Lumasiran for Patients with Primary Hyperoxaluria Type 1 and Impaired Kidney Function: 12-Month Analysis of the Phase 3 ILLUMINATE-C Trial

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Conclusions

- **Lumasiran treatment led to sustained reductions in POx in patients with PH1 and CKD stage 3b–5 (including HD), with an acceptable safety profile through Month 12**
- **Injection-site reaction (24%) was the most common treatment-related AE**
- **Two patients received isolated kidney transplants, continued lumasiran, had further reductions in POx post-transplant, and have not reinitiated dialysis**
- **Two patients received combined liver/kidney transplants. One re-initiated HD due to delayed graft function; there was no further follow-up on the other combined transplant patient**
- **The impact on systemic oxalosis and transplant outcomes will be further monitored in the extension period**

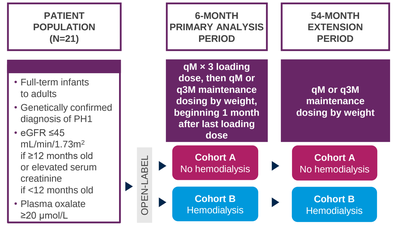
Introduction

- Primary hyperoxaluria type 1 (PH1) is a rare genetic disease characterized by excessive hepatic oxalate production due to a deficiency in the hepatic peroxisomal enzyme AGT[1,2]
- In patients with PH1 and CKD stage 3b–5 (eGFR <45 mL/min/1.73m^2), elevated plasma oxalate (POx) directly relates to the pathophysiology of systemic oxalosis, making reduction of POx a suitable clinical target in this population[1-3]
- Lumasiran, an RNAi therapeutic that decreases hepatic oxalate production by inhibiting the production of glycolate oxidase,[4-6] is approved in the United States for the treatment of PH1 to lower urinary oxalate and POx levels in pediatric and adult patients[5] and in the European Union for the treatment of PH1 in all age groups[4]
- Here, we present the 12-month analysis results from ILLUMINATE-C (ClinicalTrials.gov: NCT04152200; EudraCT: 2019-001346-17)

Methods

- ILLUMINATE-C is an ongoing multicenter, multinational, single-arm, Phase 3 study in patients with a genetically confirmed diagnosis of PH1, advanced kidney disease (CKD stage 3b–5), and elevated POx (**Figure 1**)

Figure 1. ILLUMINATE-C Study Design



ClinicalTrials.gov: NCT04152200; EudraCT: 2019-001346-17.

Results

- Patient characteristics at baseline are shown in **Table 1**. All 21 patients completed the 6-month primary analysis period and entered the extension period

Table 1. Baseline Characteristics

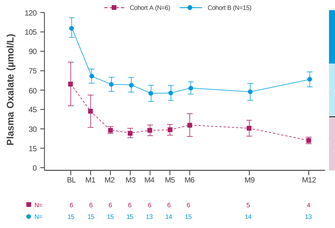
Baseline Characteristic	Cohort A (N=6)	Cohort B (N=15)	All Treated (N=21)
Age at consent, median (range), years	9 (0–40)	6 (1–59)	8 (0–59)
Female, n (%)	3 (50)	6 (40)	9 (43)
POx, median (range)[a], µmol/L	58 (23–134)	104 (56–167)	101 (23–167)
eGFR[b], median (range), mL/min/1.73m^2	16.5 (8.6–34.1)	NA	NA
Number of dialysis sessions per week, median (range)	NA	6 (3–7)	NA

[a]ULN=12.11 µmol/L for POx, as determined based on data from 75 healthy adults. POx was evaluated using a validated liquid chromatography–tandem mass spectrometry assay, which was developed by Alnylam to meet regulatory requirements and has not yet been published.
[b]N=5; eGFR was calculated only in patients age ≥12 months. eGFR (mL/min/1.73m^2) was calculated from serum creatinine based on the Modification of Diet in Renal Disease formula for patients age ≥18 years and the Schwartz Bedside Formula for patients age 1 to <18 years.

