Results from the Ongoing Phase 2 Open-Label Extension Study of Lumasiran, an Investigational RNAi Therapeutic, in Patients with Primary Hyperoxaluria Type 1 (PH1)

Yaacov Frishberg[1], Sally Hulton[2], Pierre Cochat[3], Jaap Groothoff[4], Daniella Magen[5], Jerome Harambat[6], Gesa Schalk[7], William van't Hoff[8], Dayna LeSueur[9], Tracy L. McGregor[9], Georges Deschênes[10]

[1]Shaare Zedek Medical Center, Pediatric Nephrology, Jerusalem, Israel; [2]Birmingham Children's Hospital, Pediatric Nephrology, Birmingham, United Kingdom; [3]Université Claude Bernard, Centre de Référence des Maladies Rares Néphrogones, Lyon, France; [4]Amsterdam UMC, Pediatric Nephrology, Amsterdam, The Netherlands; [5]Rambam Health Care Campus, Pediatric Nephrology, Haifa, Israel; [6]Bordeaux University Hospital, Pediatric Nephrology, Bordeaux, France; [7]University Hospital Bonn, Pediatric Nephrology, Bonn, Germany; [8]Great Ormond Street Hospital, Pediatric Nephrology, London, United Kingdom; [9]Alnylam Pharmaceuticals, Cambridge MA, United States; [10]Hospital Robert Debre, Pediatric Nephrology, Paris, France

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Disclosures

Y Frishberg: consultancy fees from Alnylam Pharmaceuticals and membership of the SRC

S Hulton: travel expenses to participate in clinical research meetings and consultancy fees paid to Birmingham Children's Hospital Renal Research Fund from Alnylam Pharmaceuticals

P Cochat: consultancy fees and invitations to scientific meetings from Alnylam Pharmaceuticals

J Groothoff: reports consultancy fees from Alnylam Pharmaceuticals and research grants from Alnylam Pharmaceuticals, Dicerna Pharmaceuticals, and UniQure Pharmaceuticals

D Magen: research funding, consultancy fees, and non-financial support from Alnylam Pharmaceuticals

J Harambat: nothing to disclose

G Schalk: nothing to disclose

W van't Hoff: travel expenses to participate in clinical research meetings and financial recompense for clinical trial participation which was paid to his institute

D LeSueur, T McGregor: employees of Alnylam Pharmaceuticals and D LeSueur, T McGregor: holds shares in Alnylam Pharmaceuticals

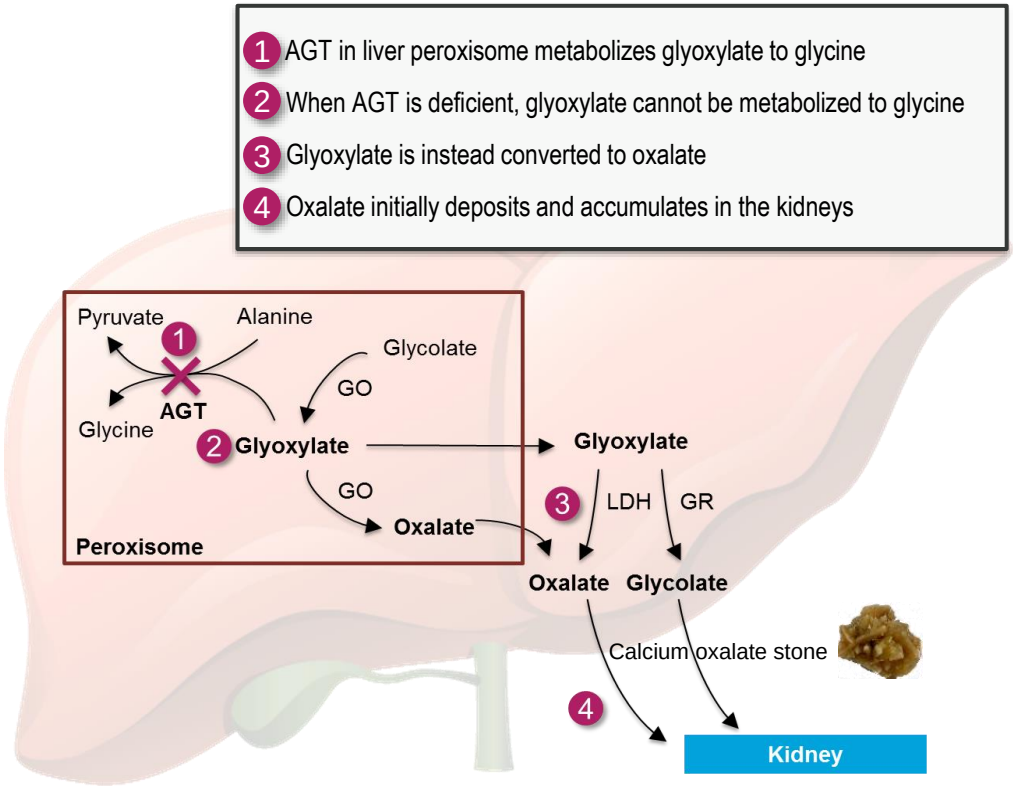
G Deschênes: consultancy fees from Alnylam Pharmaceuticals, Dicerna Pharmaceuticals, and Biocodex, and was a PI for research funded by OxThera

