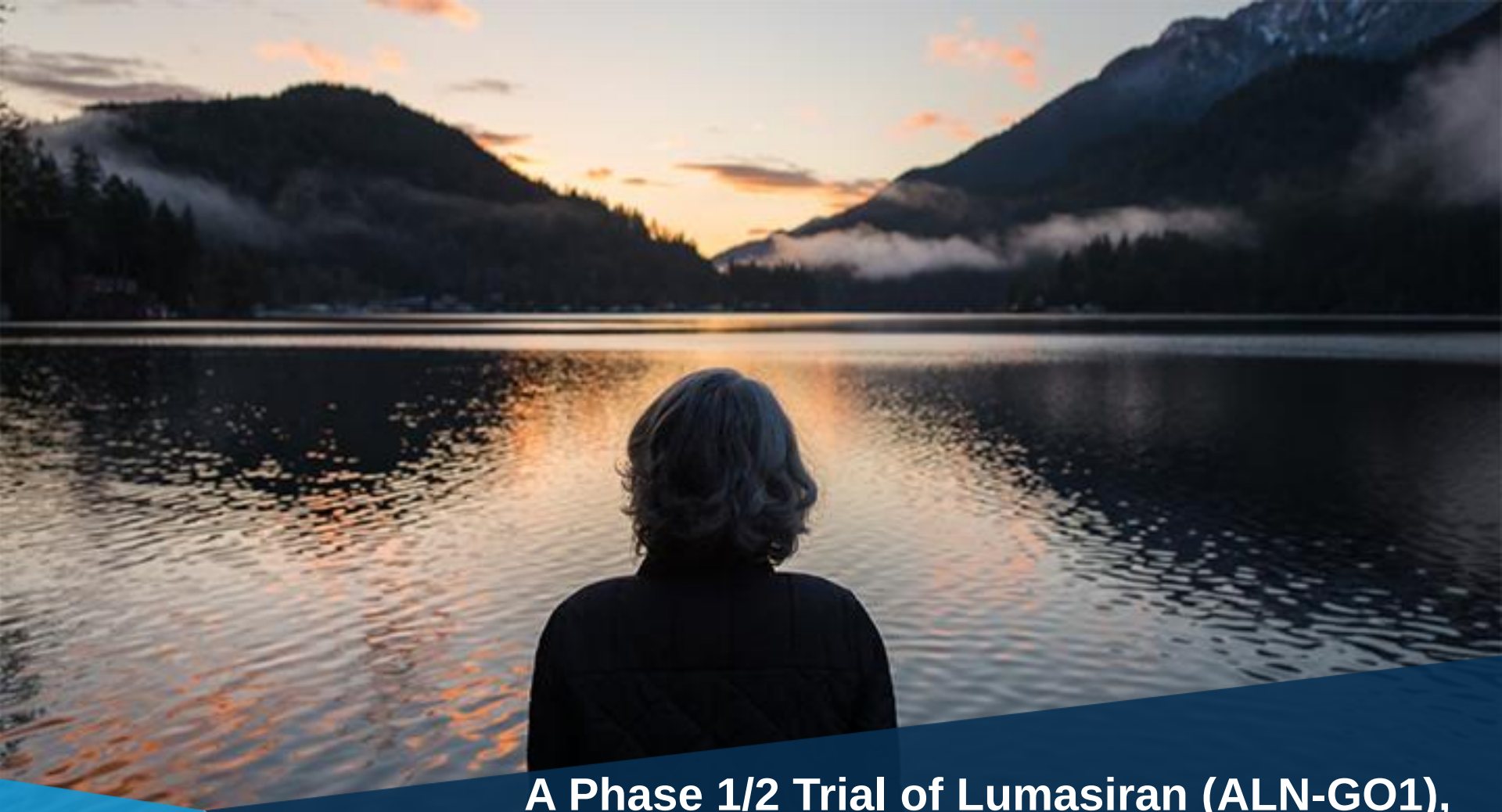

A Phase 1/2 Trial of Lumasiran (ALN-GO1), an Investigational RNAi Therapeutic for Primary Hyperoxaluria Type 1

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OxalEurope Meeting | Naples, Italy| 8 June 2018

