SAFETY AND EFFICACY OF LUMASIRAN, AN INVESTIGATIONAL RNA INTERFERENCE (RNAi) THERAPEUTIC, IN ADULT AND PEDIATRIC PATIENTS WITH PRIMARY HYPEROXALURIA TYPE 1

Interim Results of Ongoing Phase 2 OLE

April 14, 2019

Alnylam® PHARMACEUTICALS

Primary Hyperoxaluria Type 1

Rare Genetic Disorder of Increased Endogenous Oxalate Synthesis

Primary Hyperoxaluria Type 1 (PH1):

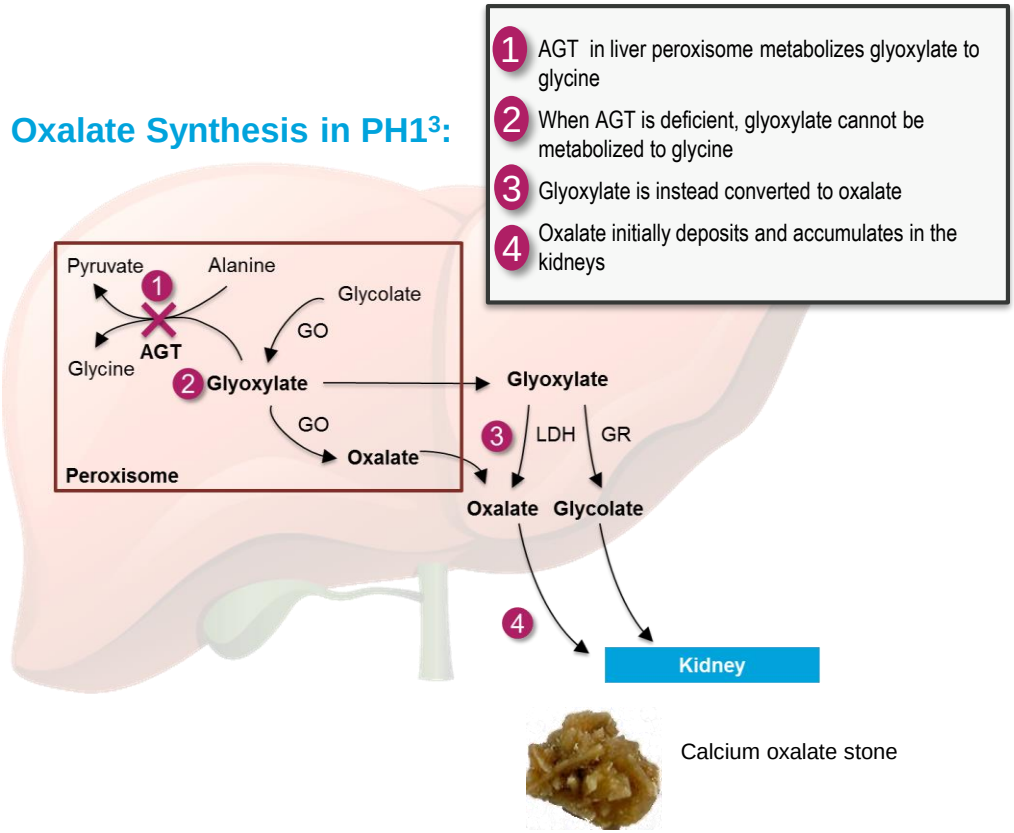
- Due to defect in liver peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT)
- Phenotype varies significantly in patients and may present at any age, typically in childhood
- Prevalence of PH1: 1-3/1,000,000 in Europe[1] and ~ 32/1,000,000 in Middle East[2]

Pathophysiology[1]:

- Overproduction of oxalate results in insoluble calcium oxalate crystals leading to urolithiasis, nephrocalcinosis, and kidney failure
- Disease course ultimately leads to multi-organ damage from systemic oxalosis

No therapies are approved for treatment of PH1

Oxalate Synthesis in PH1[3]:



1. Cochat P, et al. *New Engl J Med.* 2013. 2. Abumwais JQ, et al. *Saudi J Kid Dis Transpl.* 2012. 3. Cochat P. *Kidney Int*. 1999.

