Samantha
Regulatory Affairs, Alnylam

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

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Background

Primary Hyperoxaluria Type 1 (PH1)

Rare autosomal recessive disorder of increased endogenous oxalate synthesis due to absence of 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

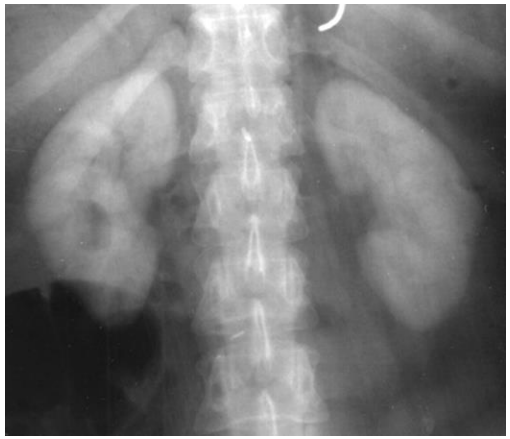
Disease course ultimately leads to multi-organ damage from systemic oxalosis, affecting bones, eyes, blood vessels, heart, thyroid, skin, among other tissues

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

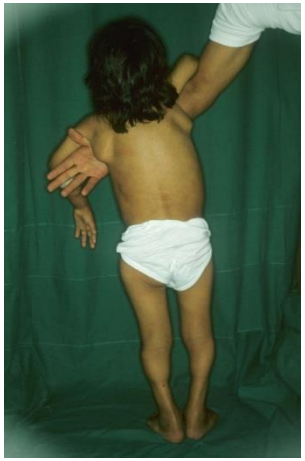
1. Cochat P, et al. *NEJM.* 2013. 2. Frishberg [Presented at IPNA 2016, Iguaçu, Brazil]

Background

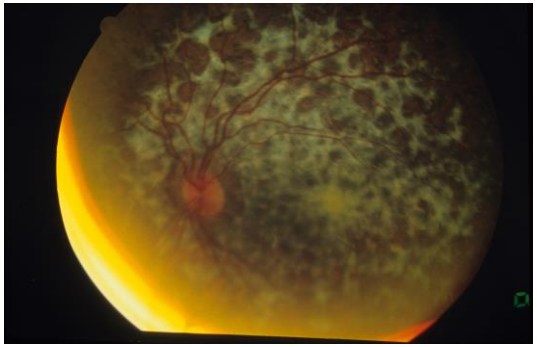
Systemic Oxalosis in PH1



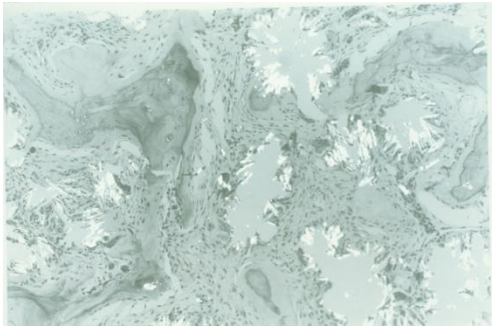
Abdominal X-ray with nephrocalcinosis bilaterally



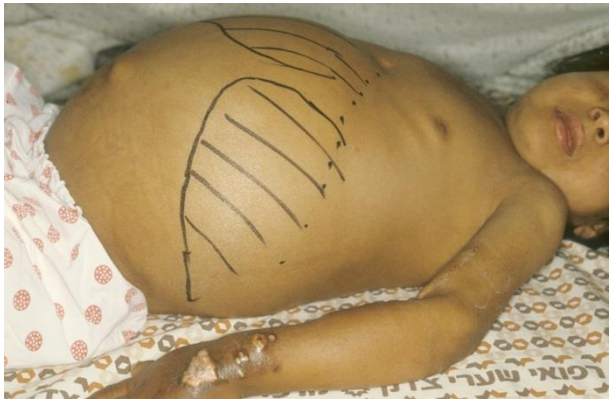
Patient with bone deformities secondary to pathologic fractures