Background

Primary Hyperoxaluria Type 1 (PH1)

Rare autosomal recessive disorder of increased endogenous oxalate synthesis due to defect in liver peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT)

Phenotype varies from ESRD in infancy to occasional stone formation in adulthood

Calcium oxalate crystals are insoluble in body fluids, resulting in renal stone formation, nephrocalcinosis, and kidney failure

Disease course ultimately leads to multi-organ damage from systemic oxalosis, affecting bones, eyes, blood vessels, heart, thyroid, skin, among other tissues

Prevalence of PH1: 1-3/1,000,000 in Europe[1] and ~ 32/1,000,000 in Middle East[2]

1. Cochat P, et al. *NEJM.* 2013. 2. Frishberg [Presented at IPNA 2016, Iguaçu, Brazil]

Background

Current Therapeutic Approaches

No approved medical therapies

Goal: Preservation of kidney function

- Decreased oxalate production with Vitamin B6 (effective in minority of patients)
- Decreased crystallization with high fluid intake, citrate

Patients with ESRD

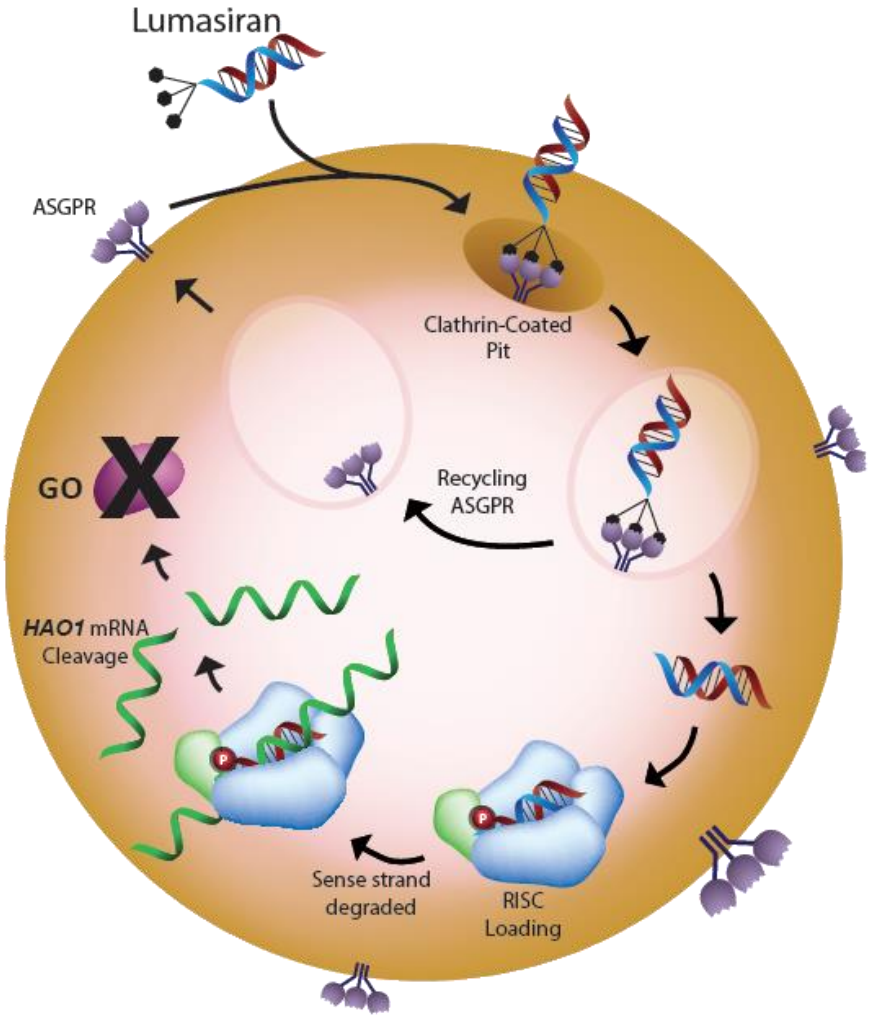
- Increased oxalate removal with intensive dialysis

