Lumasiran for Primary Hyperoxaluria Type 1: Analysis of Urinary Oxalate and eGFR Over Time in Patients With and Without Baseline Pyridoxine Use

David J. Sas[1]; Justine Bacchetta[2]; Ella Metry[3]; Michael Moritz[4]; Richard Willey[5]; Cristin Kaspar[5]; Desmond Murphy[5]; Jeffrey Saland[6]; Yaacov Frishberg[7]

[1]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA; [2]Division of Pediatric Nephrology-Rheumatology, Hôpital Femme-Mère-Enfant, Lyon, France; [3]Department of Paediatric Nephrology, Amsterdam University Medical Center, Amsterdam, Netherlands; [4]Department of Pediatric Nephrology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [5]Alnylam Pharmaceuticals, Cambridge, MA, USA; [6]Division of Pediatric Nephrology and Hypertension, Mount Sinai Kravis Children's Hospital, New York, NY, USA; [7]Division of Pediatric Nephrology, Shaare Zedek Medical Center, Jerusalem, Israel

Conclusions

- **In a post hoc analysis of long-term data from a Phase 2 and two Phase 3 trials:**
  - **After initiation of lumasiran, the B6-use and non–B6-use groups achieved similar rapid and sustained reductions in 24-hour UOx or spot UOx:Cr over time**
  - **The eGFR remained stable over time during lumasiran treatment, regardless of baseline B6 use**
- **Mean changes from baseline in eGFR for both B6-use and non–B6-use groups were minimal over 30 to 36 months**
- **This analysis provides additional evidence that lumasiran confers a UOx reduction benefit in patients on a stable regimen of vitamin B6**

Introduction

- PH1 is a rare autosomal recessive disorder characterized by overproduction of hepatic oxalate, which can lead to chronic kidney disease and systemic complications that can be life-threatening.[1,2]
- Lumasiran is an RNA interference therapeutic that reduces hepatic oxalate overproduction in patients with PH1 by reducing glycolate oxidase levels in the hepatocyte.[3]
- Sustained reductions in UOx have been demonstrated in multiple clinical trials of lumasiran.[4-9]
- Vitamin B6 (B6; pyridoxine) can reduce hepatic oxalate production in patients who have pyridoxine-responsive gene variants.[2,10]
- In the ILLUMINATE-A trial (NCT03681184) of lumasiran in patients with PH1 ≥6 years of age, the observed reduction in 24-hour UOx from baseline to 6 months was similar in patients with and without baseline B6 use.[5]
- Here, we present up to 3 years of UOx and kidney function results based on baseline B6 use for one Phase 2 and two Phase 3 trials.

Methods

- We performed a post hoc analysis of data from 3 lumasiran clinical trials to evaluate changes in UOx and eGFR in patients with and without baseline B6 use (**Table 1**).

Table 1. Lumasiran Clinical Trials in Post Hoc B6 Analysis

	Phase 2[8]	ILLUMINATE-A[5]	ILLUMINATE-B[9]
ClinicalTrials.gov identifier	NCT03350451	NCT03681184	NCT03905694
Phase	2	3	3
Design	Open-label extension study including patients from the single-blind, placebo-controlled Phase 1/2 trial (NCT02706886),[4] Part B (patients with PH1)	Randomized, double-blind, placebo-controlled study with extension period	Single-arm, open-label study with extension period
Participants (N)	20	39	18
Inclusion criteria	• Completed Phase 1/2 study, Part B • PH1 • Age 6–64 years • 24-hour UOx excretion >0.7 mmol/24h/1.73m^2 • eGFR >45 mL/min/1.73m^2	• PH1 • Age ≥6 years • 24-hour UOx excretion >0.7 mmol/24h/1.73m^2 • eGFR ≥30 mL/min/1.73m^2	• PH1 • Age <6 years • UOx:Cr greater than ULN for age • eGFR >45 mL/min/1.73m^2 if age ≥12 months or normal serum creatinine if age <12 months
Status	Completed	Completed	Active, not recruiting
Data cutoff month	M54	M36 data presented[11]	M30 data presented[12]
Total duration	Up to 54 months	Up to 60 months	Up to 60 months

- Patients were categorized by use of B6 at study baseline; UOx and eGFR data over time were analyzed by B6 use at baseline (yes: B6-use group; no: non–B6-use group).

Results

- Demographic and baseline disease characteristics in the B6-use and non–B6-use groups are shown in **Table 2**.

