

# ILLUMINATE-B, a Phase 3 Open-Label Study to Evaluate Lumasiran, an RNAi Therapeutic, in Young Children with Primary Hyperoxaluria Type 1 (PH1)

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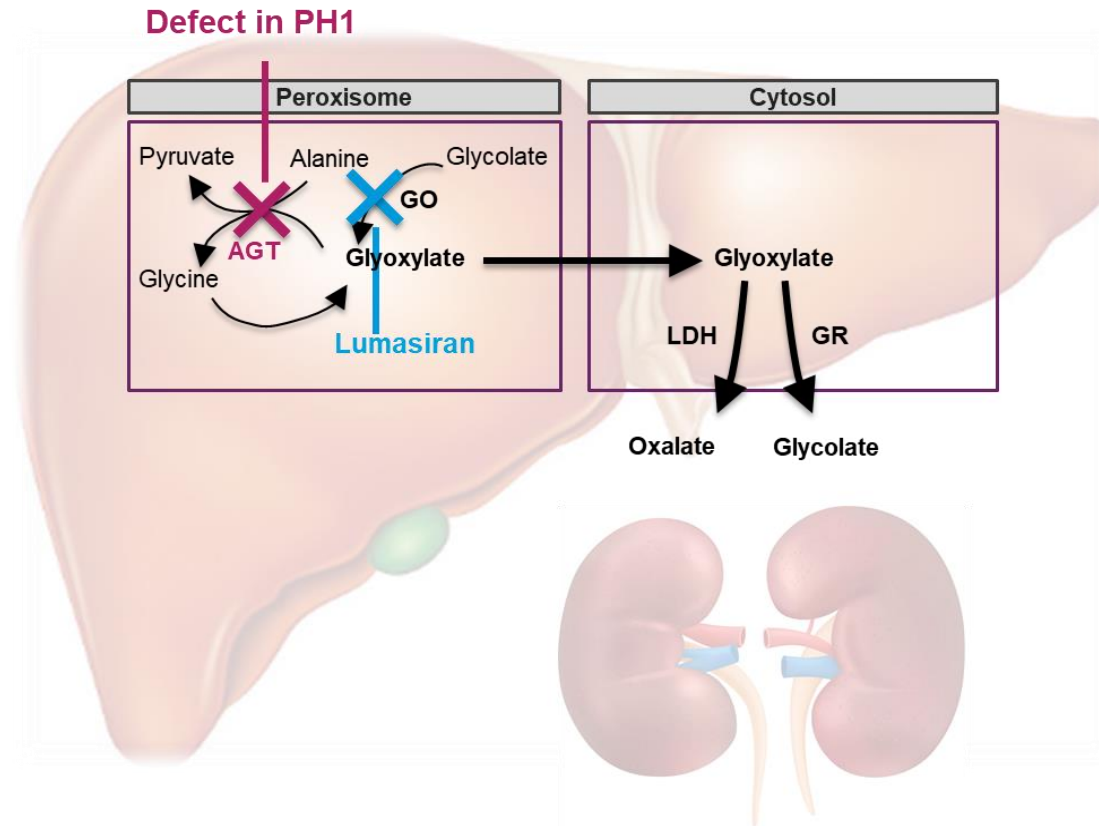
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# Disclosures

- **G Deschênes:** consultancy fees from Alnylam Pharmaceuticals, Dicerna Pharmaceuticals, and Biocodex, and was a PI for research funded by OxThera
- **P Cochat:** was a member of the French Alnylam Pharmaceuticals advisory board until July 2020, and International Dicerna advisory board until July 2020
- **D Magen:** received research funding, consultancy fees, and non-financial support from Alnylam Pharmaceuticals
- **W van't Hoff:** other from National Institute for Health Research, other from Alnylam Pharmaceuticals during the conduct of the study
- **M Michael:** principal investigator for Alnylam Pharmaceuticals
- **D Sas:** grants and other from Alnylam; personal fees from Advicenne
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- **H Shasha-Lavsky:** nothing to disclose
- **W Hayes:** received travel and accommodation expenses from Alnylam Pharmaceuticals to attend international investigators' meeting
- **A Seddighzadeh:** is a previous employee of and holds shares in Alnylam Pharmaceuticals; he is currently an employee of Apellis Pharmaceuticals
- **P Garg, A Vaishnaw, T McGregor, K Fujita, K Bae** are employees of Alnylam Pharmaceuticals and **T McGregor, A Vaishnaw, K Fujita** hold shares in Alnylam Pharmaceuticals
- **Y Frishberg:** consultancy fees from Alnylam Pharmaceuticals and membership of the SRC