Combined liver-kidney or preemptive liver transplantation

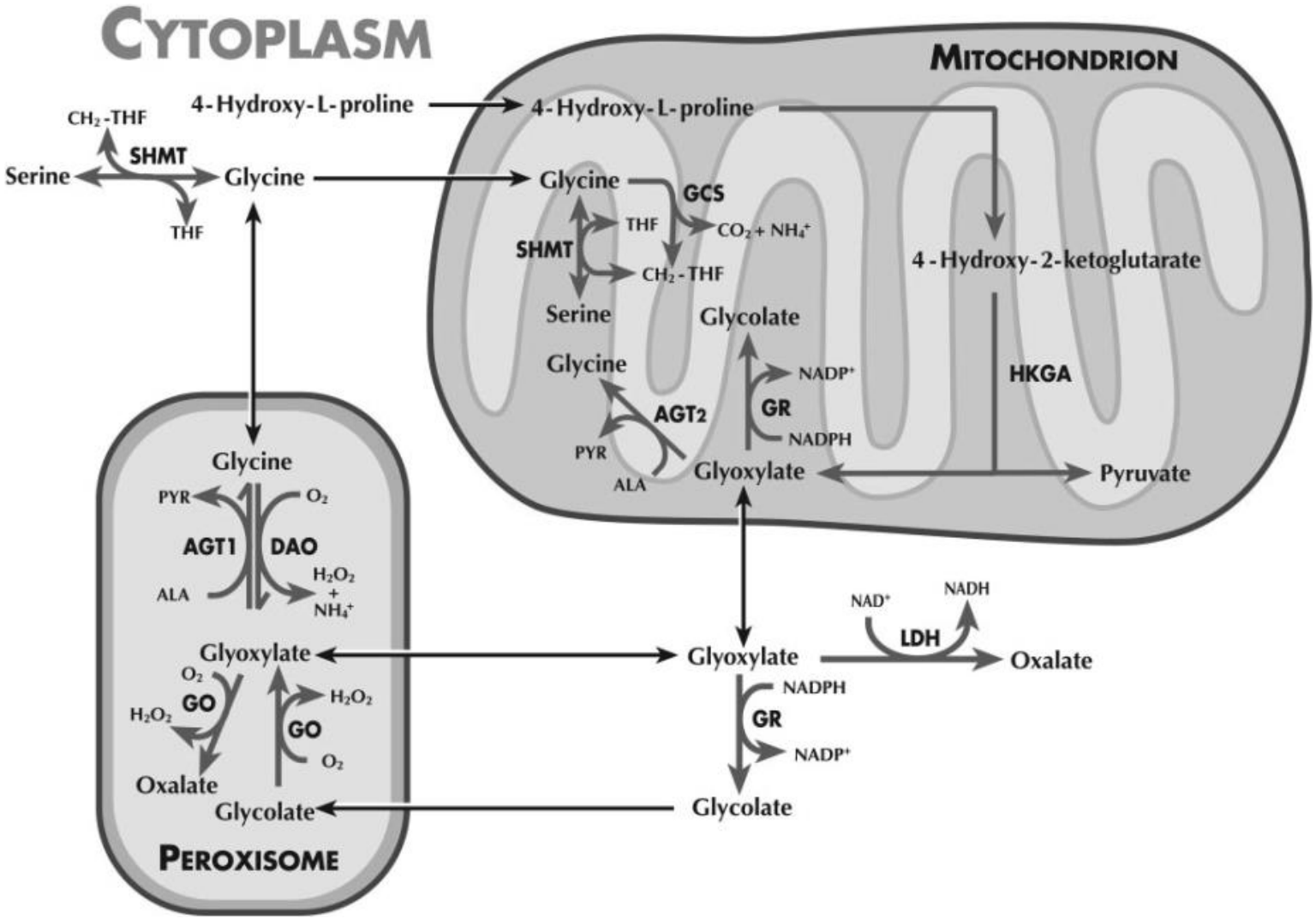
Lumasiran (ALN-GO1)

Lumasiran is an investigational RNAi therapeutic targeting glycolate oxidase (GO) in development for treatment of Primary Hyperoxaluria Type 1 (PH1)

Lumasiran is designed to reduce hepatic levels of GO enzyme (encoded by *HAO1*), thereby depleting substrate necessary for oxalate production, which directly contributes to pathophysiology of PH1



Oxalate Synthesis in Hepatocytes



Baker PR, et al. *Am J Physiol Cell Physiol*. 2004 Nov;287(5):C1359-65.

