nephrocalcinosis from Baseline in the (a) Lumasiran/Lumasiran and (b) Placebo/Lumasiran Groups



[a]Includes 2 patients whose status was "indeterminate."

- Overall, 92% (36/39) of patients had AEs (**Table 2**)
  - The most common lumasiran-related AEs were mild injection site reactions (49% of patients)

Table 2. Safety Profile of Lumasiran[a]

Event, N (%)	Placebo/Lumasiran (N=13)	Lumasiran/Lumasiran (N=26)	All Lumasiran (N=39)
Any AE	12 (92)	24 (92)	36 (92)
Serious AE[b]	1 (8)	3 (12)	4 (10)
Severe AE[c]	0	2 (8)	2 (5)
AE leading to discontinuation of study treatment[d]	0	1 (4)	1 (3)
AEs occurring in ≥15% of patients (all lumasiran)[e]			
Injection site reactions[f]	6 (46)	13 (50)	19 (49)
Abdominal pain during lumasiran treatment	1 (8)	7 (27)	8 (21)
Headache during lumasiran treatment	2 (15)	5 (19)	7 (18)
COVID-19 during lumasiran treatment	3 (23)	3 (12)	6 (15)
Death	0	0	0

[a]Placebo/lumasiran includes patients who received placebo during the 6-month double-blind period and switched to lumasiran during the extension period. Lumasiran/lumasiran includes patients who received lumasiran during the 6-month double-blind period. All lumasiran includes all patients who received any lumasiran during the study.
[b]Abdominal pain (N=2 patients), dysuria (N=1 patient), nephrectomy (N=1 patient), postprocedural complication (N=1 patient), and urosepsis (N=1 patient); none of the serious AEs were considered related to lumasiran by the investigator.
[c]Postprocedural complication (N=1 patient) and urosepsis (N=1 patient), considered not related to lumasiran by the investigator.
[d]Fatigue and disturbance in attention, considered not related to lumasiran by the investigator, which began during the double-blind period.
[e]All terms are MedDRA preferred terms except for injection site reactions.
[f]Defined as AEs that were mapped to the high-level term "Injection Site Reactions" or events reported by the sites as injection site reactions.

Abbreviations: AE, adverse event; BL, baseline; BSA, body surface area; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; MedDRA, Medical Dictionary for Regulatory Activities; mRNA, messenger ribonucleic acid; M, month; PH1, primary hyperoxaluria type 1; POx, plasma oxalate; PY, patient-years; SC, subcutaneous; SD, standard deviation; SEM, standard error of the mean; siRNA, small interfering ribonucleic acid; ULN, upper limit of normal; UOx, urinary oxalate.

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