Relationship of Baseline Weight and Response to Lumasiran in Patients With Primary Hyperoxaluria Type 1 on Hemodialysis

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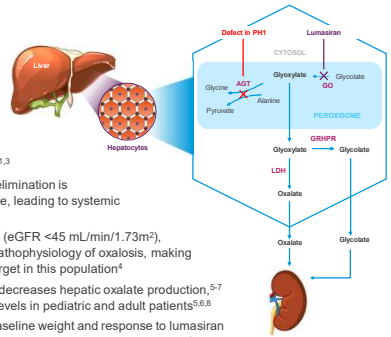
Conclusions

- **Patients treated with lumasiran experienced consistent reductions in POx levels, irrespective of weight category**
- **Although lower-weight subgroups had higher baseline median predialysis POx values, the LS mean reductions in POx at Month 6 were comparable across the subgroups**

Introduction

- Primary hyperoxaluria type 1 is a rare genetic disorder characterized by excessive hepatic oxalate production due to a deficiency in the hepatic peroxisomal enzyme AGT (**Figure 1**)[1,2]
- Excess oxalate is excreted mainly by the kidneys; excess urinary oxalate can crystallize and result in recurrent kidney stones, nephrocalcinosis, progressive kidney disease, and ultimately kidney failure[1,3]
- As kidney function declines, oxalate elimination is compromised and POx levels increase, leading to systemic oxalosis and multi-organ damage[1,2]
- In PH1 patients with CKD stage 3b–5 (eGFR <45 mL/min/1.73m^2), elevated POx directly relates to the pathophysiology of oxalosis, making reduction of POx a suitable clinical target in this population[4]
- Lumasiran, an RNAi therapeutic that decreases hepatic oxalate production,[5-7] is approved to lower urinary oxalate levels in pediatric and adult patients[5,6,8]
- We report the relationship between baseline weight and response to lumasiran using data from patients on hemodialysis at enrollment in ILLUMINATE-C (ClinicalTrials.gov: NCT04152200; EudraCT: 2019-001346-17)

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

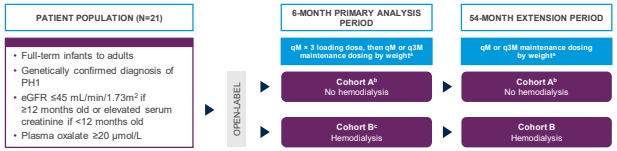


Methods

Patients and Study Design

- ILLUMINATE-C is a 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 2**)
  - The study includes 2 cohorts: Cohort A, patients who were not on hemodialysis at screening, and Cohort B, patients who were on stable hemodialysis at screening

Figure 2. ILLUMINATE-C Patients and Study Design



[a]Patients weighing <10 kg received loading doses of 6 mg/kg qM for 3 months and then maintenance doses of 3 mg/kg qM; patients weighing 10 to <20 kg received loading doses of 6 mg/kg qM for 3 months and then maintenance doses of 6 mg/kg q3M; patients weighing ≥20 kg received loading doses of 3 mg/kg qM for 3 months and then maintenance doses of 3 mg/kg q3M. Maintenance dosing was started 1 month after the last loading dose.
[b]Cohort A patients who experience progression of kidney impairment over time and begin to require hemodialysis therapy may cross over to Cohort B. No patient crossed over during the 6-month primary analysis period.
[c]No changes to dialysis regimen (except when medically necessary) or kidney transplantation were permitted during the primary analysis period.

Analyses

- In a post hoc analysis, Cohort B patients were stratified by baseline weight (<10, 10 to <20, ≥20 kg; **Table 1**)
- Changes from baseline in POx and plasma glycolate were analyzed after 6 months of lumasiran treatment

Table 1. Lumasiran Weight-Based Dosing

Body Weight	Loading Dose	Maintenance Dose (begin 1 month after the last loading dose)
Less than 10 kg	6 mg/kg once monthly for 3 doses	3 mg/kg once monthly
10 kg to less than 20 kg	6 mg/kg once monthly for 3 doses	6 mg/kg once every 3 months (quarterly)
20 kg and above	3 mg/kg once monthly for 3 doses	3 mg/kg once every 3 months (quarterly)