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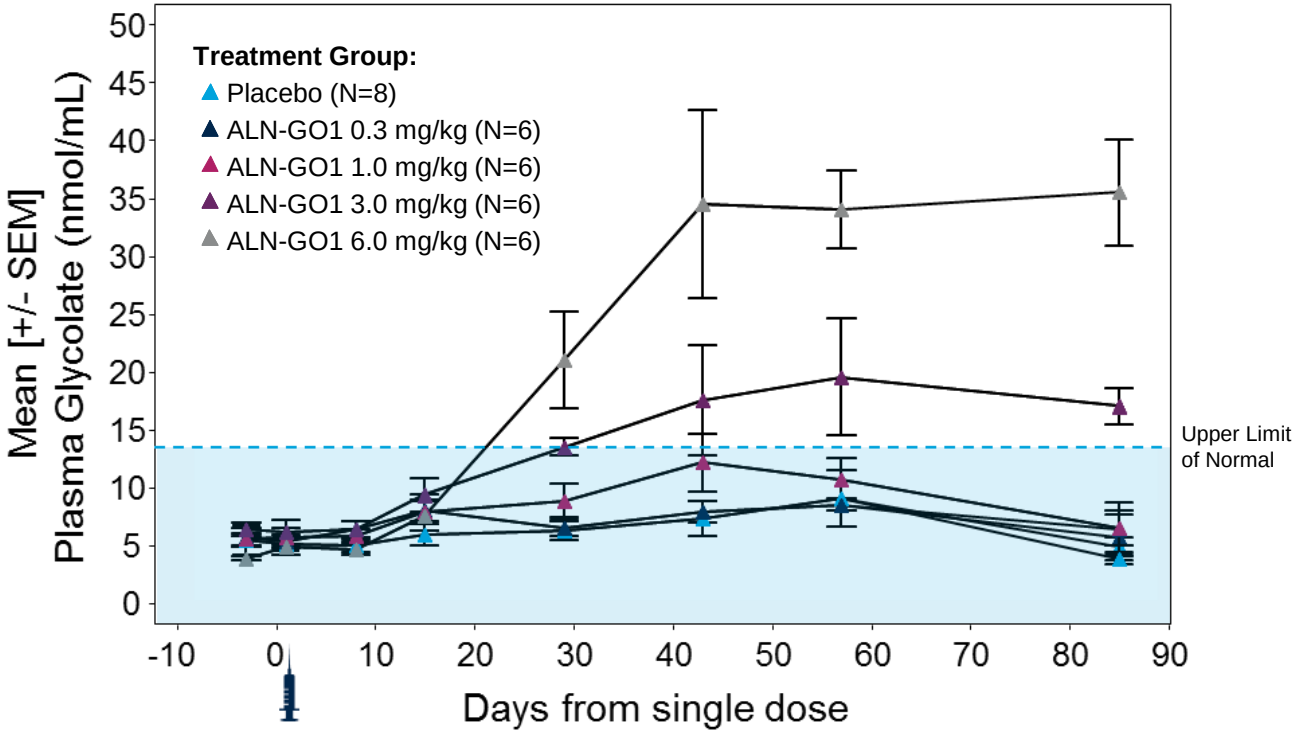
Lumasiran Phase 1/2 Part A Study Results: Plasma Glycolate Levels in Healthy Volunteers

Dose-dependent increase in plasma glycolate levels in healthy volunteers after single dose of lumasiran[1]



- No reports of Serious Adverse Events
- Majority of AEs were mild or moderate; one severe AE, not related to study drug
- Most common treatment related AE reported was self-limited localized pain at injection site during drug administration (4 patients, 17%)

1. Milliner [Presented at IPNA 2016, Iguaçu, Brazil]

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Reported Cases of Known or Suspected GO Inactivity

Lumasiran targets GO, key enzyme in pathway of hepatic oxalate production. Many patients with PH1 already have elevated glycolate levels as part of their disease pathophysiology. No known negative impact of elevated glycolate levels.

