Efficacy and Safety of Lumasiran for Infants and Young Children with Primary Hyperoxaluria Type 1: 30-Month Analysis of the Phase 3 ILLUMINATE-B Trial

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Conclusions

- **In infants and young children with PH1, lumasiran treatment resulted in sustained reductions in UOx and POx through Month 30, with an acceptable safety profile. The most common lumasiran-related AEs were mild, transient injection-site reactions**
- **Clinical outcomes data were encouraging, including stable kidney function through Month 30, improved nephrocalcinosis through Month 24, and low kidney stone event rates through Month 30**

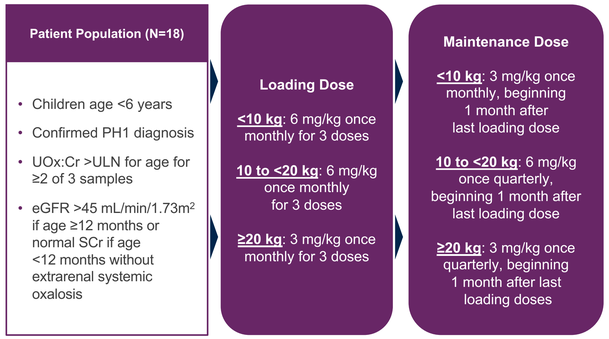
Introduction

- PH1 is a genetic disorder resulting in excess hepatic oxalate production, which can lead to urolithiasis, nephrocalcinosis, and ultimately chronic kidney disease, kidney failure, and systemic oxalosis[1]
- Lumasiran, a liver-directed RNA interference therapeutic that reduces UOx and POx levels, demonstrated sustained efficacy with an acceptable safety profile over 12 months in infants and young children age ≤6 years with PH1 participating in ILLUMINATE-B (NCT03905694)[2]
- Here, we present outcomes of lumasiran treatment through Month 30 of ILLUMINATE-B

Methods

- ILLUMINATE-B is an ongoing, Phase 3, multinational, open-label, single-arm study (**Figure 1**)
- A primary analysis was conducted at 6 months[3]; patients are now in an extension period of up to 54 months

Figure 1. ILLUMINATE-B Study Design



- The primary endpoint was percent change in spot UOx:Cr from baseline to Month 6 (previously described)[3]
- Secondary endpoints included absolute and percent change from baseline in UOx excretion, proportion of patients with UOx excretion ≤ULN and ≤1.5 × ULN for age, absolute and percent change from baseline in POx, and change from baseline in eGFR
  - Oxalate was measured with a validated LC-MS/MS assay
- Changes in nephrocalcinosis and kidney stone event rates were exploratory endpoints

Results

- All 18 patients enrolled in ILLUMINATE-B entered the extension period and remain in the study
- Baseline demographic and clinical characteristics are shown in **Table 1**

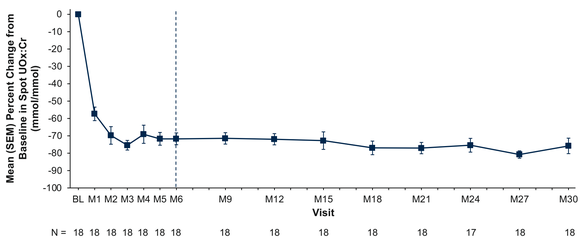
Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	All Treated (N=18)
Age at consent, median (range), months	50.1 (3–72)
Age at diagnosis, median, months	16.3
Time from diagnosis to first dose date, median, months	23.5
Genotype,[a] n (%)	
PR/*	3 (17)
M/M or M/N	10 (56)
N/N	5 (28)
Pyridoxine use, n (%)	11 (61)
Spot UOx:Cr, median (range), mmol/mmol[b,c]	0.469 (0.166–1.708)
POx, median (range), µmol/L[d]	11.5 (6.6–30.6)
eGFR, median (range), mL/min/1.73m²[e]	111 (65–174)

[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.[4]
[b]1 mmol/mmol=0.796 mg/mg.
[c]Age-related reference ranges in spot UOx:Cr: <1 year, 0.015–0.26 mmol/mmol; 1 to <5 years, 0.011–0.12 mmol/mmol; 5 to 12 years, 0.06–0.15 mmol/mmol.[1,5]
[d]ULN=12.11 µmol/L for POx, as determined based on data from 75 healthy adults.
[e]eGFR was calculated based on the Schwartz Bedside formula[6] for patients ≥12 months, N=16; eGFR was not calculated for 2 patients because their age at baseline was <12 months.

- Mean spot UOx:Cr decreased from 0.63 mmol/mmol at baseline to 0.11 mmol/mmol at Month 30; mean percent change from baseline was −76% (**Figure 2**)

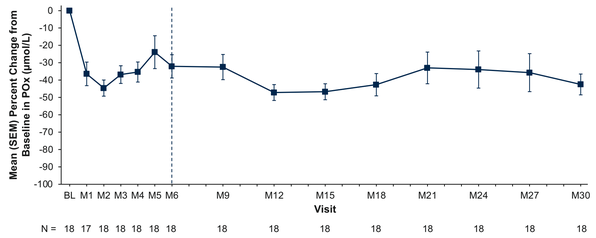
Figure 2. Percent Change from Baseline in Spot UOx:Cr



BL represents the baseline value; mean of all assessments collected prior to the first dose of lumasiran.
Non-quarterly visits from the extension period are not displayed.
End of the primary analysis period is represented by the vertical dashed line.