Retinal oxalosis



Histology of bone marrow with multiple calcium oxalate crystals



Marked hepatosplenomegaly due to extra-medullary erythropoiesis; also skin manifestation of oxalosis on left arm

Images used with permission

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 (Formerly 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

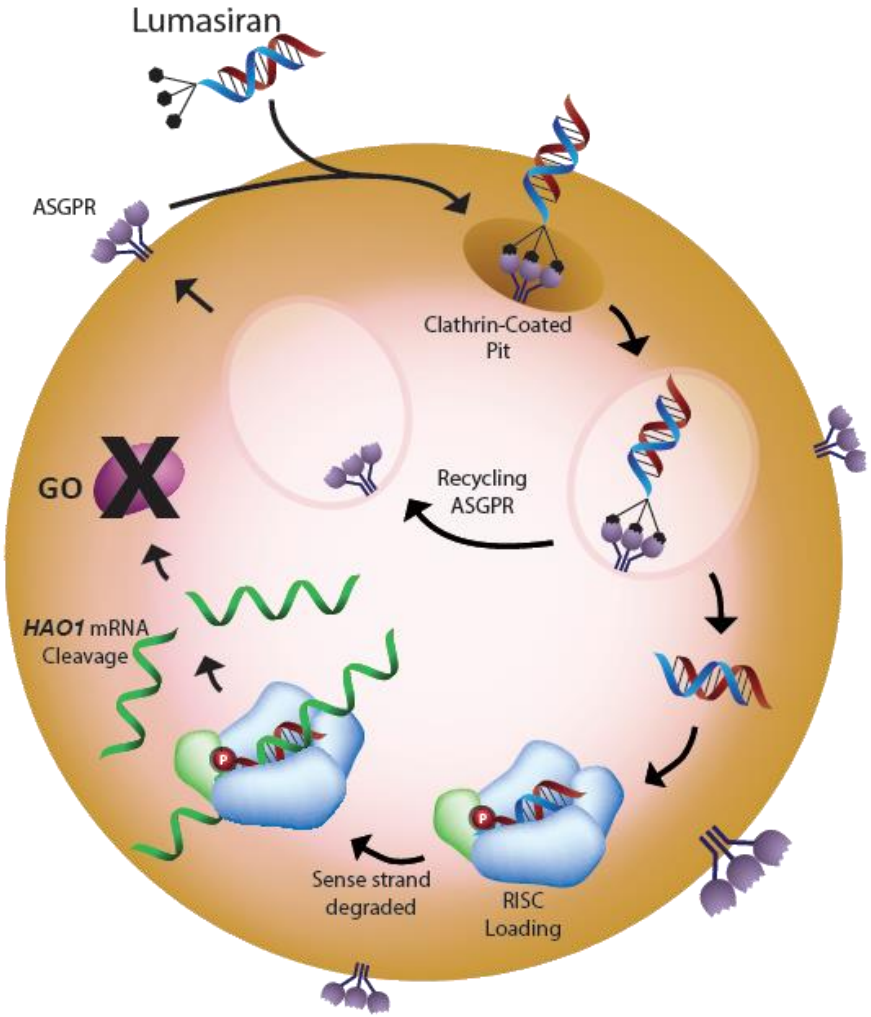
Investigational Therapeutic Approach: RNA Interference

Harness natural pathway of gene silencing to regulate protein production

Sequence-dependent degradation of target mRNA confers exquisite specificity

Conjugation to GalNAc allows subcutaneous administration and efficient delivery to hepatocytes