# Primary Hyperoxaluria Type 1 and Lumasiran

- Patients with PH1 overproduce oxalate due to a deficiency in hepatic peroxisomal enzyme AGT<sup>1</sup>
- Excess oxalate can lead to recurrent kidney stones, nephrocalcinosis, progressive kidney failure, and multiorgan damage from systemic oxalosis<sup>1,2</sup>
- Majority of patients experience symptoms before 10 years of age<sup>1,3,4</sup>
- Current management options are limited and new therapies that can reduce hepatic oxalate production are urgently needed
- Lumasiran is an investigational, subcutaneously administered RNAi therapeutic that decreases hepatic oxalate production by inhibiting the production of glycolate oxidase (GO)<sup>5</sup>
- A previously-reported Phase 3 study evaluating lumasiran in patients with PH1 ≥6 years old with an eGFR ≥30 mL/min (ILLUMINATE-A) demonstrated a substantial reduction in urinary and plasma oxalate levels, along with an acceptable safety profile<sup>6</sup>



**Here, we present results from ILLUMINATE-B, an ongoing open-label Phase 3 study to evaluate efficacy and safety of lumasiran in young children <6 years old with PH1**

# Study Design

## ILLUMINATE-B (NCT03905694)

- Open-label Phase 3 study with up to 60 months of treatment with lumasiran (6-month primary analysis period followed by 54-month extension period)

### Patient Population (N=18)

- Infants and children <6 years with genetically confirmed PH1 diagnosis
- eGFR >45 mL/min/1.73 m<sup>2</sup> if ≥12 months old; non-elevated serum creatinine if <12 months old

### Primary Endpoint

- Percent change in spot urinary oxalate:creatinine ratio from baseline to Month 6 (average of Month 3 to Month 6)

### Secondary Endpoints<sup>a</sup>

- Absolute change in urinary oxalate excretion from baseline to Month 6
- Percent and absolute change in plasma oxalate from baseline to Month 6
- Proportion of patients with urinary oxalate excretion ≤ULN and ≤1.5 × ULN at Month 6
- Change in eGFR from baseline to Month 6

### Lumasiran Weight-Based Dosing

Patient Weight	Loading Dose	Maintenance Dose
<10 kg	6.0 mg/kg qM × 3	3.0 mg/kg qM
≥10 kg to <20 kg	6.0 mg/kg qM × 3	6.0 mg/kg q3M
≥20 kg	3.0 mg/kg qM × 3	3.0 mg/kg q3M

# Baseline Demographics and Disease Characteristics

	<10 kg (N=3)	10 to <20 kg (N=12)	≥20 kg (N=3)	All Treated (N=18)
Median age, months (range)	10 (3, 14)	50 (23, 72)	62 (54, 72)	50 (3, 72)
Female sex, n (%)	1 (33)	9 (75)	0	10 (56)
Race, n (%)				
White	1 (33)	12 (100)	3 (100)	16 (89)
Other	2 (67)	0	0	2 (11)
Median body weight, kg (range)	8.6 (6.2, 9.5)	14.5 (11.6, 18.0)	23.0 (20.3, 24.3)	14.5 (6.2, 24.3)
Mean spot UOx:Cr ratio (SD), mmol/mmol	1.362 (0.306)	0.497 (0.279)	0.433 (0.230)	0.631 (0.426)
Mean plasma oxalate (SD), μmol/L	23.3 (6.8)	10.9 (4.1)	12.5 (5.8)	13.2 (6.5)