8 year old boy[1] • Marked elevations of urinary glycolate • Homozygous deleterious *HAO1* mutation • Healthy liver and healthy kidneys • Triple A-like Syndrome (*GMPPA*)	14 month old boy[2] • Marked elevations of urinary glycolate • Normal AGT activity on liver biopsy • Healthy liver and healthy kidneys • *HAO1* not sequenced
Adult woman[3] • Homozygous *HAO1* mutation detected as part of broad sequencing effort • Healthy liver and kidneys • Three healthy pregnancies	9 month infant girl[4] • Congential Hyperinsulinism (*ABCC8*) • Marked elevations of urinary glycolate • *HAO1* mutations detected • Elevated oxalate in spot urines • Negative sequencing for PH1/PH2/PH3

AGT, alanine:glyoxylate aminotransferase; GO, glycolate oxidase; PH, primary hyperoxaluria

1. Frishberg Y, et al. *Journal of Medical Genetics*. 2014; 2. Craigen WJ. *J Inherit Metab Dis*. 1996; 3. Narasimhan VM, et al. *Science*. 2016; 4. Clifford-Mobley O, et al. *Pediatr Nephrol*. 2017.

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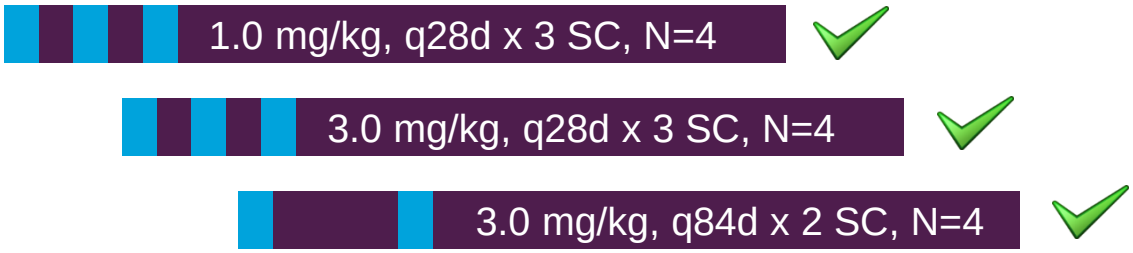
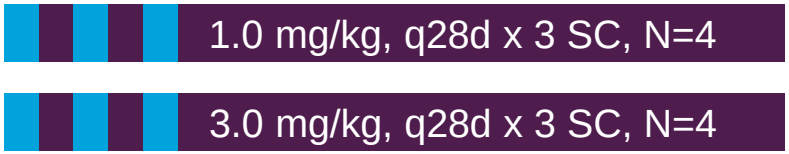
Lumasiran Phase 1/2 Study*

Study Design† & Demographics: Part B (Patients with PH1)

Multiple-Ascending Dose (MAD) | Randomized 3:1, Single-blind, Placebo-controlled



Expansion Cohorts | Open-label



Dosing Complete

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

*Data as of: March 29, 2018
†NCT02706886; EudraCT Number: 2015-004407-23
PH1, primary hyperoxaluria type 1; eGFR, estimated glomerular filtration rate

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Lumasiran Phase 1/2 Study*

Patient Demographics & Exposure: Part B (Patients with PH1)

Characteristic	Result (N=20)
Mean age, years (range)	14.9 (6–43)
Age <18 years	80 %
Gender, females	65 %
Mean weight, kg (range)	49.9 (21.3-110.0)
Mean eGFR, mL/min/1.73m^2 (range)	77 (42–131)

*Data as of: March 29, 2018
PH1, primary hyperoxaluria type 1; eGFR, estimated glomerular filtration rate

Lumasiran Phase 1/2 Study Initial Results*

Safety: Part B (Patients with PH1)

Multiple doses of lumasiran well tolerated in patients with PH1

75% of patients (n=15) with PH1 reported at least one adverse event (AE)

- No AEs led to study discontinuation
- Most AEs were mild or moderate in severity and unrelated to study drug
- 2 patients reported severe AEs; 1 patient with pyelonephritis during placebo dosing; 1 patient with renal colic and kidney stone after lumasiran dosing deemed unrelated to study drug
- Most common AEs (≥3 pts) were abdominal pain, headache, nasopharyngitis, pyrexia, and vomiting
- Injection site reactions have been reported in 2 patients; ISRs have been mild, transient and self-limited