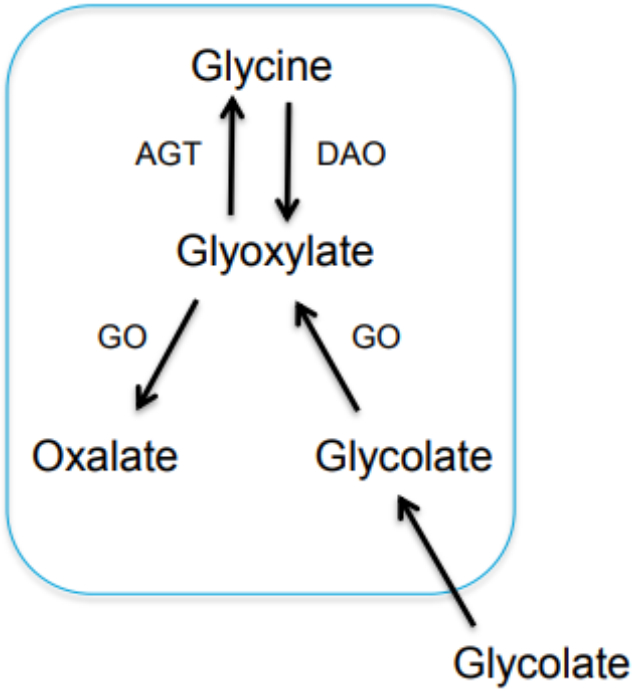
General approach clinically validated with human proof-of-concept in multiple clinical development programs across several diseases



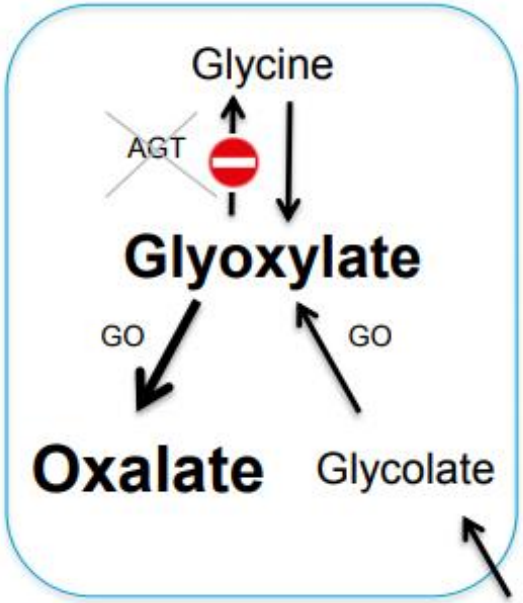
Lumasiran Therapeutic Hypothesis

Knockdown of Liver GO Enzyme to Reduce Oxalate

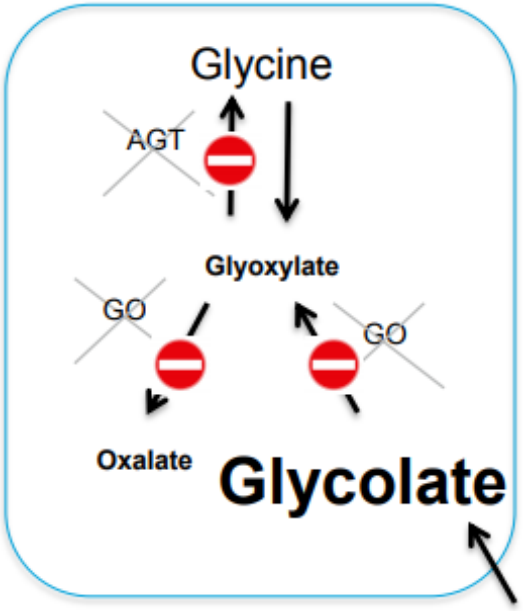
Healthy Pathway



PH1 Pathway



PH1 Pathway + Lumasiran



AGT, alanine:glyoxylate aminotransferase; DAO, D-amino acid oxidase; GO, glycolate oxidase; PH1, primary hyperoxaluria type 1

