24hr and Random Spot Urine Collections Were Comparable in Assessing Oxalate Excretion and Response to Treatment in Primary Hyperoxaluria Type 1

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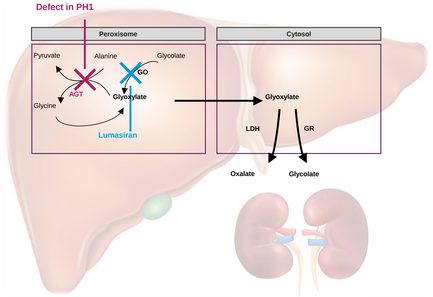
Conclusions

- **Pooled data from lumasiran clinical trials demonstrated a positive correlation with similar intra-patient variability between spot urinary oxalate:creatinine ratio and 24-hour urinary oxalate excretion**
- **The response to lumasiran as measured by the two methods of quantifying urinary oxalate excretion was comparable in patients with PH1**
- **These results indicate that spot urinary oxalate:creatinine ratio is a reliable parameter for assessing oxalate excretion and response to treatment in patients with PH1, serving as an alternative to 24-hour urine collection**

Introduction

- PH1 is characterized by increased oxalate production due to a deficiency in the hepatic peroxisomal enzyme AGT[1,2] (**Figure 1**)
- Excess oxalate can lead to recurrent kidney stones, nephrocalcinosis, progressive kidney failure, and multiorgan damage from systemic oxalosis[1,2]
- 24-hour urine collections are the gold standard for evaluating urinary oxalate excretion; however, they are time-consuming, require a high commitment, and are not always feasible in children
- Spot urine collections may serve as an alternative to quantify urinary oxalate levels in the absence of 24-hour samples[3-5]
- Lumasiran is an RNAi therapeutic approved by the FDA for the treatment of PH1 to lower urinary oxalate levels in pediatric and adult patients[6]
  - Lumasiran decreases hepatic oxalate production by inhibiting the production of GO[7] (**Figure 1**)
- Using data from lumasiran clinical trials, we evaluated the comparability of 24-hour and spot urine collection methods in assessing pretreatment oxalate excretion and response to lumasiran in patients with PH1

Figure 1. Defect in Glyoxylate Metabolism in Hepatocytes of Patients With Primary Hyperoxaluria Type 1 and Lumasiran Therapeutic Hypothesis



Methods

- Lumasiran data used in this analysis were derived from 4 studies: a phase 1/2 study and its phase 2 open-label extension, and the phase 3 studies ILLUMINATE-A and ILLUMINATE-B (**Table 1**)

Table 1. Summary of Lumasiran Clinical Studies That Contributed Data in the Current Analysis

Study	Phase 1/2 Study Part B (NCT03350451) N=20	Phase 2 Open-Label Extension Study (NCT03350451) N=20	Phase 3 ILLUMINATE-A Study (NCT03681184) N=39	Phase 3 ILLUMINATE-B Study (NCT03905694) N=18
Study design	Multiple ascending doses	Long-term extension study up to 54 months of dosing	6-month double-blind, placebo-controlled period followed by a long-term extension period of up to 54 months	Single-arm, open-label study with a 6-month primary analysis period followed by a long-term extension period of up to 54 months
Patient population	• Patients with PH1 • 6–64 years old • eGFR >45 mL/min/1.73m^2	• Patients with PH1 who completed phase 1/2 study, part B	• Patients with PH1 • ≥6 years old • eGFR ≥30 mL/min/1.73m^2	• Patients with PH1 • <6 years old • eGFR >45 mL/min/1.73m^2[a]

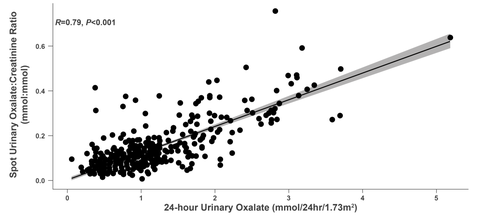
[a]Normal serum creatinine if <12 months old.