Serious Adverse Events (SAEs)

- One patient had SAEs of nephrolithiasis and pyelonephritis during placebo dosing
- Three patients had SAEs after lumasiran dosing; one patient with nephrolithiasis, one patient with gastroenteritis, and one patient with abdominal pain and pyrexia; no SAEs were considered related to study drug

No clinically significant laboratory or hematologic changes

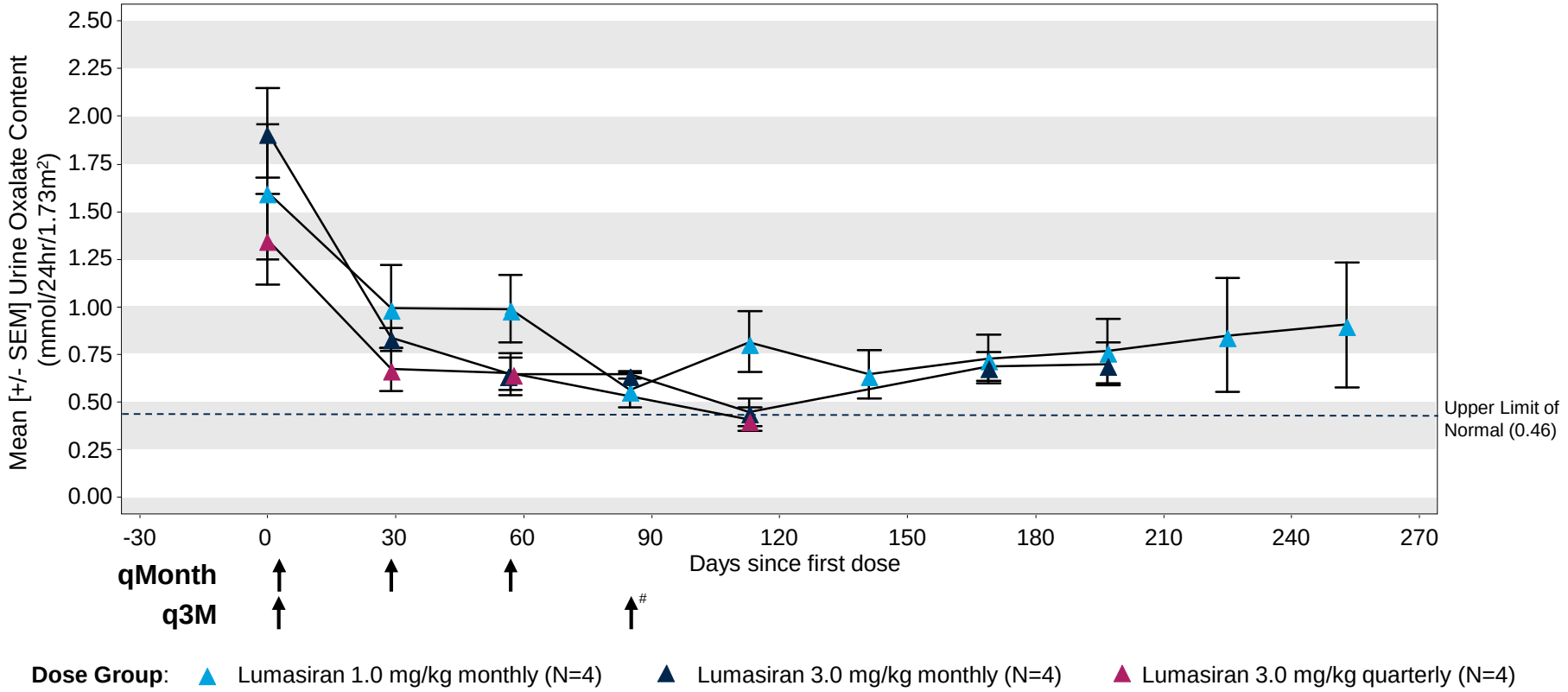
*Data as of: March 29, 2018
PH1, primary hyperoxaluria 1

Lumasiran Phase 1/2 Study Initial Results*

Pharmacodynamics: Part B (Patients with PH1)