Background and Rationale

Primary Hyperoxaluria Type 1 (PH1)

- PH1 is caused by deficiency in hepatic peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT)
- Hepatic overproduction of oxalate leads to recurrent kidney stones, nephrocalcinosis, progressive renal failure, and multiorgan damage from systemic oxalosis **(Figure 1)**
- Diagnosed prevalence: ~1 to 3 cases per 1 million population, with higher prevalence in parts of the Middle East and North Africa[1,2]
- Age and severity of symptoms at diagnosis highly variable[1,3]
- No therapies currently approved for PH1 treatment

Figure 1. Oxalate Synthesis in PH1



AGT, alanine:glyoxylate aminotransferase; GO, glycolate oxidase; GR, glyoxylate reductase/hydroxypyruvate reductase; LDH, lactate dehydrogenase; PH1, primary hyperoxaluria type 1

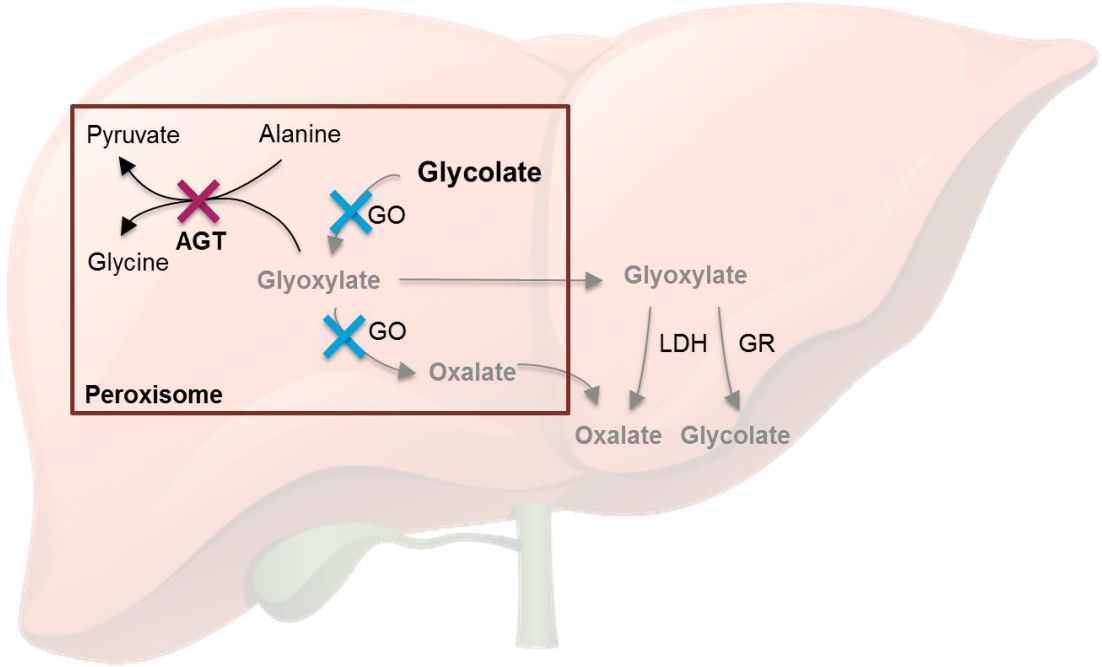
1. Cochat & Rumsby. *N Engl J Med* 2013;369:649–58; 2. Kamoun & Lakhoua. *Pediatr Nephrol* 1996;10:479–82; 3. Cochat. *Kidney Int* 1999;55:2533–47