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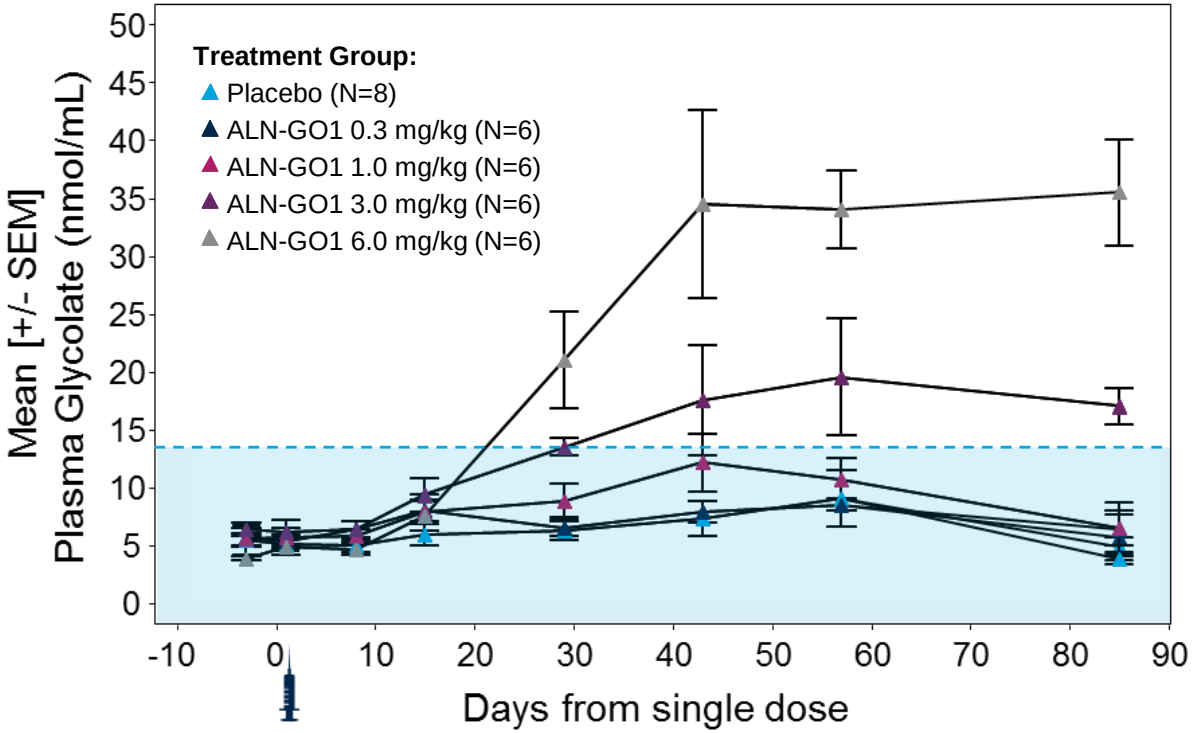
Lumasiran Phase 1/2 Part A Study Results: Plasma Glycolate Levels in Healthy Volunteers

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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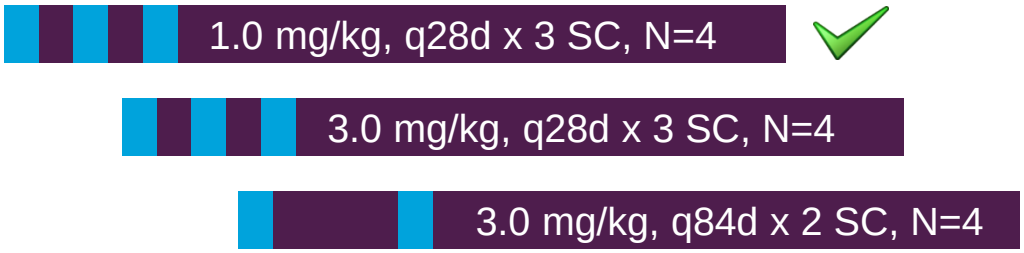
Lumasiran Phase 1/2 Study*