Mean maximal reduction in urinary oxalate of 64% relative to baseline after lumasiran dosing in patients in Cohorts 1-3 (n=12)

- Mean reduction in urinary oxalate of 63% relative to baseline was observed at study day 85 (n=9†)



*Data as of: March 29, 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 patient in quarterly cohort has not yet reached Day 85 post lumasiran dosing

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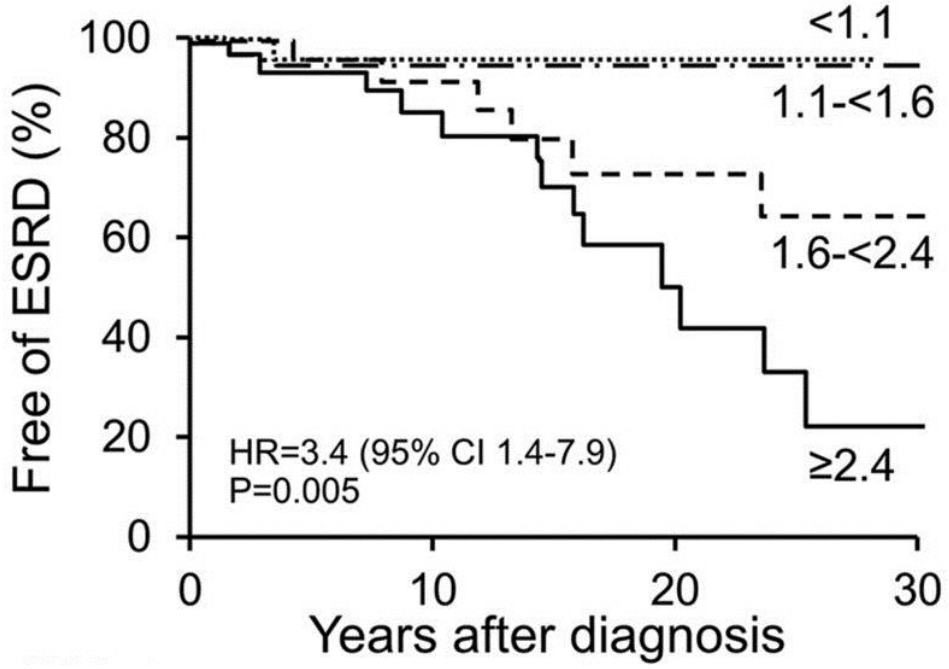
Significance of Decreasing Urinary Oxalate

Lumasiran lowered UOx below 0.7 mmol/24hr/1.73m^2 in all patients, including patients with baseline levels ≥ 1.6 mmol/24hr/1.73m^2



Renal survival was examined by quartile of urine oxalate (UOx) excretion (mmol/24hr/1.73m^2) at diagnosis of patients enrolled in the RKSC PH registry. Among patients with PH who did not have ESRD at diagnosis, renal survival estimates were lower in those with highest level of urinary oxalate excretion.

ESRD, end stage renal disease; PH, primary hyperoxaluria; RKSC, Rare Kidney Stone Consortium
Zhao et al. CJASN 2016;11:119-126

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Lumasiran Phase 1/2 Initial Study Results*

Summary and Next Steps

Lumasiran (ALN-GO1) is a subcutaneously administered investigational RNAi therapeutic designed to reduce hepatic production of oxalate in patients with Primary Hyperoxaluria Type 1 (PH1)

Multiple doses of lumasiran have been well tolerated by patients with PH1 with no drug related SAEs or discontinuations from study

Patients receiving lumasiran experienced substantial and sustained reductions in urinary oxalate, supporting the therapeutic hypothesis that RNAi mediated inhibition of glycolate oxidase may alleviate pathologic overproduction of oxalate in this devastating disease

Data support the continued development of lumasiran, with phase 3 study planned to initiate in mid-2018

- Alnylam also plans to study additional patients of younger ages and those with more severe manifestations of PH1, including renal failure and systemic oxalosis

*Data as of: March 29, 2018
RNAi, RNA interference; SAE, serious adverse event

Acknowledgements

Thank you to the patients, investigators, and study staff who participated in these studies

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