Background and Rationale Continued

Lumasiran (ALN-GO1)[1]

- Subcutaneously administered investigational RNA interference (RNAi) therapeutic
- Harnesses natural RNAi mechanism
- Decreases hepatic oxalate production by targeting glycolate oxidase **(Figure 2)**
- In the Phase 1/2 study in patients with PH1 (NCT02706886), lumasiran demonstrated clinically significant and sustained reductions in urinary and plasma oxalate to normal or near-normal levels, with an acceptable safety profile[2]

Figure 2. Lumasiran Therapeutic Hypothesis



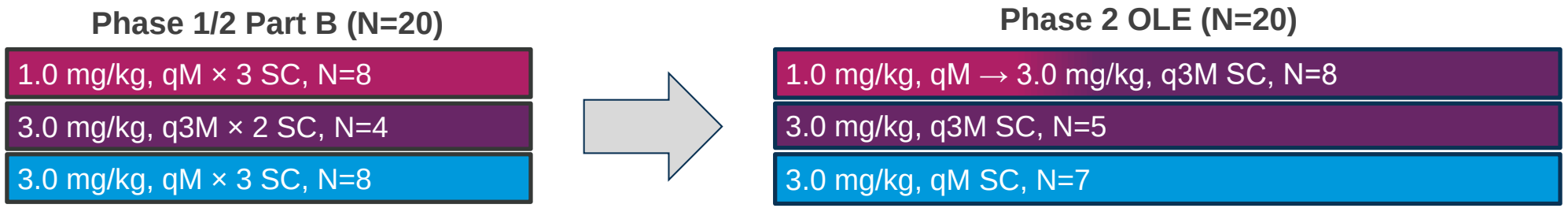
AGT, alanine:glyoxylate aminotransferase; GO, glycolate oxidase; GR glyoxylate reductase/hydroxypyruvate reductase; LDH, lactate dehydrogenase; PH1, primary hyperoxaluria type 1; RNAi, RNA interference

1. Liebow et al. *J Am Soc Nephrol* 2017;28:494–503; 2. McGregor. Oxalosis & Hyperoxaluria International Workshop, June 21–22, 2019. Boston, MA, USA

Methods

Patients Completing the Phase 1/2 Study Were Eligible to Enroll in the Phase 2 Open-Label Extension (OLE) Study (NCT03350451)

- All 20 patients enrolled in Phase 1/2 completed the study and enrolled in the OLE
- Data presented here are for all patients dosed in the Phase 2 OLE, as of January 30, 2020
- Dosing for a median of 15 (range: 11–22) months
- Since the data cut, all patients have been transitioned to 3.0 mg/kg q3M



Inclusion criteria: Ages 6–64 years; eGFR >45 mL/min/1.73m^2; urinary oxalate excretion >0.70 mmol/24 h/1.73m^2

Oxalate Assay

- All data presented here use a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) assay developed for Phase 3 studies. Previous presentations of the Phase 1/2 and Phase 2 OLE studies used an enzymatic assay to measure urinary oxalate. Pearson correlation coefficient for the two methods was 0.925

eGFR, estimated glomerular filtration rate; LC-MS/MS, liquid chromatography tandem mass spectrometry; OLE, open-label extension; q3M, every 3 months; qM, every month; SC, subcutaneously