Lumasiran

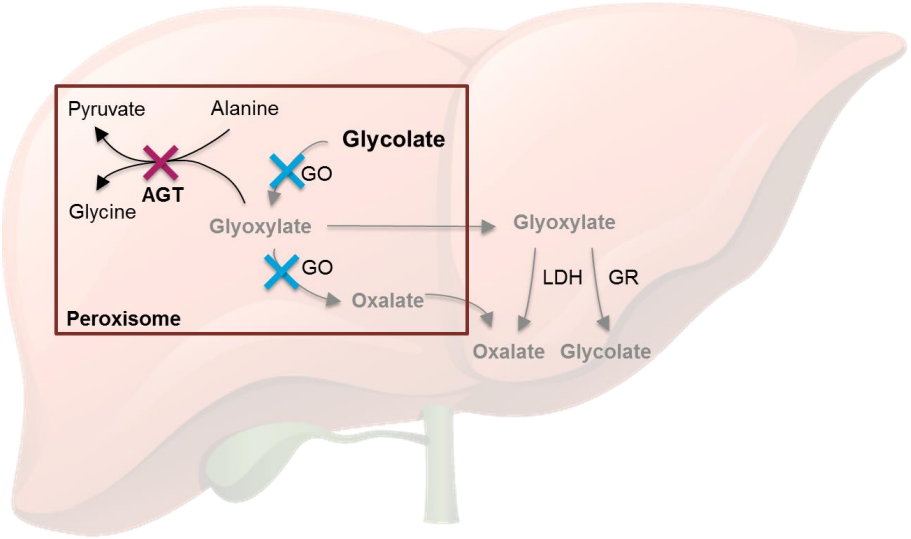
Investigational RNAi Therapeutic for Primary Hyperoxaluria Type 1

Lumasiran (ALN-GO1):

- Subcutaneously-administered small interfering RNA (siRNA)
  - Harnesses natural RNA interference (RNAi) mechanism

Therapeutic Hypothesis:

- Lumasiran targets liver hydroxyacid oxidase 1 (*HAO1*) mRNA, decreasing production of glycolate oxidase (GO) and hence reduces hepatic oxalate production



Liebow A, et al. J Am Soc Nephrol. 2017.

Lumasiran Phase 1/2 and Phase 2 OLE

Study Design

Patients previously dosed in Phase 1/2† study eligible to enroll into Phase 2^ open-label extension (OLE) study

- All patients completed follow-up in Phase 1/2 have enrolled in OLE (N=20)
  - Data presented here represent 18 patients dosed in Phase 2 OLE, as of 8 Feb 2019
    - Preliminary efficacy data of urinary oxalate and urinary oxalate/creatinine ratio includes 9 and 10 patients, respectively, who have reached Day 85
- Patients have been on study for a median of 4 months (range: 0.03–8.36; N=18)

Phase 1/2 Part B – Patients with PH1 (N=20)

- 1.0 mg/kg, q28d x 3 SC, N=8
- 3.0 mg/kg, q28d x 3 SC, N=8
- 3.0 mg/kg, q84d x 2 SC, N=4

Washout period‡
(mean 279 days)

Phase 2 OLE (N=18)

- 1.0 mg/kg, q28d SC, N=3
- 3.0 mg/kg, q28d SC, N=6
- 3.0 mg/kg, q84d SC, N=9

Inclusion Criteria:

- Patients with PH1
- Ages 6-64 years
- eGFR > 45 ml/min/1.73m^2
- Urinary oxalate excretion ≥ 0.70 mmol/24h/1.73m^2