- Time-matched spot and 24-hour urinary oxalate collections were available to allow for comparison of absolute value change from baseline in 61 patients (530 samples) and percent change from baseline in 59 patients (466 samples)
  - The 24-hour urine collection was BSA-corrected to remove variability due to differences in body size and is reported as mmol/24hr/1.73m^2 (1 mmol/24hr/1.73m^2=90 mg/24hr/1.73m^2)
  - Spot urine (random single-void urine) values were normalized by urine creatinine concentrations and results are expressed as urinary oxalate:creatinine ratio in mmol/mmol (1 mmol/mmol=0.796 mg/mg) to account for differences in urinary dilution
  - The correlation between absolute value and percent change from baseline in spot and 24-hour urinary oxalate was determined using the Pearson correlation
- The intra-patient variability (measured by the coefficient of variation) of spot urine and 24-hour urine samples across timepoints were calculated and compared using time-matched samples available from 55 patients with PH1 who participated in the phase 1/2, phase 2 open-label extension, and phase 3 ILLUMINATE-A studies
  - Placebo data were from patients who received placebo only; lumasiran steady-state data were from the phase 1/2 study 3 mg/kg cohort (months 3 to 6), the phase 2 open-label extension study (months 3 to 12), and the phase 3 ILLUMINATE-A study lumasiran arm (months 3 to 6); patients enrolled in ILLUMINATE-B study did not have a sufficient number of time-matched samples at the time of this analysis

Results

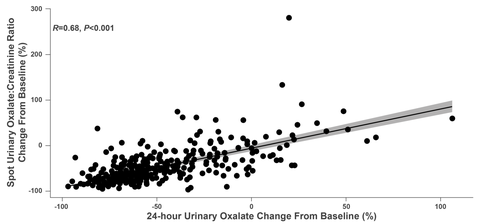
- Pooled analyses showed a statistically significant, positive correlation between 24-hour urinary oxalate and spot urinary oxalate:creatinine ratio for absolute values (**Figure 2**) and percent change from baseline (**Figure 3**)

Figure 2. Correlation Between Absolute Values of BSA-Corrected 24-hour Urinary Oxalate and Spot Urinary Oxalate:Creatinine Ratio



The line and shaded area represent the linear regression line and its 95% CI.

Figure 3. Correlation Between Percent Change From Baseline Values of BSA-Corrected 24-hour Urinary Oxalate and Spot Urinary Oxalate:Creatinine Ratio



The line and shaded area represent the linear regression line and its 95% CI.

- Intra-patient variabilities were similar between 24-hour urinary oxalate excretion and spot urinary oxalate:creatinine ratio (**Table 2**)

Table 2. Intra-patient Variability Comparison of Spot Urinary Oxalate:Creatinine Ratio and 24-hour Urinary Oxalate Excretion

Data Used for Comparison	Method of Urine Collection	N[a]	Within-patient Variability (%CV)	
			Mean	95% CI
Placebo	Spot oxalate:creatinine ratio	14	30.18	23.55, 36.8
	24-hour oxalate BSA-corrected	14	29.11	21.9, 36.32
	CV difference (%)	14	1.07	−6.05, 8.18
Lumasiran steady-state	Spot oxalate:creatinine ratio	42	30.90	23.76, 38.03
	24-hour oxalate BSA-corrected	42	24.83	21.3, 28.35
	CV difference (%)	42	6.07	−1.14, 13.28

[a]Total N=55. One patient contributed placebo data in the phase 1/2 study and lumasiran steady-state data in the phase 2 open-label extension study.

- The time course and magnitude of response to lumasiran in patients with PH1 were comparable between the 24-hour urinary oxalate and spot urinary oxalate:creatinine ratio methods
  - The mean (SEM) percent reduction in urinary oxalate from baseline of phase 1/2 study to month 6 of the phase 2 open-label extension study was comparable between 24-hour urinary collections (70.7% [3.8]) and spot urinary oxalate:creatinine ratio (74.5% [4.1]) (**Table 3**)
  - The least-squares mean reduction from months 3 to 6 in urinary oxalate was comparable between 24-hour urinary oxalate (65.4%) and spot urinary oxalate:creatinine ratio (63.6%) in the lumasiran arm of the ILLUMINATE-A study (**Table 3**; **Figure 4**)
  - These results were similar to those observed using spot urinary oxalate:creatinine ratio (72.0%) from younger children enrolled in the ILLUMINATE-B study (**Table 3**; **Figure 4**)
  - Two patients in ILLUMINATE-B had 24-hour urine collections at baseline and month 6; the mean (SEM) percent reduction from baseline in those patients was 68.4% (5.6)