Results

Table 1. Patient Demographics and Disease Characteristics (N=20)[a]

Characteristic	
Mean age, years (range)	16 (7–44)
Age <18 years	75%
Female	65%
Mean weight, kg (range)	50.0 (21.3–112.5)
Mean eGFR, mL/min/1.73m^2 (range)	77 (42–131)
Mean 24-hour urinary oxalate excretion, mmol/24 hr/1.73m^2 (range)[a]	2.24 (0.94–5.18)
Mean 24-hour urinary oxalate:creatinine ratio, mmol/mmol (range)[a]	0.28 (0.11–0.56)

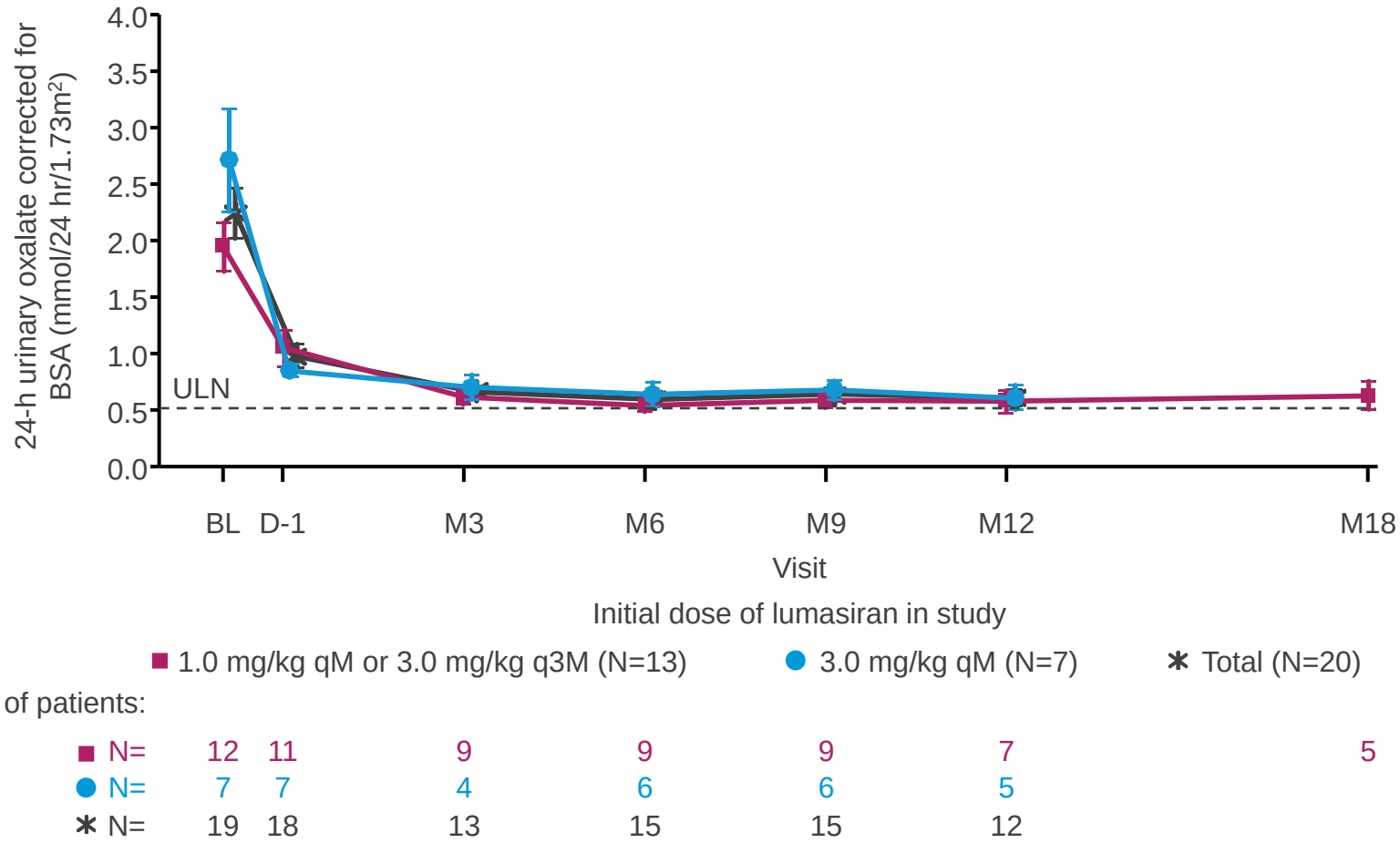
[a]Baseline disease characteristics are from the derived baseline in Phase 1/2 study
eGFR, estimated glomerular filtration rate