- Doses listed are the initial dose patients received in the Phase 2 OLE
- Patients were started at their original dose from the Phase 1/2 study unless different dose approved prior to dosing

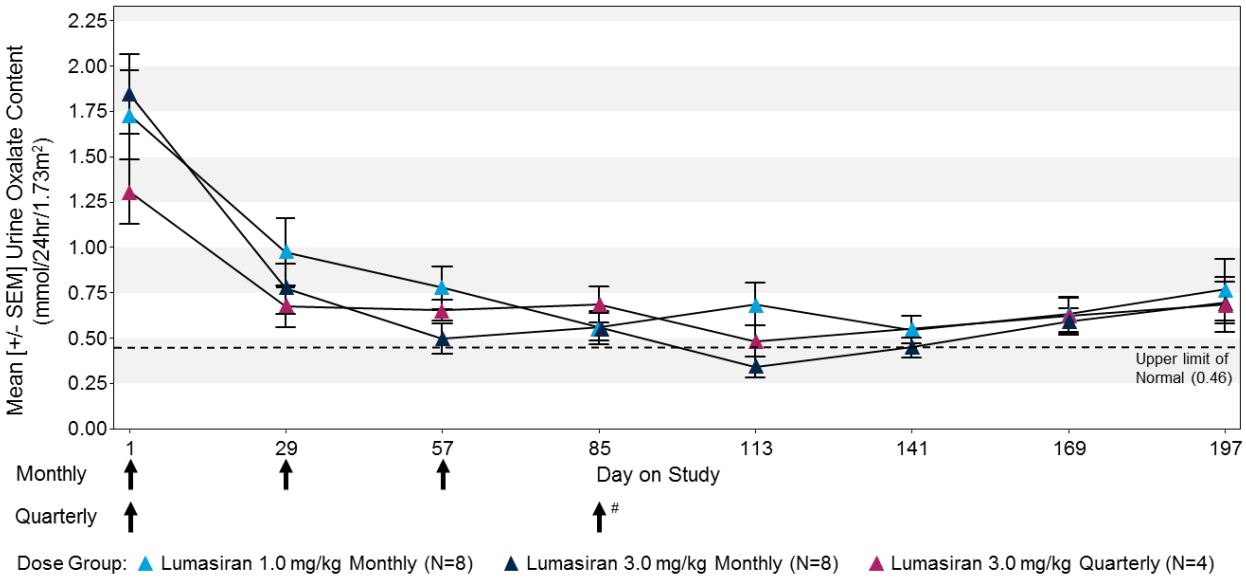
†ClinicalTrials.gov Identifier: NCT02706886; EudraCT Number: 2015-004407-23; ^ClinicalTrials.gov Identifier: NCT03350451; EudraCT Number: 2016-003134-24; ‡Patients were required to be followed for at least 84 days after the last dose of study drug in Phase 1/2 and meet the eligibility criteria to enroll into Phase 2 OLE

Lumasiran Phase 1/2 Study Part B

Summary of Results

20 Patients Enrolled

- Multiple doses of lumasiran demonstrated an acceptable safety profile in patients with PH1 with no discontinuations from study or drug related SAEs
- Mean maximal reduction in urinary oxalate of 75% (range: 43-87%) relative to baseline after lumasiran dosing in all cohorts†
  - The mean reduction relative to baseline 28 days post last dose of lumasiran was 66%



Data cut-off: 15 Aug 2018 ; Only data points with at least 3 contributing patients are represented.

