Impact of Baseline Urinary Oxalate on Response to Lumasiran in Patients With Primary Hyperoxaluria Type 1

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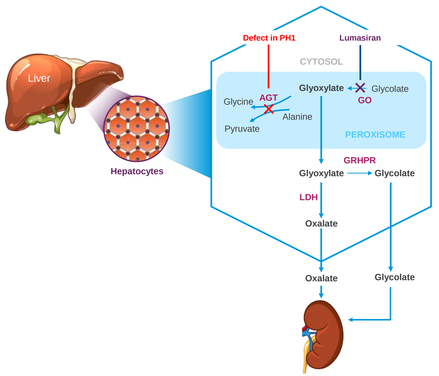
Conclusions

- **Treatment with lumasiran led to reduced UOx excretion in all patients, irrespective of baseline 24-hour UOx**
- **Although patients with the highest level of baseline excretion were less likely to achieve near-normal levels, they had the largest reductions in UOx; thereby suggesting the potential for clinical benefit**

Introduction

- Primary hyperoxaluria type 1 (PH1) 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] As kidney function declines, oxalate elimination is compromised and POx increases, leading to systemic oxalosis and multi-organ damage[2,4]
- Lumasiran is a subcutaneously administered, liver-directed RNAi therapeutic to lower UOx levels in pediatric and adult patients with PH1[5,6]
  - Lumasiran decreases hepatic oxalate production by inhibiting the production of GO[5-7] (**Figure 1**)
- We report the relationship between baseline UOx excretion and response to lumasiran using data from the ILLUMINATE-A study, a randomized, double-blind, placebo-controlled Phase 3 trial designed to evaluate efficacy and safety of lumasiran in children and adults with PH1

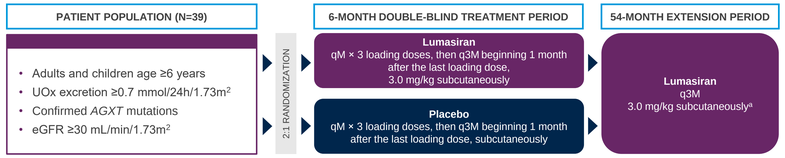
Figure 1. Defect in Glyoxylate Metabolism in Hepatocytes of Patients With PH1 and Lumasiran Therapeutic Hypothesis



Methods

- ILLUMINATE-A (NCT03681184) includes a 6-month double-blind period followed by a 54-month extension period (**Figure 2**)
- In this post hoc analysis, patients were stratified into tertiles by baseline 24-hour UOx excretion:
  - Tertile 1: ≤1.56 mmol/24h/1.73m^2
  - Tertile 2: >1.56 to ≤1.92 mmol/24h/1.73m^2
  - Tertile 3: >1.92 mmol/24h/1.73m^2
- Change from baseline and the proportion of patients with 24-hour UOx excretion ≤1.5 × ULN (0.514 mmol/24h/1.73m^2) were analyzed after 6 months of lumasiran treatment

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 the 39 patients enrolled, 13, 14, and 12 patients were in Tertile 1, Tertile 2, and Tertile 3, respectively

Table 1. ILLUMINATE-A: Baseline Characteristics by Tertile[a]

Baseline Characteristic[b]	Tertile 1 (N=13)	Tertile 2 (N=14)	Tertile 3 (N=12)	Pairwise *P* value*			Overall *P* value**
				Tertile 1 vs 2	Tertile 2 vs 3	Tertile 1 vs 3	
Age at diagnosis, mean (SD), years	5.6 (4.4)	13.6 (16.0)	6.6 (9.9)				
eGFR, mean (SD), mL/min/1.73m^2	93.1 (26.5)	82.0 (25.5)	68.6 (24.6)	0.718	0.374	0.038	0.064
24-Hour UOx excretion corrected for BSA[c], mean (SD), mmol/24h/1.73m^2	1.1 (0.3)	1.7 (0.1)	2.5 (0.4)	<0.001	<0.001	<0.001	<0.001
POx, mean (SD), µmol/L[d]	13.9 (8.7)	14.0 (4.9)	21.6 (9.6)	0.830	0.041	0.044	0.020
Plasma glycolate, mean (SD), µmol/L	85.9 (49.4)	112.6 (48.8)	162.8 (60.4)	0.188	0.047	0.007	0.003
Number of kidney stone events in the 12 months prior to consent[e], n (%)							
0	10 (77)	6 (43)	8 (67)				
1–5	3 (23)	7 (50)	2 (17)				
6–10	0	1 (7)	1 (8)				
>10	0	0	1 (8)				
Mean (SD)	0.3 (0.6)	1.6 (2.0)	5.3 (14.3)				

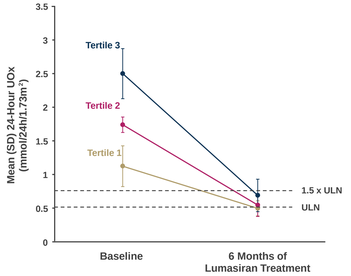
[a]The tertile is based on the 33.33 and 66.67 percentiles. [b]Baseline is defined as the last non-missing value prior to the first dose of lumasiran. [c]ULN is 0.514 mmol/24h/1.73m^2=45 mg/24h/1.73m^2 (1 mmol/24h/1.73m^2=88 mg/24h/1.73m^2). [d]ULN is 12.11 µmol /L. [e]A kidney stone event is defined 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. *Pairwise *P* values are based on the 2-sided Wilcoxon rank sum test. **Overall *P* value is based on the Kruskal-Wallis test.