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

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



Dosing Complete

- Population: PH1 patients, ages 6-64 years; eGFR>45 ml/min/1.73m^2; Urinary oxalate excretion ≥ 0.70 mmol/24h/1.73m^2
- Outcome evaluations: Safety, Pharmacokinetics and Pharmacodynamics

Demographics (Cohorts 1 & 2)

- Age range: 6-19 years
- Gender: 5 Female, 3 Male
- Race: 1 Arabic, 2 Asian, 1 Asian Indian, and 4 Caucasian

*Data as of: 03 October 2017
PH1, primary hyperoxaluria type 1; eGFR, estimated glomerular filtration rate

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Lumasiran Phase 1/2 Study Initial Results*

Safety: Part B (Patients with PH1)

Lumasiran generally well tolerated in patients with PH1

No study discontinuations

No drug related Serious Adverse Events (SAEs)

- Five total SAEs: Kidney stones, Pyelonephritis, Gastroenteritis with Dehydration
- Three SAEs during placebo dosing (Kidney stones and pyelonephritis)

Majority of AEs were mild or moderate and unrelated to study drug

- One treatment related AE reported: bruise at injection site

No clinically significant laboratory or hematologic changes

*Data as of: 03 October 2017
PH1, primary hyperoxaluria 1

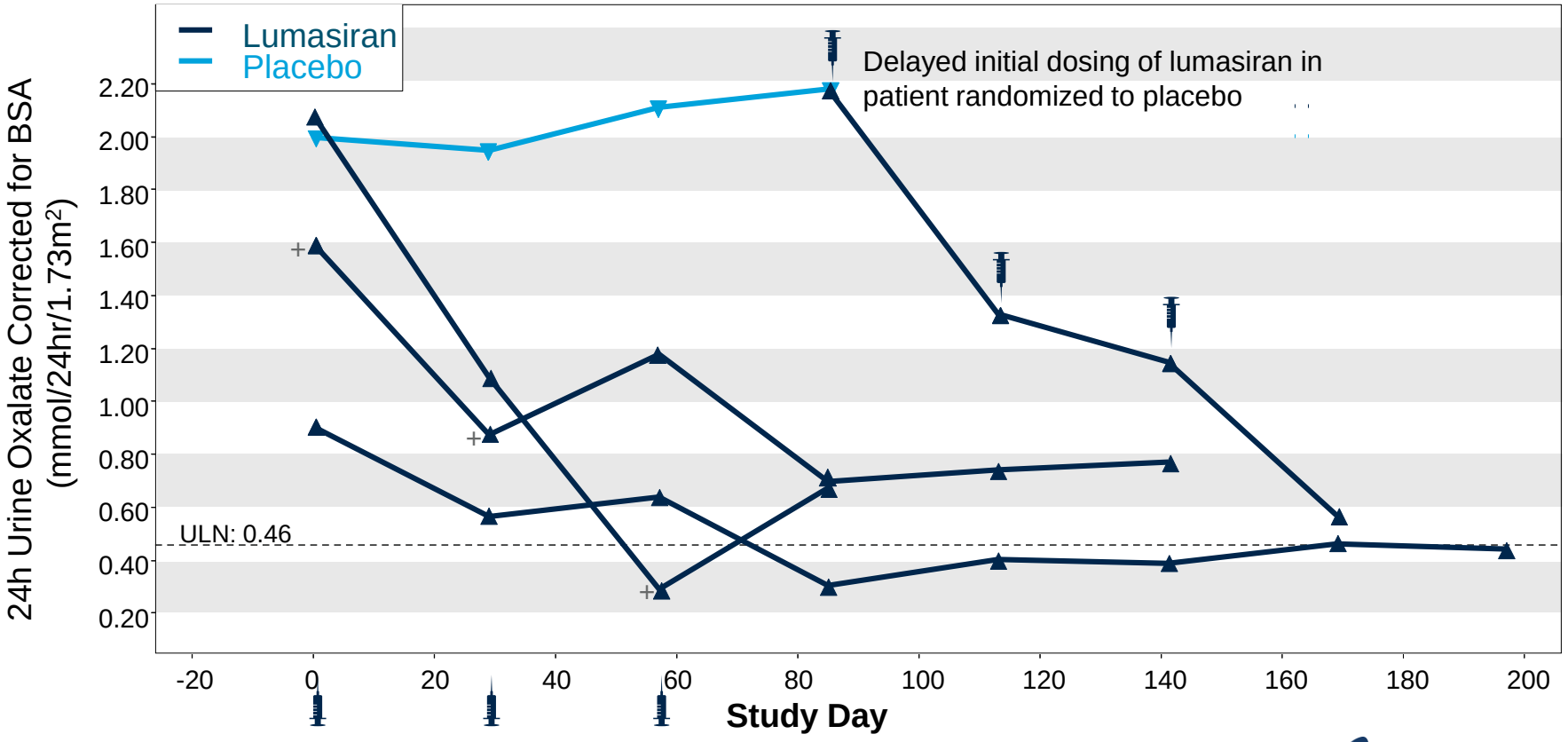
Lumasiran Phase 1/2 Study Initial Results*