†Patients who completed the Study Day 85 visit and had a valid 24-hour urinary oxalate assessment; placebo data not shown due to limited valid collections

#Patients randomized to placebo received subsequent dosing of lumasiran and are included in the lumasiran dosing cohort in which they were randomized with day 1 relative to first dose of lumasiran; patient randomized to placebo in 3 mg/kg quarterly dosing only received a single dose of lumasiran on Day 1

PH1, primary hyperoxaluria type 1; SAE, serious adverse event; Frishberg Y et al. Pediatr Neprol. 2018 (Abstracts – 51st ESPN Meeting, Antalya, Tukey, October 2018)

Phase 2 OLE Patient Demographics*

Baseline Characteristics (from Phase 1/2)	Results (N=18)
Mean age, years (range)	15.1 (6 – 43)
Age <18 years	78%
Gender, females	67%
Mean weight, kg (range)	50.1 (21.3 – 110)
Mean eGFR, mL/min/1.73m^2 (range)	74 (42–131)
Mean Urine Oxalate Content, mmol/24hr/1.73m^2 (range)	1.66 (0.83–2.97)
Mean 24-hour Urine Oxalate:Creatinine Ratio (range)	0.17 (0.07–0.30)

*Data cut-off: 8 Feb 2019

Lumasiran Phase 2 OLE*

Safety

Continued dosing with lumasiran was well tolerated in patients with PH1

- No discontinuations from study treatment
- A single patient (1/18; 5.6%) reported 2 SAEs (traumatic brain injury and bone contusion†); none assessed as related to study drug
- AEs reported in 12/18 (66.7%) of patients;
  - Majority of AEs were reported in single patients, were mild in severity and assessed as unrelated to study drug
- 3/18 (16.7%) patients reported injection site reactions; all were mild and assessed as related to study drug
- No clinically significant laboratory changes

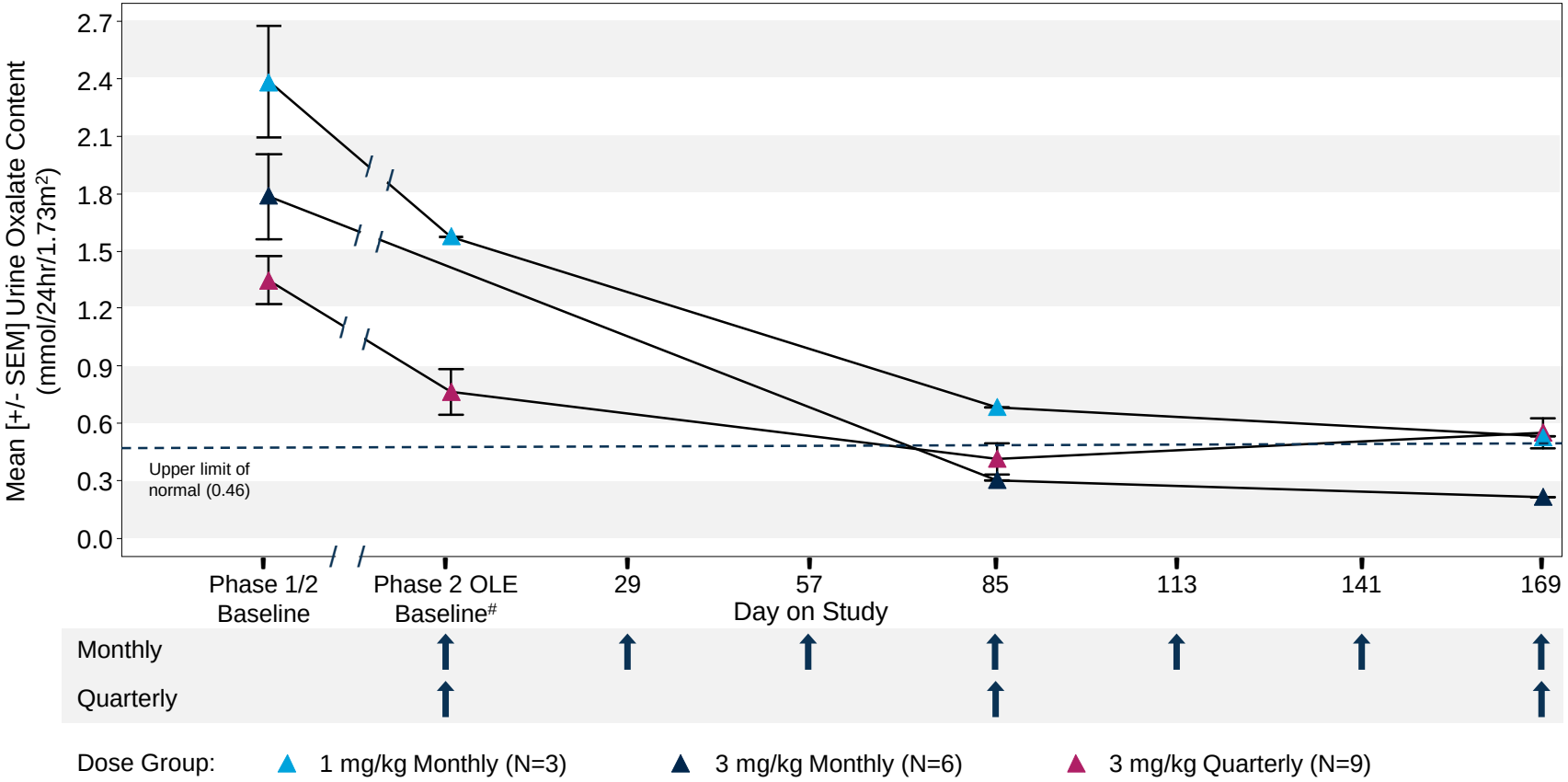
*Data cut-off: 8 Feb 2019; †SAE of traumatic brain injury and contusion was sustained during a car accident