Results

Urinary Oxalate Content in 24-Hour Urinary Collections

- Patients experienced sustained reductions in urinary oxalate excretion, with similar responses between dosage regimens **(Figure 3)**
- Mean maximal reduction in urinary oxalate of 74.5% (range: 35.7–88.3%) relative to Phase 1/2 baseline (N=17)[a]
- 17/18[a] (94.4%) patients achieved normal or near-normal (≤1.5 × ULN)[b] levels of urinary oxalate

Figure 3. Mean (± SEM) of Actual 24-Hour Urinary Oxalate Values (Corrected for BSA)



[a]N reflects number of patients with samples meeting the validity criteria, including sufficient creatinine content. [b]ULN=0.514 mmol/24 hr/1.73m^2; 1.5 × ULN=0.77 mmol/24 hr/1.73m^2

BL, baseline; BSA, body surface area; D, day; M, month; q3M, every 3 months; qM, every month; SEM, standard error of the mean; ULN, upper limit of normal

Results

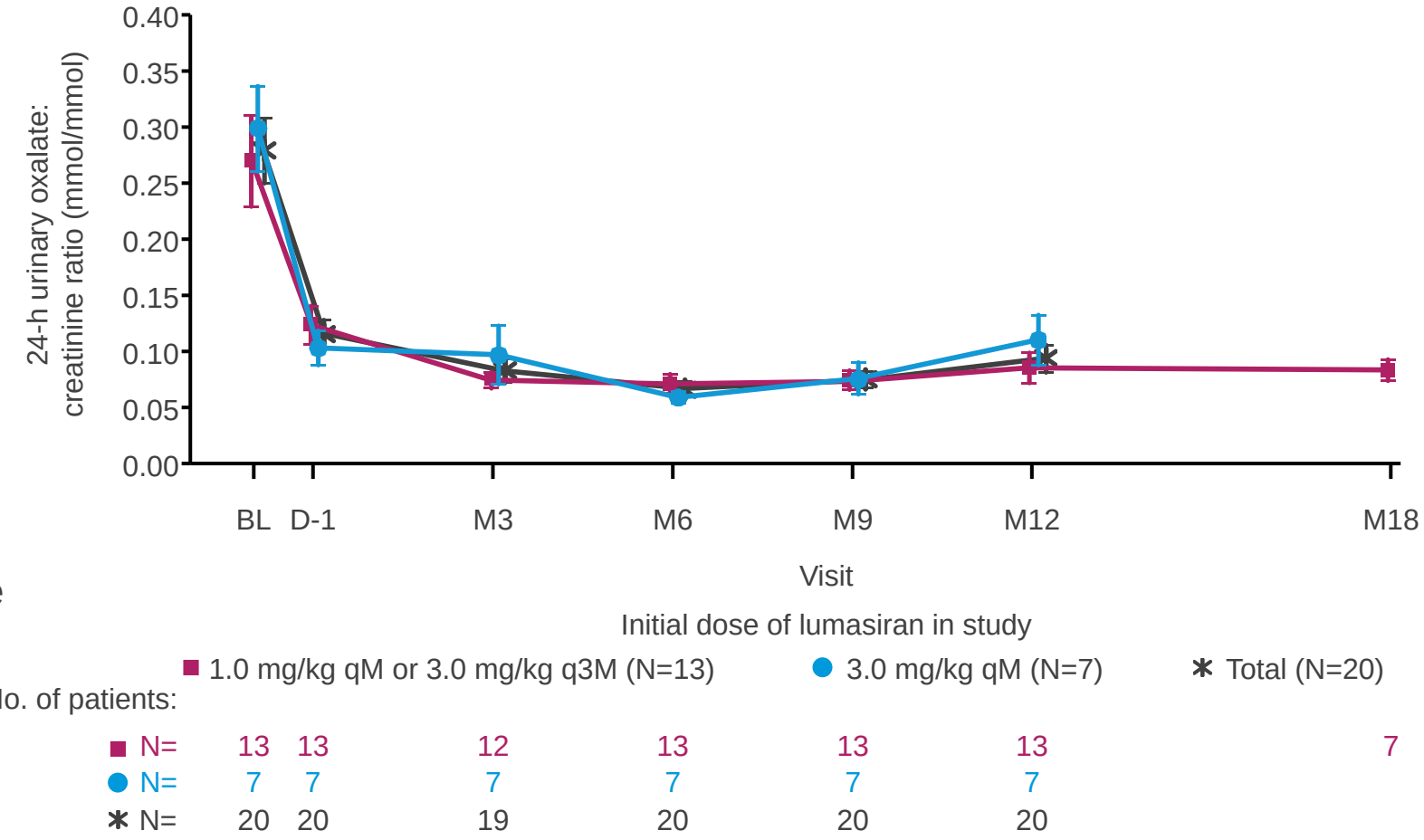
Urinary Oxalate:Creatinine Ratio in 24-Hour Urinary Collections