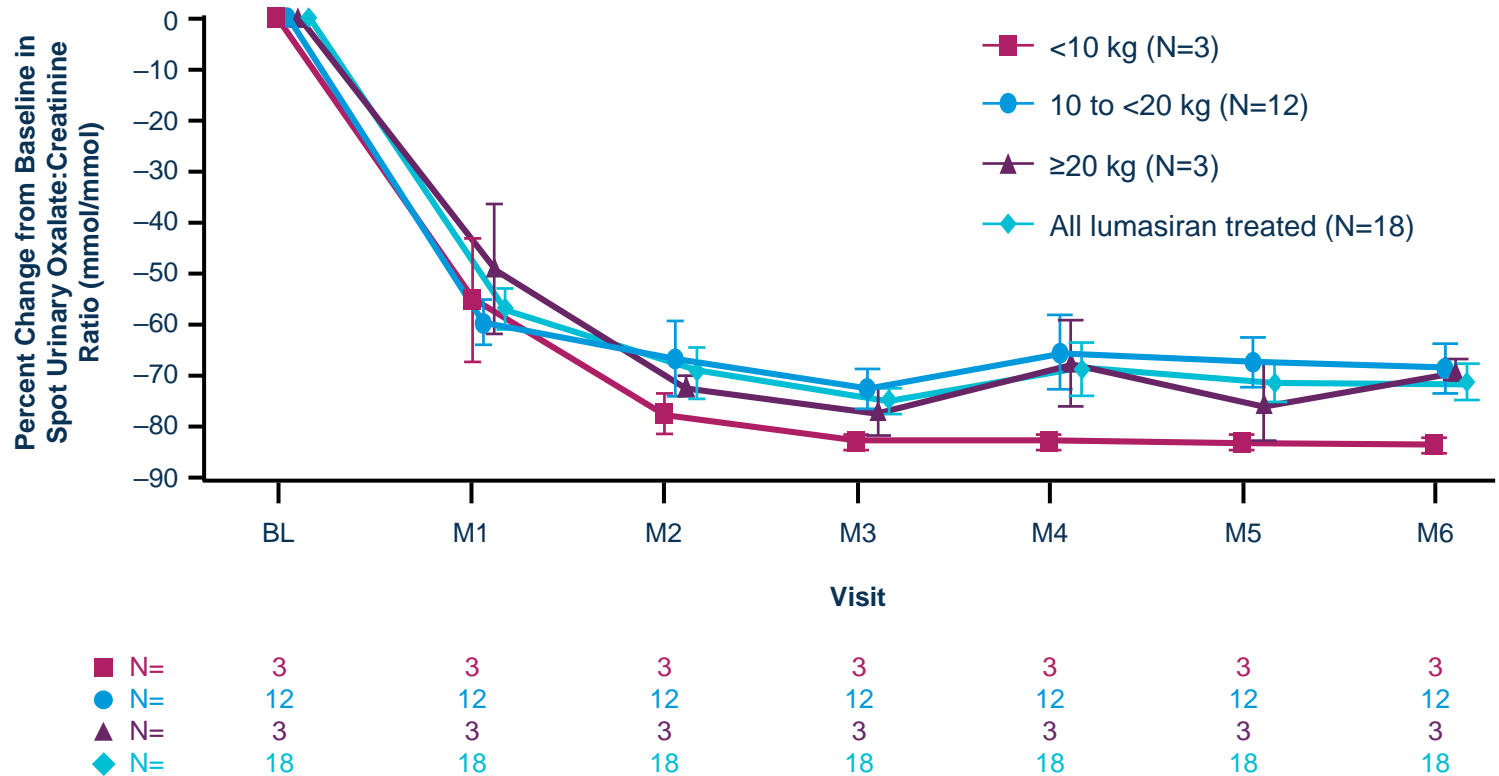
<sup>a</sup>For full list of endpoints see <https://clinicaltrials.gov/ct2/show/NCT03905694?term=lumasiran&draw=2&rank=2>

Cr, creatinine; eGFR, estimated glomerular filtration rate; qM, monthly; q3M, every 3 months; RSE, renal stone event; SD, standard deviation; ULN, upper limit of normal; UOx, urinary oxalate