Lumasiran Phase 2 OLE*

Pharmacodynamics: Urinary Oxalate Content

Mean maximal reduction in urinary oxalate of 72% (range: 41-90%) relative to Phase 1/2 baseline after lumasiran dosing in all cohorts (N=9)†

The mean reduction relative to Phase 1/2 baseline at day 85 was 69% (N=7)



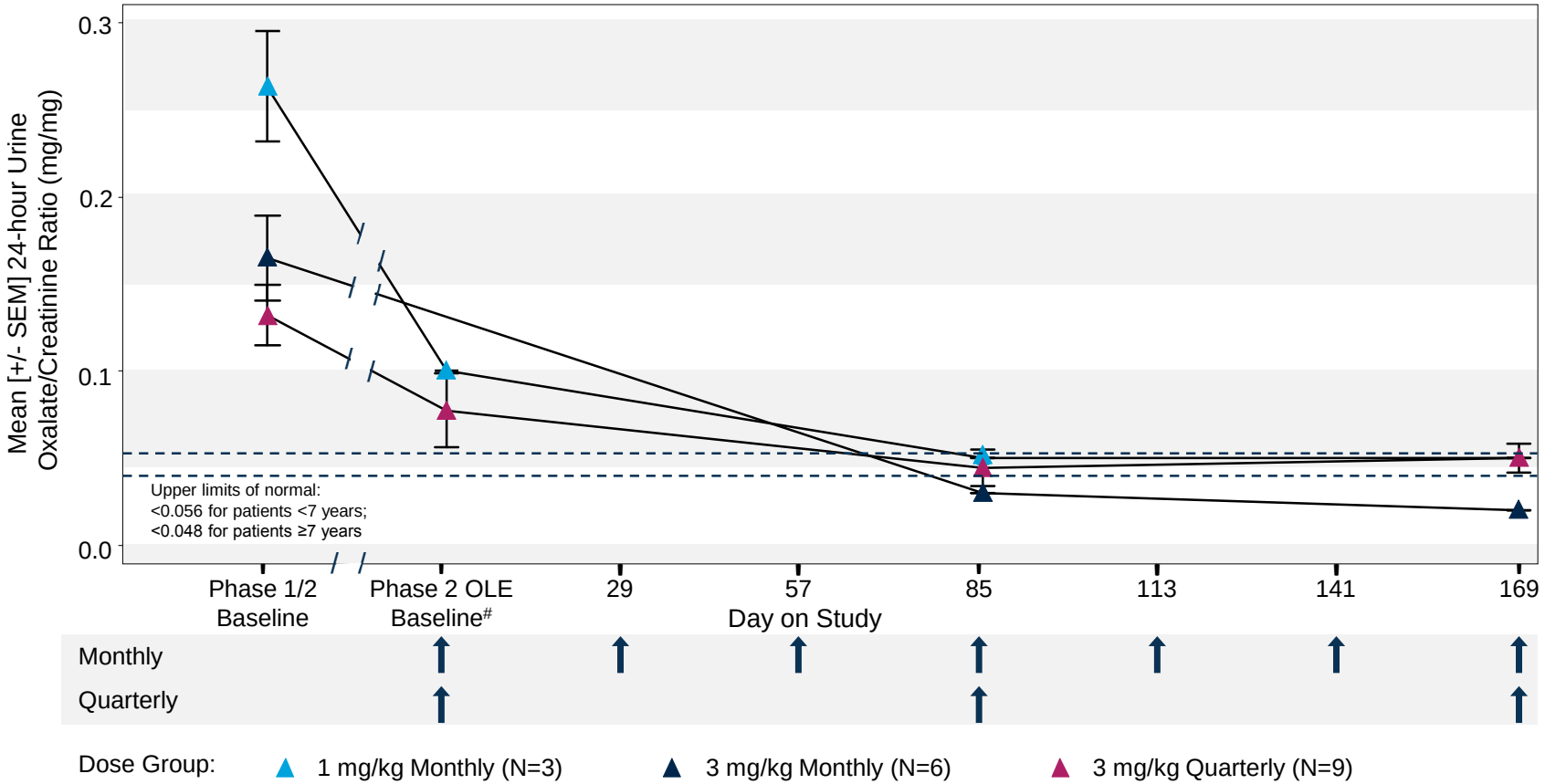
*Data cut-off: 8 Feb 2019; †Patients who had a valid 24-hour urinary oxalate at or after Day 85; #Patients with a urinary oxalate assessment performed in the Phase 1/2 study collected within 30 days before Day 1 were not required to repeat the assessment

Lumasiran Phase 2 OLE*

Pharmacodynamics: 24-hour Urine Oxalate/Creatinine Ratio

Mean maximal reduction in urinary oxalate/creatinine ratio of 77% (range: 57-91%) relative to Phase 1/2 baseline after lumasiran in all cohorts (N=10)†

The mean reduction relative to Phase 1/2 baseline at day 85 was 70% (N=9)



*Data cut-off: 8 Feb 2019; †Patients who have urine oxalate/creatinine ratio at or after Day 85; #Patients with urine oxalate/creatinine ratio performed in the Phase 1/2 study collected within 30 days before Day 1 were not required to repeat the assessment

Lumasiran Phase 2 OLE*

Summary

Primary hyperoxaluria type 1 (PH1) is a devastating disease characterized by the overproduction of oxalate, which results in renal stone formation, nephrocalcinosis and progressive kidney failure, ultimately leading to multi-organ dysfunction

Lumasiran is a subcutaneously administered investigational RNAi therapeutic specifically designed to reduce hepatic production of oxalate in patients with PH1

All patients who have completed follow-up in Phase 1/2 have enrolled in ongoing Phase 2 OLE

Multiple doses of lumasiran demonstrated an acceptable safety profile in patients with PH1 with no discontinuations from study treatment or drug-related SAEs

Patients in Phase 2 OLE experienced clinically significant and sustained reductions in urinary oxalate

Phase 3 ILLUMINATE-A† currently enrolling adults and children with PH1

*Data cut-off: 8 Feb 2019
RNAi, RNA interference; OLE, open-label extension SAE, serious adverse event
†NCT03681184

Alnylam PHARMACEUTICALS