- Patients experienced sustained reductions in urinary oxalate:creatinine ratio, with similar responses between dosage regimens **(Figure 4)**
- Mean maximal reduction in urinary oxalate:creatinine ratio of 77.5% (range: 55.3–95.8%) (N=20)

Additional Measures

- Plasma oxalate levels decreased (mean maximal reduction 55.2%, N=19)
- Mean eGFR values were stable over time

Figure 4. Mean (± SEM) of Actual Values in 24-Hour Urinary Oxalate:Creatinine Ratio



BL, baseline; D, day; eGFR, estimated glomerular filtration rate; M, month; q3M, every 3 months; qM, every month; SEM, standard error of the mean

Results

Safety and Tolerability

- Continued dosing with lumasiran was generally well tolerated in patients with PH1
- Adverse events (AEs) were reported in 19/20 (95.0%) patients; all were mild or moderate in severity and the majority were assessed as unrelated to study drug
- The most common drug-related AEs reported were mild, transient injection-site reactions
- No discontinuations or drug-related serious AEs were reported
- No clinically significant laboratory changes were reported
- No AEs of kidney stones were reported

Table 2. Post hoc Analysis Conducted Based on Data Collected for Renal Stone Adverse Events[a]

	Patients Reporting >1 Renal Stone	Total Number of Renal Stones	Duration of Follow-Up (patient-years)
Historical (prior 12 months)[b]	6/20	9	20
Phase 1/2 Part B	4/20	7	7.8[c]
Phase 2 OLE	0/20	0	26.4[d]

[a]Renal stones not collected as an efficacy endpoint; any renal stone meeting AE definition is reported and recorded as an AE. Renal stones were identified in AE listings by medical review. [b]Patients reported number of renal stones in the 12 months prior to enrollment in the Phase 1/2 Study. [c]From first dose to last dose + 84 days. [d]From first dose to data cut-off: January 30, 2020. Interval between Phase 1/2 Part B and Phase 2 OLE not represented in these data

AE, adverse event; OLE, open-label extension; PH1, primary hyperoxaluria type 1

Conclusions

- During this period of the phase 2 OLE study, lumasiran continues to demonstrate an acceptable safety profile with no discontinuations from study treatment or drug-related serious adverse events
- Continued therapy with lumasiran maintained reduction of urinary oxalate to levels near or below the upper limit of normal
- The most common drug-related AEs reported were mild, transient injection-site reactions
- No adverse events of kidney stones were reported in this OLE period
- These data provide long-term efficacy and safety with data for up to 22 months of exposure to lumasiran

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OLE, open-label extension