Pharmacodynamics: Part B (Patients with PH1)

Cohort 1: 1 mg/kg q28d x 3 doses

Lumasiran reduced urinary oxalate excretion >50%, relative to baseline

- Mean maximum reduction of 66%; maximum reduction of 74%

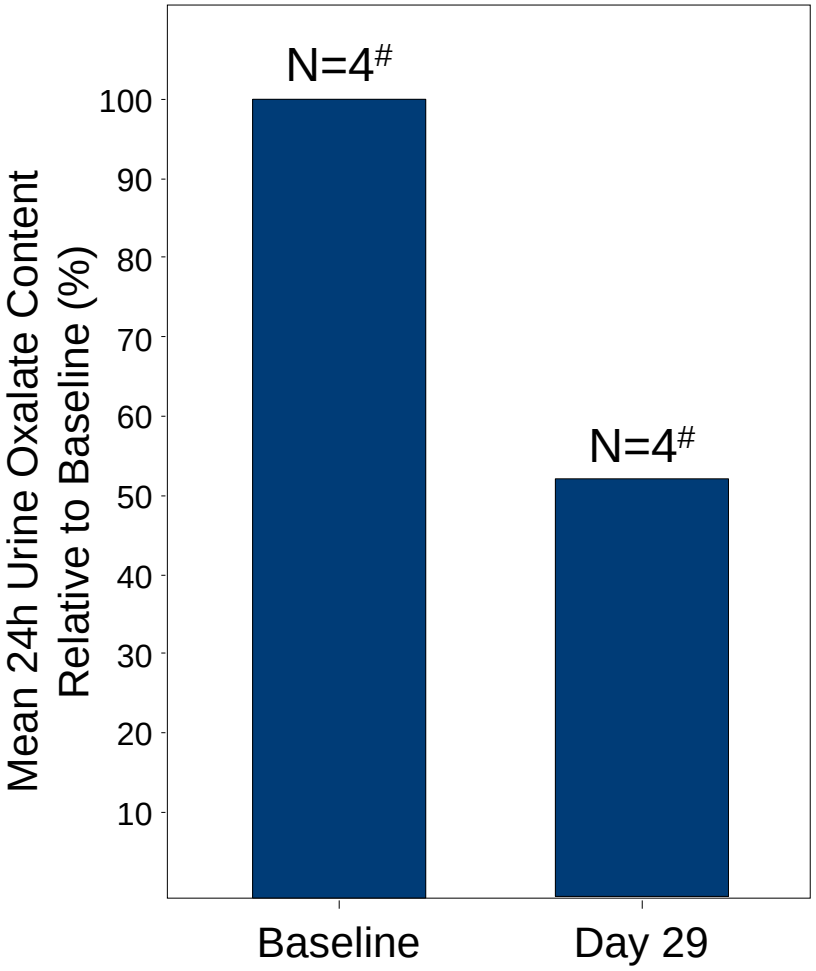


*Data as of: 03 October 2017

⁺Possible incomplete collection leading to falsely low oxalate result

Lumasiran Phase 1/2 Study Initial Results*

Pharmacodynamics: Part B (Patients with PH1)