- Mean POx decreased from 13.2 µmol/L at baseline to 6.3 µmol/L at Month 30 (ULN: 12.11 µmol/L); mean percent change from baseline was −42% (**Figure 3**)

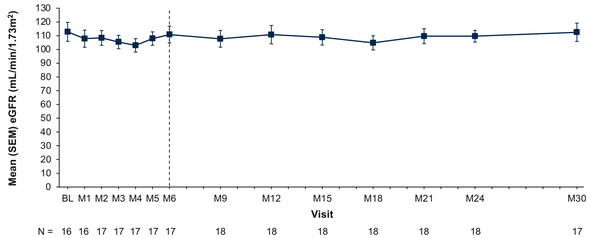
Figure 3. Percent Change from Baseline in POx Levels



BL represents the baseline value; mean of all assessments collected prior to the first dose of lumasiran.
Non-quarterly visits from the extension period are not displayed.
End of the primary analysis period is represented by the vertical dashed line.
The LLOQ is 5.55 µmol/L. Reductions in POx below the LLOQ were conservatively imputed as 5.55 µmol/L.

- eGFR remained stable through Month 30 (**Figure 4**)

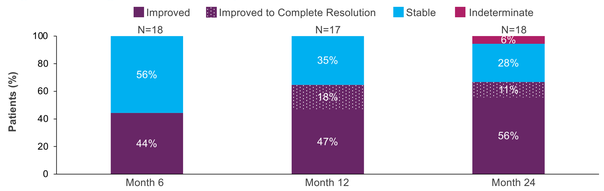
Figure 4. eGFR



BL is the last non-missing value collected prior to the first dose of lumasiran.
Non-quarterly visits from the extension period are not displayed.
eGFR is calculated based on the Schwartz Bedside formula[6] in patients ≥12 months of age at the time of the assessment.
End of the primary analysis period is represented by the vertical dashed line.
Baseline values are not available for 2 patients who were <12 months of age at that time point.

- Among 18 patients, nephrocalcinosis grade improved at Month 24 in 12 (67%), was indeterminate in 1 (6%), and remained stable in 5 (28%); of the 5 stable patients, 4 had no nephrocalcinosis at baseline and remained stable with no nephrocalcinosis at Month 24 (**Figure 5**)

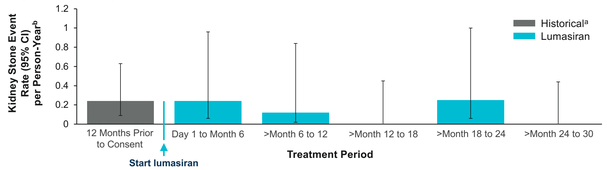
Figure 5. Change in Medullary Nephrocalcinosis Grade



Worsened = grade higher than baseline; stable = grade same as baseline; improved = grade lower than baseline; indeterminate = one side improved and the other side worsened. There were no patients with worsening nephrocalcinosis grade. Change in nephrocalcinosis grade was indeterminate in 1 patient.
Renal ultrasound was not performed at Month 30.

- Kidney stone event rates remained low through Month 30 (**Figure 6**)

Figure 6. Kidney Stone Event Rates



[a]Historical group: patient-reported history of kidney stone events; annualized rate was not calculated for patients age <6 months.
[b]Rate is calculated as total number of kidney stone events divided by total person-years during the respective period. The 95% CI for the event rate was obtained using a generalized linear model for a Poisson distribution unless the rate was 0, in which case the upper bound of the 95% CI was calculated using the exact Poisson method. "Kidney stone event" is defined as an event involving one or more of the following: healthcare provider visit for kidney stone, medication for renal colic, stone passage, and macroscopic hematuria caused by kidney stone.

- Median (range) exposure to lumasiran was 32.6 (27.5–35.3) months
- Five (28%) patients had AEs considered related to lumasiran by the investigator (**Table 2**)
  - The most common lumasiran-related AEs were mild, transient injection-site reactions (3 patients [17%]); symptoms included erythema, discoloration, and pain at the injection site
  - There were no clinically relevant changes in laboratory measures, vital signs, or electrocardiograms related to lumasiran

Table 2. Safety Profile of Lumasiran

Event, n (%)	All Treated (N=18)
AEs	18 (100)
Treatment-related AEs[a]	5 (28)
AEs leading to treatment discontinuation	0
AEs leading to study withdrawal	0
Serious AEs	1 (6)[b]
Severe AEs	0
Death	0

[a]Treatment-related AEs included injection-site reactions, blood bilirubin increase, and headache.
[b]One patient had a serious AE of viral infection (moderate in severity; considered unrelated to lumasiran by the investigator) during the 6-month primary analysis period, which was reported previously.[3]

Abbreviations: AE, adverse event; BL, baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LLOQ, lower limit of quantitation; M, month; PH1, primary hyperoxaluria type 1; POx, plasma oxalate; SCr, serum creatinine; ULN, upper limit of normal; UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio.

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