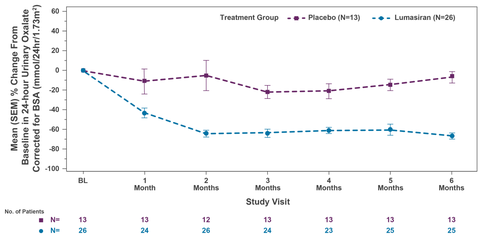
Table 3. Mean Percent Reduction From Baseline to Month 6 in Urinary Oxalate Measured by 24-hour Urinary Oxalate and Spot Urinary Oxalate:Creatinine Ratio

Study and Treatment	N	24-hour Urinary Oxalate BSA-corrected	Spot Urinary Oxalate:Creatinine Ratio
		Mean (SEM) Percent Reduction From Baseline to Month 6	
Phase 2 OLE Lumasiran	20	−70.7% (3.8)[a]	−74.5% (4.1)[b]
ILLUMINATE-B Lumasiran	18	−68.4% (5.6)[c]	−71.7% (3.4)
		Least-squares Mean (95% CI) Percent Reduction From Baseline to Month 6 (Average of Month 3 Through 6)	
ILLUMINATE-A Placebo	13	−11.8% (−19.5, −4.1)	−4.5% (−15.9, 6.8)
ILLUMINATE-A Lumasiran	26	−65.4% (−71.3, −59.5)	−63.6% (−72.2, −55.0)
ILLUMINATE-B Lumasiran	18	Not calculated	−72.0% (−77.5, −66.4)

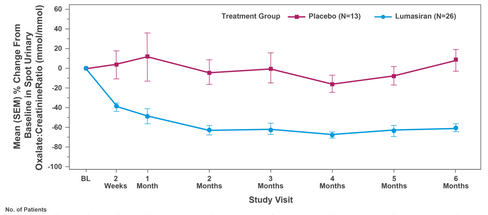
[a]N=14; [b]N=19; [c]N=2.

Figure 4. Response to Lumasiran and Placebo

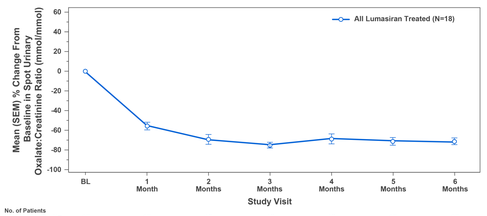
A. ILLUMINATE-A, 24-hour Urinary Oxalate



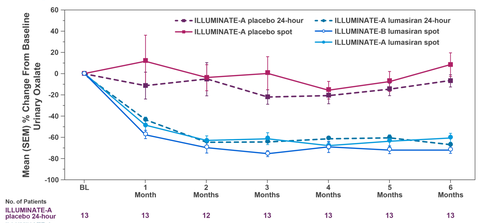
B. ILLUMINATE-A, Spot Urinary Oxalate:Creatinine Ratio



C. ILLUMINATE-B, Spot Urinary Oxalate:Creatinine Ratio



D. ILLUMINATE-A and ILLUMINATE-B, 24-hour Urinary Oxalate and Spot Urinary Oxalate:Creatinine Ratio



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Abbreviations: AGT, alanine-glyoxylate aminotransferase; BL, baseline; BSA, body surface area; CI, confidence interval; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; GO, glycolate oxidase; GR, glyoxylate reductase/hydroxypyruvate reductase; LDH, lactate dehydrogenase; PH1, primary hyperoxaluria type 1; *R*, Pearson's correlation coefficient; RNAi, ribonucleic acid interference; SEM, standard error of the mean.
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