POx Through Month 12

- Reductions in POx were sustained through Month 12 (**Figure 2**)

Figure 2. Plasma Oxalate Actual Values at Each Visit Through Month 12[a]

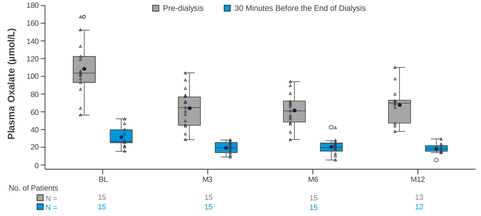


POx Mean (SEM) Percent Change from Baseline at Months 6 and 12	
Cohort B	M6: 40.3% (5.3%) M12: 34.3% (6.9%)
Cohort A	M6: 20.3% (31.2%) M12: 69.3% (6.9%)

[a]In Cohort A, baseline was defined as the mean of all POx samples (µmol/L) 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 (µmol/L) collected prior to the first dose of lumasiran.

- Mean (SEM) absolute reduction in POx from baseline at Month 12 was 60.7 (20.1) and 42.4 (9.0) µmol/L in Cohorts A and B, respectively (**Figure 2**)

Figure 3. Distribution of Pre- and Post-dialysis Plasma Oxalate Levels in Cohort B Through Month 12



Filled circles represent means; horizontal lines represent medians; triangles represent observed values for individual patients; open circles represent outliers.

Most Burdensome Symptoms

- The 3 most burdensome symptoms at baseline for each patient were identified by the investigator
- Investigators subsequently noted whether each patient's most burdensome symptoms were stable/unchanged, improved, or worsened; no patient had symptoms categorized as worsened in this survey
- The most burdensome symptoms improved or remained stable with lumasiran in all patients with at least one burdensome symptom (**Table 2**)

Table 2. Change in Most Burdensome Symptoms at Month 12 Relative to Baseline[a,b]

	Cohort A (N=6)				Cohort B (N=15)			
	Total at Baseline	Improved at M12	Stable at M12	Data Not Available at M12	Total at Baseline	Improved at M12	Stable at M12	Data Not Available at M12
Fatigue	2	1	1	0	10	4	4	2
Nausea/decreased appetite	1	1	0	0	4	1	3	0
Bone pain	1	1	0	0	3	2	0	1
Decreased mobility	0	0	0	0	4	0	3	1
Shortness of breath	0	0	0	0	3	1	1	1
Kidney stone–associated pain	2	0	2	0	0	0	0	0
Daytime somnolence	0	0	0	0	1	0	0	1
Other symptom	0	0	0	0	3	2	1	0

[a]Investigators selected up to 3 symptoms from the following: bone pain, daytime somnolence, decreased mobility, fatigue, kidney stone–associated pain, nausea/decreased appetite, shortness of breath, skin ulcerations, vision loss, not applicable, and other.
[b]Analysis not prespecified.

Safety

- Overall total median duration of lumasiran exposure was 14.2 months (range: 8.3–19.7) with 195 doses given
- The most frequently reported AEs were pyrexia (38%) and injection-site reaction (24%) (**Table 3**)
  - The majority of AEs were mild or moderate in severity
- The most common lumasiran-related adverse events were mild, transient injection-site reactions (24% [5/21] of patients); the most common symptoms included hematoma, erythema, and discoloration
- Two patients discontinued study treatment and withdrew from the study due to combined liver/kidney transplants
- There were no treatment discontinuations or withdrawals from the study due to AEs related to lumasiran
- There were no serious or severe AEs related to lumasiran and no deaths