Results (continued)

Change in 24-Hour UOx Values After 6 Months of Lumasiran Treatment

- Mean (SD) absolute and percent reduction in UOx after 6 months of lumasiran treatment was largest in Tertile 3 and smallest in Tertile 1 (**Figure 3**)
  - Tertile 1: 0.63 (0.39) mmol/24h/1.73m^2; 51.1% (20.6%)
  - Tertile 2: 1.18 (0.15) mmol/24h/1.73m^2; 68.4% (8.9%)
  - Tertile 3: 1.81 (0.42) mmol/24h/1.73m^2; 71.9% (10.4%)

Figure 3. Mean (SD) of Actual 24-Hour UOx Values at Baseline and After 6 Months of Lumasiran Treatment



Baseline tertile is based on baseline relative to the first dose of lumasiran for all patients. ULN=0.514 mmol/24h/1.73m^2.

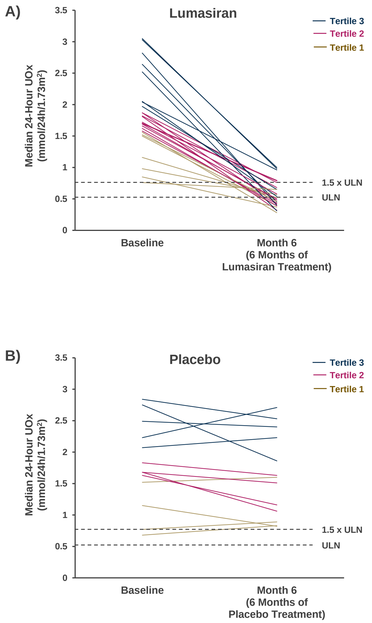
Proportion of Patients With 24-Hour UOx ≤1.5 × ULN After 6 Months of Lumasiran Treatment

- All (100%) of Tertile 1, 85% of Tertile 2, and 58% of Tertile 3 patients achieved UOx levels ≤1.5 × ULN after 6 months of lumasiran treatment
- Although Tertile 3 had the smallest proportion of patients achieving UOx ≤1.5 × ULN, UOx was reduced to within the normal range in 25% of patients in Tertile 3 after 6 months of lumasiran treatment

Individual Patient Data During the Double-blind Period

- All patients who received lumasiran during the double-blind period had a reduction in 24-hour UOx at Month 6 (6 months of lumasiran treatment) (**Figure 4A**)
- There was no clear pattern of change in 24-hour UOx levels at Month 6 among patients who received placebo during the double-blind period (**Figure 4B**)

Figure 4. Median of Actual 24-Hour UOx Values During the Double-blind Period at Baseline and Month 6: A) After 6 Months of Lumasiran; B) After 6 Months of Placebo



Individual Patient Data During the First 6 Months of Lumasiran Treatment

- All patients who crossed over from placebo to lumasiran had a reduction in 24-hour UOx after 6 months of lumasiran treatment (**Figure 5**)
- All patients in the lumasiran/lumasiran and placebo/lumasiran groups had a reduction in 24-hour UOx after 6 months of lumasiran treatment (**Figure 6**)

Figure 5. Median of Actual 24-Hour UOx Values During the Extension Period at Month 6 and Month 12

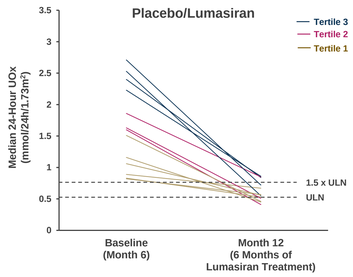
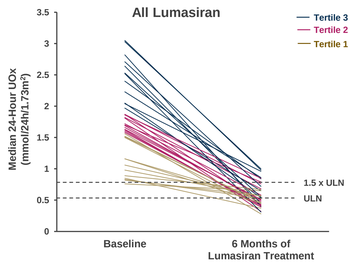


Figure 6. Median of Actual 24-Hour UOx Values at Baseline and After 6 Months of Lumasiran Treatment (Lumasiran/Lumasiran and Placebo/Lumasiran)



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Disclosures: DJS: grants and other from Alnylam Pharmaceuticals, and personal fees from Advicenne. **JB:** consulting fees from Alnylam Pharmaceuticals, Dicerna, and Biocodex Pharmaceuticals. **TN, JG, & TB:** employees of and shareholders in Alnylam Pharmaceuticals. **SG:** non-financial support and grants from Alnylam Pharmaceuticals, and grants from Dicerna Pharmaceuticals. **Abbreviations:** *AGT*, alanine-glyoxylate aminotransferase; *AGXT*, alanine-glyoxylate aminotransferase gene; BSA, body surface area; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyltransferase; GO, glycolate oxidase; GRHPR, glyoxylate reductase/hydroxypyruvate reductase; LDH, lactate dehydrogenase; PH1, primary hyperoxaluria type 1; q3M, once every 3 months; qM, once monthly; qM × 3, once monthly for 3 consecutive months; RNAi, RNA interference; SD, standard deviation; ULN, upper limit of normal; UOx, urinary oxalate. **References: 1.** Frishberg Y, et al. *Clin J Am Soc Nephrol.* 2021;16:1025-36. **2.** Cochat P, Rumsby G. *N Engl J Med.* 2013;369:649-58. **3.** Lieske JC, et al. *Am J Nephrol.* 2005;25:290-6. **4.** Danpure CJ. Primary hyperoxaluria. 2019. Available at: https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225543281. Accessed: January 11, 2022. **5.** Oxlumo [summary of product characteristics]. Amsterdam, Netherlands: Alnylam Netherlands; 2020. **6.** Oxlumo [package insert]. Cambridge, MA: Alnylam Pharmaceuticals; 2020. **7.** Liebow A, et al. *J Am Soc Nephrol.* 2017;28:494-503.

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