Table 2. Baseline Characteristics

	Phase 2[a] (N=20)		ILLUMINATE-A[b] (N=39)		ILLUMINATE-B (N=18)	
Baseline B6 use	**Yes (N=13)**	**No (N=7)**	**Yes (N=22)**	**No (N=17)**	**Yes (N=11)**	**No (N=7)**
Age at consent, median (range), years	11 (6-43)	14 (6-31)	11.5 (6-47)	19 (6-60)	4.5 (1-6)	3.4 (0-5)
Female, n (%)	9 (69)	4 (57)	7 (32)	6 (35)	5 (45)	5 (71)
Race,[c] n (%)						
White	11 (85)	4 (57)	16 (73)	14 (82)	10 (91)	6 (86)
Asian	2 (15)	2 (29)	4 (18)	2 (12)	0 (0)	0 (0)
Other	0 (0)	1 (14)	1 (5)	1 (6)	1 (9)	1 (14)
More than 1 race	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)
BMI, mean (SD), kg/m^2	19.9 (5.2)	23.0 (6.5)	20.3 (5.8)	25.1 (6.0)	14.6 (1.8)	16.2 (1.6)
Genotype category,[d] n (%)						
PR/*	2 (15)	0 (0)	11 (50)	6 (35)	3 (27)	0 (0)
M/M or M/N	7 (54)	3 (43)	6 (27)	4 (24)	6 (55)	4 (57)
N/N	4 (31)	4 (57)	5 (23)	7 (41)	2 (18)	3 (43)
eGFR, mean (SD), mL/min/1.73m^2	69.7 (16.9)	91.5 (24.8)	81.1 (27.8)	82.3 (26.3)	114.4 (33.1)	110.2 (17.4)

[a]In Phase 2 (patients with eGFR >45mL/min/1.73m^2), age at consent was determined during the Phase 1 parent study. [b]In ILLUMINATE-A (patients with eGFR ≥30 mL/min/1.73m^2), N=13 were randomized to placebo for the 6-month double-blind period and crossed over to lumasiran during the extension period; N=26 were randomized to lumasiran for the double-blind period and continued lumasiran during the extension period. [c]There were no patients in any of the 3 trials in the following race categories: Black or African American, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander.
[d]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,[13] categorized as unlikely to cause a complete lack of AGT protein production and assumed no AGT protein production, respectively. The asterisk (*) denotes any genotype of PR, M, or N (M, missense; N, nonsense; PR, pyridoxine-responsive).

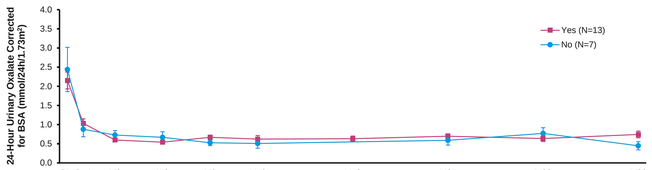
- Of patients with B6 use at baseline, 77%, 91%, and 55% remained on B6 at the latest data cutoff for Phase 2, ILLUMINATE-A, and ILLUMINATE-B, respectively; of patients not using B6 at baseline, none initiated it during the studies.
  - Overall, 10% to 44% of enrolled patients across the 3 studies had a B6-responsive genotype.
  - Most patients with a B6-responsive genotype were taking B6 at baseline (65%-100%).

Urinary Oxalate

- The B6-use and non–B6-use groups both achieved similar rapid and sustained reductions in 24-hour UOx or spot UOx:Cr over time (**Figure 1**)

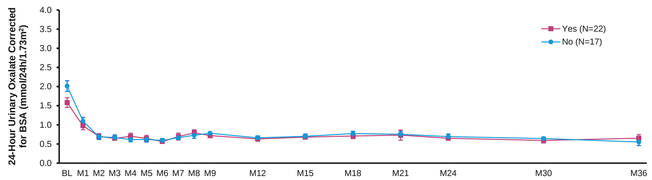
Figure 1. Mean (SEM) Urinary Oxalate Over Time in Lumasiran Trial Data, by Baseline Pyridoxine (B6) Use (Yes/No)

A. Phase 2[a]



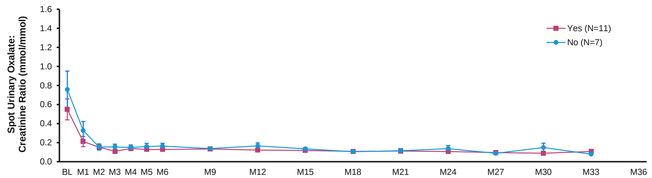
No. of Patients:	BL	D -1	M3	M6	M9	M12	M18	M24	M30	M36
Yes	13	11	8	10	11	9	10	11	11	12
No	6	7	5	5	4	3	2	6	7	4

B. ILLUMINATE-A[b]



No. of Patients:	BL	M1	M2	M3	M4	M5	M6	M7	M8	M9	M12	M15	M18	M21	M24	M30	M36
Yes	22	21	22	22	11	12	21	11	11	20	20	20	20	11	20	20	10
No	17	17	17	16	12	13	17	13	13	17	16	17	17	12	16	16	11