# Primary Endpoint: Percent Change in Urinary Oxalate Excretion from Baseline to Month 6

## Rapid and Sustained Reduction in Spot Urinary Oxalate:Creatinine Ratio across All Weight Groups

- Lumasiran led to a least squares mean reduction of 72.0% in spot urinary oxalate:creatinine ratio from baseline to Month 6 (average change of Months 3–6)
- Urinary oxalate levels were reduced by:
  - 84.2% in patients <10 kg
  - 69.1% in patients 10 to <20 kg
  - 69.7% in patients ≥20 kg
- A sensitivity analysis assessing percent change from baseline in ratio of spot urinary oxalate:creatinine ratio to ULN (age-dependent),<sup>1</sup> gave a similar reduction (least squares mean reduction of 70.2%)



Data in graph are presented as mean ± SEM of observed values.

BL, baseline; M, month; SEM, standard error of the mean; ULN, upper limit of normal

1. Matos et al. *Am J Kidney Dis* 1999;34:e1; ULN for urinary oxalate:creatinine is age dependent, ranging from 0.22 mmol/mmol in patients 1-6 months old to 0.07 mmol/mmol for patients 5-7 years old. (1 mmol/mmol=0.796 mg/mg)

# Secondary Endpoints

## Lumasiran Demonstrated Positive Results across Secondary Endpoints, Including Additional Measures of Urinary and Plasma Oxalate

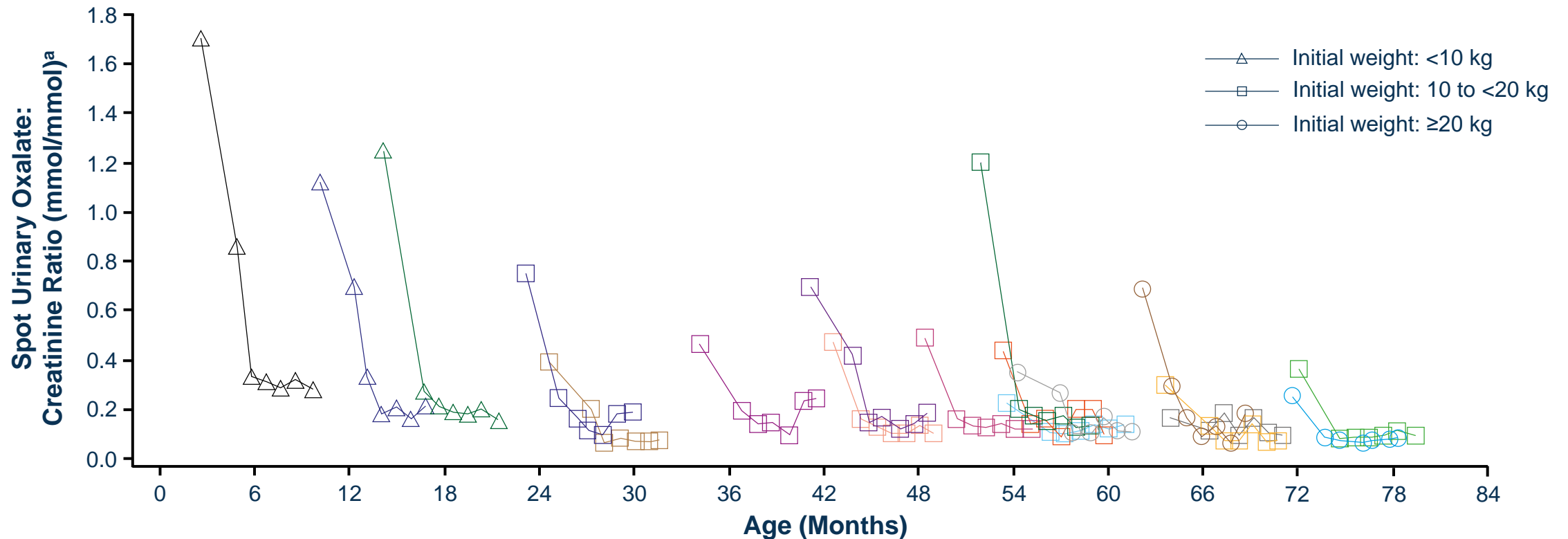
	Parameter	Result (N=18)
Absolute change in urinary oxalate:creatinine ratio from baseline to Month 6 <sup>a</sup> (mmol/mmol)	LS mean (95% CI)	-0.493 <sup>b</sup> (-0.523, -0.462)
Percent change in plasma oxalate from baseline to Month 6 <sup>a</sup>	LS mean (95% CI)	-31.7 (-39.5, -23.9)
Absolute change in plasma oxalate from baseline to Month 6 <sup>a</sup> (μmol/L)	LS mean (95% CI)	-5.2 (-6.2, -4.2)
Proportion of patients with urinary oxalate excretion below threshold at Month 6, n (%)	≤ULN <sup>1</sup>	1 (6%)
	≤1.5 × ULN	9 (50%)
Change in eGFR from baseline to Month 6 (mL/min/1.73 m <sup>2</sup> ) <sup>b</sup>	Mean (SD)	-0.3 (15.4)