Table 3. Safety Overview

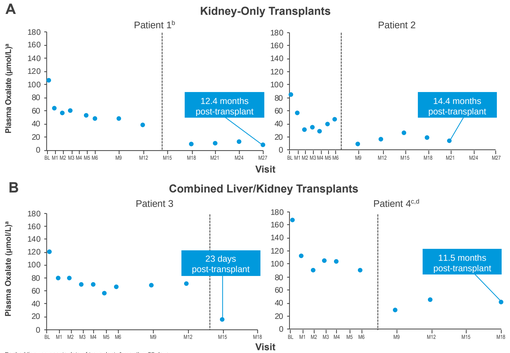
Event, N (%)	Cohort A (N=6)	Cohort B (N=15)	All Treated (N=21)
Patients with ≥1 AE	5 (83)	14 (93)	19 (90)
AEs occurring in ≥2 patients in either cohort			
Pyrexia	1 (17)	7 (47)	8 (38)
Injection-site reaction	1 (17)	4 (27)	5 (24)
Diarrhea	1 (17)	3 (20)	4 (19)
Anemia	1 (17)	2 (13)	3 (14)
Device-related infection	0	3 (20)	3 (14)
Abdominal pain	0	2 (13)	2 (10)
Accidental overdose	0	2 (13)	2 (10)
Ear infection	0	2 (13)	2 (10)
Kidney and liver transplant	0	2 (13)	2 (10)
Kidney transplant	0	2 (13)	2 (10)
SARS-CoV-2 test positive	0	2 (13)	2 (10)
Blood phosphorus increased	2 (33)	0	2 (10)
AEs leading to discontinuation of study treatment	0	2 (13)	2 (10)[a]
AEs leading to withdrawal from the study	0	2 (13)	2 (10)[a]
Severe AEs	1 (17)	6 (40)	7 (33)[b]
Serious AEs	2 (33)	11 (73)	13 (62)[c]
Death	0	0	0

[a]The 2 AEs that led to discontinuation and withdrawal were liver/kidney transplants.
[b]Severe AEs that occurred in 2 patients included liver/kidney transplant and kidney transplant. Severe AEs that occurred in 1 patient included spontaneous hematoma, device-related thrombosis, pyrexia, herpes simplex, arteriovenous fistula thrombosis, graft complication, blood creatinine increased, seizure, acute kidney injury, urinoma, arteriovenous fistula operation, and dialysis device insertion. No severe AEs were determined to be related to lumasiran.
[c]Serious AE that occurred in 4 patients was pyrexia. Serious AEs that occurred in 2 patients included device-related infection, liver/kidney transplant, and kidney transplant. No serious AEs were determined to be related to lumasiran.

Hemodialysis and Transplant Outcomes

- Two Cohort A patients (baseline eGFR 8.6 and 16.0 mL/min/1.73m^2) initiated HD
- In Cohort B, 2 patients received kidney transplants and 2 patients received liver/kidney transplants (**Figure 4**):
  - Both patients who received kidney transplants discontinued HD and continued lumasiran. POx decreased further post-transplant. Lumasiran was well tolerated in both patients, with no treatment-related AEs reported for either patient post-transplant. The post-transplant eGFR in these patients ranged from 120 to 143 mL/min/1.73m^2 and 25 to 34 mL/min/1.73m^2, respectively
  - One patient who received a liver/kidney transplant discontinued HD (Patient 3) and the other patient (Patient 4) continued HD because of persistent delayed graft function due to acute tubular necrosis. Both patients discontinued lumasiran (genetic deficiency in liver was corrected). The post-transplant eGFR in the patient who discontinued HD was not available because the patient did not complete safety follow-up visits; the other patient's eGFR was not interpretable given they remained on HD through the end of safety follow-up

Figure 4. POx in Patients Who Received Kidney-Only Transplants (A) and Combined Liver/Kidney Transplants (B)



Dashed line represents date of transplant. 1 month = 28 days.
[a]Pre-dialysis POx if patient was receiving HD at the time the sample was drawn.
[b]Month 15 POx sample not available due to reaching blood volume limit.
[c]Month 15 POx sample not available; patient ended study treatment after Month 6 assessments and remained on study for safety follow-up assessments thereafter.
[d]Patient continued HD post-transplant because of persistent delayed graft due to acute tubular necrosis.

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