C. ILLUMINATE-B



No. of Patients:	BL	M1	M2	M3	M4	M5	M6	M9	M12	M15	M18	M21	M24	M27	M30	M33	M36
Yes	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	10	2
No	7	7	7	7	7	7	7	7	7	7	7	7	6	7	7	6	0

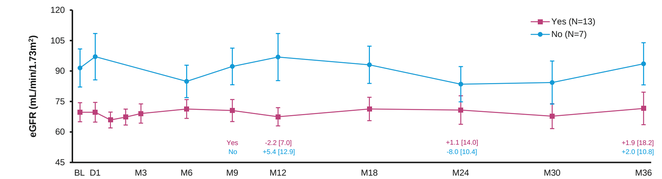
The mean and SEM are not displayed when the number of patients at the visit is <3.
[a]In Phase 2, age at consent was determined during the Phase 1 parent study. [b]In ILLUMINATE-A, N=13 were randomized to placebo for the 6-month double-blind period and crossed over to lumasiran during the extension period; N=26 were randomized to lumasiran for the double-blind period and continued lumasiran during the extension period.

eGFR

- In general, eGFR remained stable over time in both the B6-use and non-B6-use groups (**Figure 2**).

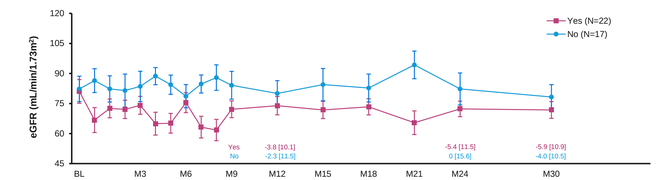
Figure 2. Mean (SEM) eGFR Over Time in Lumasiran Trial Data, by Baseline Pyridoxine (B6) Use (Yes/No)

A. Phase 2[a]



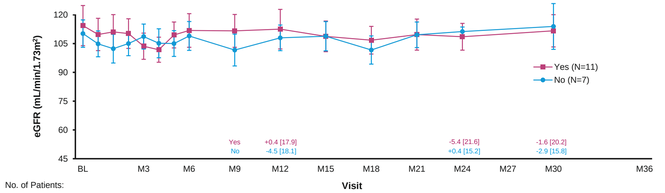
No. of Patients:	BL	D1	M3	M6	M9	M12	M18	M24	M30	M36
Yes	13	11	8	8	8	13	13	13	13	13	13	13
No	7	6	2	2	2	7	7	7	7	7	7	7

B. ILLUMINATE-A[b]



No. of Patients:	BL	M3	M6	M9	M12	M15	M18	M21	M24	M30
Yes	22	12	21	21	21	12	12	21	11	11	20	20	20	20	11	20	20
No	17	12	17	17	17	13	13	17	12	13	17	17	16	17	13	17	17

C. ILLUMINATE-B[c]



No. of Patients:	BL	M3	M6	M9	M12	M15	M18	M21	M24	M27	M30	M36
Yes	10	10	10	11	11	11	11	11	11	11	2	11	2
No	6	6	6	6	6	6	6	7	7	7	1	6	0

The mean and SEM are not displayed when the number of patients at the visit is <3. Labels at M12, M24, M30 (ILLUMINATE-A and ILLUMINATE-B), and M36 (Phase 2) show mean [SD] change in eGFR actual values (mL/min/1.73m^2) from baseline at the corresponding assessment. eGFR was not assessed in patients aged <12 months; eGFR was calculated based on the Schwartz bedside formula for patients aged ≥12 months to <18 years, and the Modification of Diet in Renal Disease formula for patients aged ≥18 years.
[a]In Phase 2, age at consent was determined during the Phase 1 parent study. [b]In ILLUMINATE-A, N=13 were randomized to placebo for the 6-month double-blind period and crossed over to lumasiran during the extension period; N=26 were randomized to lumasiran for the double-blind period and continued lumasiran during the extension period. [c]eGFR was not assessed in 2 patients at baseline because they were aged <12 months.

- Mean changes from baseline in eGFR at M12, M24, and M30/M36 were low (range, −8.0 to 5.4 mL/min/1.73m^2) in B6-use and non–B6-use groups.
- In the Phase 2 study, eGFR levels were generally lower in patients with B6 use versus no B6 use at baseline.

Limitations: Interpretation of our results may be limited due to the post hoc nature of the analysis and the small sample size.

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Abbreviations: BL, baseline; BMI, body mass index; BSA, body surface area; D, day; eGFR, estimated glomerular filtration rate; ID, identifier; M, month; N, nonsense; PH1, primary hyperoxaluria type 1; POx, plasma oxalate; PR, pyridoxine-responsive; UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio; ULN, upper limit of normal.
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