<sup>a</sup>Average of month 3 through month 6 <sup>b</sup>-0.493 mmol/mmol = -0.392 mg/mg (1 mmol/mmol=0.796 mg/mg) <sup>b</sup>N=16; eGFR only calculated in patients ≥12 months of age  
CI, confidence interval; eGFR, estimated glomerular filtration rate; LS, least squares; SD, standard deviation; ULN, upper limit of normal

1. Matos et al. *Am J Kidney Dis* 1999;34:e1; ULN for urinary oxalate:creatinine is age dependent, ranging from 0.22 mmol/mmol in patients 1-6 months old to 0.07 mmol/mmol for patients 5-7 years old. (1 mmol/mmol=0.796 mg/mg)

# Patient Values in Spot Urinary Oxalate:Creatinine Ratio from Baseline to Month 6

## Rapid and Sustained Reduction in Oxalate:Creatinine Ratio in All Patients



<sup>a</sup>1 mmol/mmol=0.796 mg/mg

1. Matos et al. *Am J Kidney Dis* 1999;34:e1; ULN for urinary oxalate:creatinine is age dependent, ranging from 0.22 mmol/mmol in patients 1-6 months old to 0.07 mmol/mmol for patients 5-7 years old. (1 mmol/mmol=0.796 mg/mg)

# Exploratory Endpoints: Renal Stones and Nephrocalcinosis

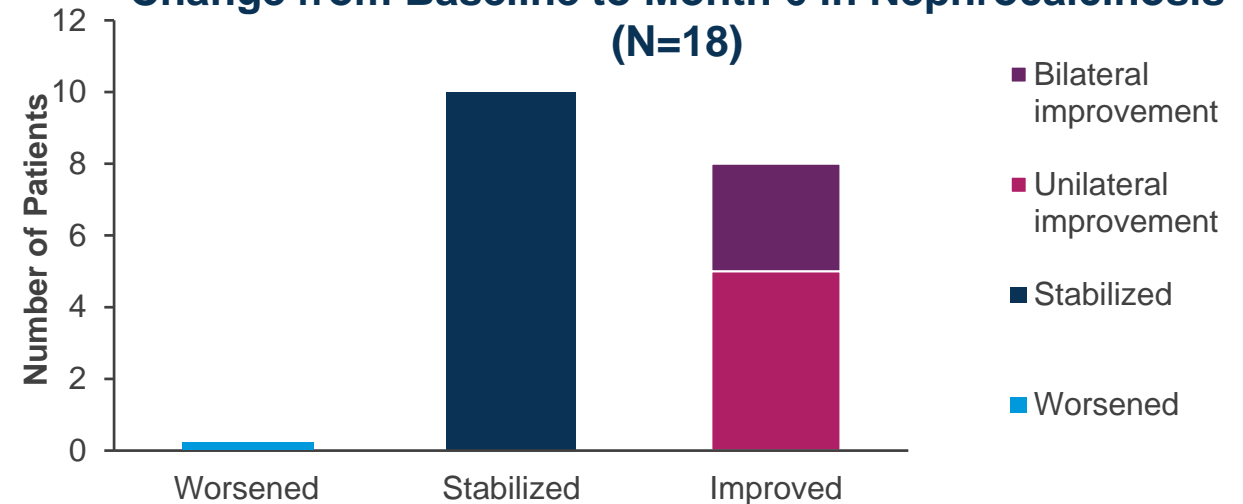
## No Change in Renal Stone Event Rates after Lumasiran Treatment; Improved Nephrocalcinosis in 8/18 Patients