Results

- Patient characteristics at baseline are shown in **Table 2**

Table 2. Cohort B: Baseline Characteristics by Weight Category

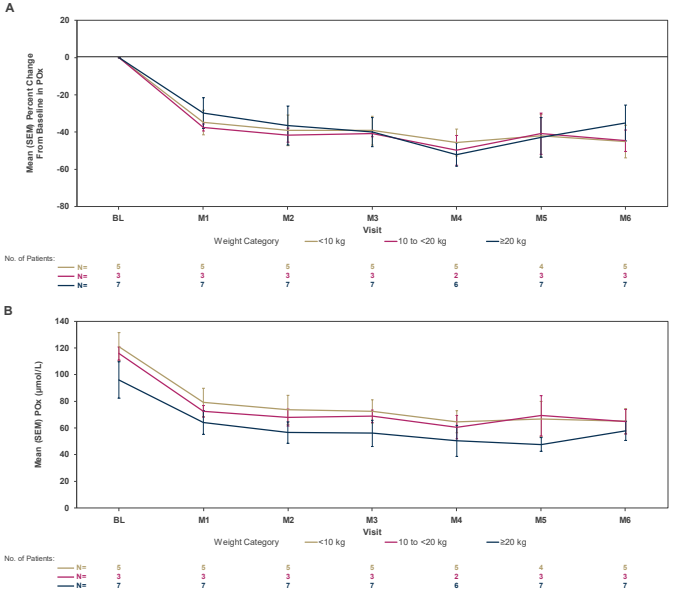
Baseline Characteristic	<10 kg (N=5)	10 to <20 kg (N=3)	≥20 kg (N=7)	Overall Cohort B (N=15)
Age at consent, median (range), years	1.2 (1–3)	6.0 (2–6)	18.0 (16–59)	6.0 (1–59)
Female, n (%)	3 (60)	2 (67)	1 (14)	6 (40)
Time from diagnosis to first dose, median (range), years	1.0 (0.5–3.3)	0.8 (0.5–6.0)	1.6 (0.6–36.7)	1.4 (0.5–36.7)
Genotype[a], n (%)				
PR/*	1 (20)	1 (33)	3 (43)	5 (33)
M/M or M/N	2 (40)	1 (33)	4 (57)	7 (47)
N/N	2 (40)	1 (33)	0	3 (20)
Pyridoxine use, n (%)	2 (40)	1 (33)	4 (57)	7 (47)
Predialysis POx[b], median (range), µmol/L	122.3 (93.1–152.3)	119.0 (106.3–122.5)	97.1 (56.3–167.0)	103.7 (56.3–167.0)
Plasma glycolate, median (range), µmol/L	273.5 (249.0–487.0)	499.5 (366.5–655.0)	178.0 (73.9–563.5)	273.5 (73.9–655.0)
Age at start of current dialysis[c], median (range), years	1.0 (1–4)	4.5 (2–6)	17.3 (16–58)	6.2 (1–58)
Number of dialysis sessions per week, median (range)	6.0 (3–7)	6.0 (5–6)	5.0 (3–6)	6.0 (3–7)

[a]M=missense; N=nonsense; PR=pyridoxine-responsive; *=any genotype of PR, M, or N. PR was defined as NM_000030.3(AGXT):c.508G>A (p.Gly170Arg) or NM_000030.3(AGXT):c.454T>A (p.Phe152Ile). M and N were defined based on a publication by Mandrile et al.[9]
[b]ULN=12.11 µmol/L (1.09 mg/mL) for POx, as determined based on data from 75 healthy adults.
[c]Stable hemodialysis regimen for at least 4 weeks.

Predialysis POx Through Month 6 by Weight Category

- Lumasiran led to comparable LS mean reductions from baseline in POx at Month 6 (average of Month 3 to Month 6) across subgroups (41.3%–44.4%; **Figure 3**)

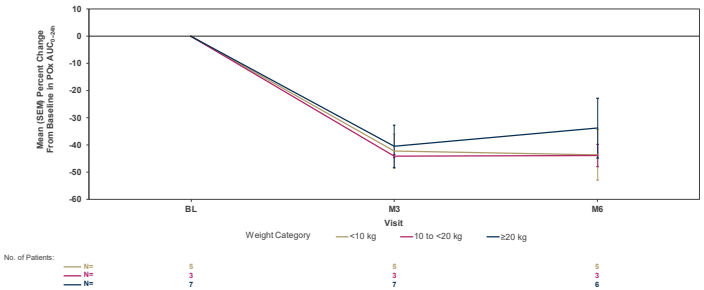
Figure 3. Plasma Oxalate Mean (SEM) Percent Change From Baseline at Each Visit (A) and Actual Values at Each Visit (B) by Weight Category



Plasma Oxalate $AUC_{0–24h}$ and Plasma Glycolate Through Month 6 by Weight Category

- POx AUC is intended to evaluate the effect of lumasiran on the POx levels between dialysis sessions
- Lumasiran demonstrated comparable reductions in POx $AUC_{0–24h}$ across weight categories at Month 6 (**Figure 4**)
- Plasma glycolate initially increased and then plateaued across weight categories

Figure 4. Mean (SEM) Percent Change From Baseline in POx $AUC_{0–24h}$ Between Dialysis Sessions by Weight Category



Safety

- AEs related to lumasiran were comparable across subgroups (**Table 3**)
- No severe or serious AEs related to lumasiran were reported
- No treatment-emergent anti-drug antibodies were observed

Table 3. Safety Overview

Event, n (%)	<10 kg (N=5)	10 to <20 kg (N=3)	≥20 kg (N=7)	Overall Cohort B (N=15)
AEs	4 (80)	3 (100)	5 (71)	12 (80)
Lumasiran-related AEs	1 (20)	2 (67)	2 (29)	5 (33)
AEs occurring in ≥10% of patients				
Pyrexia	3 (60)	1 (33)	1 (14)	5 (33)
Injection-site reaction	1 (20)	2 (67)	1 (14)	4 (27)
Device-related infection	0	1 (33)	1 (14)	2 (13)
Diarrhea	1 (20)	0	1 (14)	2 (13)
Serious AEs	3 (60)	1 (33)	1 (14)	5 (33)
Lumasiran-related serious AEs	0	0	0	0
Severe AEs	1 (20)	1 (33)	1 (14)	3 (20)
Lumasiran-related severe AEs	0	0	0	0
AEs leading to discontinuation of study treatment	0	0	0	0
AEs leading to withdrawal from study	0	0	0	0
Death	0	0	0	0

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Abbreviations: AGT, alanine-glyoxylate aminotransferase; AUC, area under the curve; BL, baseline; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GO, glycolate oxidase; GRHPR, glyoxylate reductase/hydroxypyruvate reductase; LDH, lactate dehydrogenase; LS, least squares; M, month; PH1, primary hyperoxaluria type 1; POx, plasma oxalate; 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; ULN, upper limit of normal.

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