Cohort 2: 3 mg/kg q28d x 3 doses

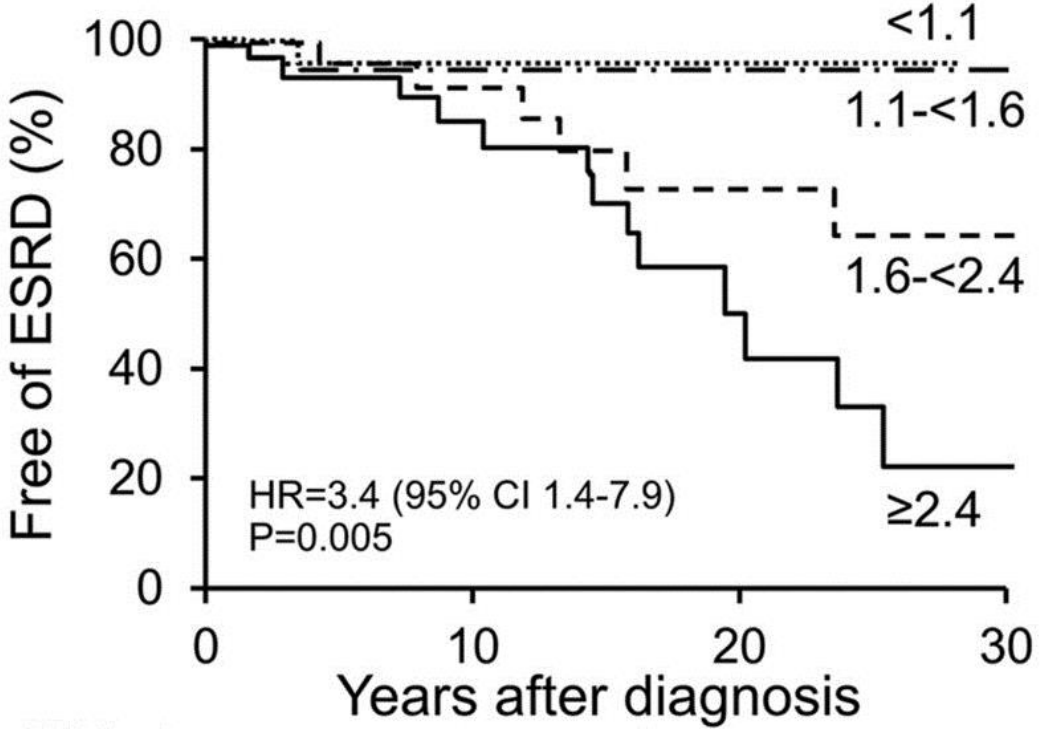
After first dose of lumasiran or placebo, mean urinary oxalate excretion at Day 29 decreased by mean of 47%.#

Placebo included in aggregated data as patients remain blinded in ongoing study

*Data as of: 03 October 2017

Significance of Decreasing Urinary Oxalate

Lumasiran lowered UOx below 1.1 mmol/24hr/1.73m^2 in all patients with baseline excretion ≥ 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. 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.

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): 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

Lumasiran treatment achieved substantial reductions in urinary oxalate levels in all patients treated, suggesting potential of substrate reduction therapy through RNAi-mediated glycolate oxidase inhibition

Continued investigation of lumasiran will explore dose optimization for oxalate lowering in patients

- Alnylam 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: 03 October 2017
RNAi, RNA interference; SAE, serious adverse event

Acknowledgements

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ALN-GO1-001 Investigators

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