Renal stone events

	Reported History (12 Months Prior to Consent)	Lumasiran Treated Period (6 Months)
Patients with renal stone events	3	2
Total renal stone events	4	2
Renal stone event rate (person-year) <sup>a</sup>	0.24 (95% CI 0.09, 0.63)	0.24 (95% CI 0.06, 0.96)

- A renal stone event was defined as one of the following: visit to healthcare provider because of a renal stone, medication for renal colic, stone passage, macroscopic hematuria due to a renal stone
- The low rates of renal stone events in these patients were unchanged between the 12-month historical recall and the first 6 months of treatment

Change from Baseline to Month 6 in Nephrocalcinosis (N=18)



- Nephrocalcinosis was graded on a standardized 4-point scale<sup>1</sup> as ascertained by renal ultrasound at baseline and Month 6, centrally read by a radiologist blinded to the timepoint
- 14/18 patients had nephrocalcinosis at baseline
- After 6 months of lumasiran treatment, no patient worsened, 10 remained stable, and 8 showed improvement in nephrocalcinosis
  - Of improved patients, 3 improved in both kidneys, 5 in one kidney

<sup>a</sup>Excludes patients <6 months old; annualized rate is reported for patients 6 to <12 months old, patients ≥12 months old have 12-month follow-up time

<sup>1</sup>Dick et al. *Pediatr Radiol* 1999;29:69-72.



# Lumasiran Safety Profile

- No deaths, discontinuations or withdrawals, or severe AEs
- One serious AE occurred which was considered not related to lumasiran<sup>a</sup>
- Most common drug-related AE was injection-site reactions in 3 (17%) patients; all were mild and transient
- No clinically relevant changes in laboratory measures, vital signs, or electrocardiograms related to lumasiran were observed
- No hepatic events were reported

n (%)	<10 kg (N=3)	10 to <20 kg (N=12)	≥20 kg (N=3)	All Treated (N=18)
At least 1 AE	3 (100)	12 (100)	3 (100)	18 (100)
At least 1 drug-related AE	0	2 (17)	2 (67)	4 (22)
Injection-site reaction	0	2 (17)	1 (33)	3 (17)
Headache	0	0	1 (33)	1 (6)
At least 1 serious AE	0	0	1 (33) <sup>a</sup>	1 (6) <sup>a</sup>
At least 1 severe AE	0	0	0	0
Discontinuations/ withdrawal	0	0	0	0
Death	0	0	0	0

<sup>a</sup>Viral infection, considered not related to the study drug by the Investigator  
AE, adverse event; SAE, serious adverse event

# Summary

- PH1 is a rare devastating disease, with high morbidity and mortality, which often presents during childhood
- Current management options for PH1 are limited and new therapies that can reduce the production of hepatic oxalate, the key toxic metabolite in PH1, are urgently needed
- In patients <6 years, lumasiran treatment led to a substantial reduction (72.0%) from baseline to Month 6 in urinary oxalate, the cause of progressive kidney failure in patients with PH1
- Lumasiran led to a 31.7% reduction in plasma oxalate and eGFR remained stable during treatment
- Preliminary results at Month 6 showed no change in renal stone event rates and 8/18 patients showed improvements in nephrocalcinosis; data will continue to be collected in the ongoing extension period
- Lumasiran demonstrated an acceptable safety profile
  - The most common drug-related AE was injection-site reactions in 17% of patients, all of which were mild and transient
- These efficacy and safety results in infants and young children under 6 are consistent with those observed in older children and adults participating in ILLUMINATE-A

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